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supply by depressing mitochondrial function and cytochrome synthesis (Holtzman and Shen Hsu, 1976).

Lead also affects the male gamete. Industrial exposure of men resulting in PbB levels possibly as low as 40-50 µg/dl resulted in abnormal sperm number and vigor (Lancrajan et al., 1975; Wildt et al., 1983). Sperm abnormalities, reduced fertility, and altered testicular function have also been observed among male mice exposed to low doses of lead (Hilderbrand et al., 1973; Maker et al., 1975; Wryobeck and Bruce, 1978; Donovan et al., 1980). Such changes may be related to observations of compromised viability of progeny to mice exposed to lead before conception (Stowe and Goyer, 1971).

Although the data base is limited, the available studies suggest that low level exposure of mothers and fathers to lead might induce post-natal developmental delays and increase the risk of reproductive abnormalities. OSHA reviewed the available literature in 1978 and concluded that men and women planning to have children should maintain PbB levels at or below 30 µg/dl (OSHA, 1978). Defining a PbB at which effects on other aspects of reproductive function (e.g., loss of vigor, erectile dysfunction) would begin to be of concern must await further research.

6. Possible Genotoxicity/Carcinogenicity

At high concentrations (>500 ppm), dietary lead acetate induced renal tumors in experimental animals (Azar et al., 1973; see CD, Figure 12.5). A dietary lead acetate level of 500 ppm produced a PbB of 80 µg/dl in dogs within 2 years; defining a corresponding exposure level be in humans is difficult to determine, however.

Since lead is capable of transforming cells directly in culture (Dipaolo et al., 1978; Casto et al., 1979) and affecting DNA-to-DNA and DNA-to-RNA transcription (Sirover and Loeb, 1976; Robinson et al., 1984),

lead may serve as an initiator of carcinogenic activity. Lead's ability to induce chromosomal aberrations (CD, Table 12-20) is also indicative of its ability to initiate carcinogenic activity. In addition, lead may be a promoter of carcinogenesis, as indicated by its ability to increase DNA, RNA, and protein synthesis (Choie and Richter, 1974 a,b) and to enhance the development of renal tumors in rats previously treated with a known carcinogenic initiator (Hiasu et al., 1983). Lead's sequestration in the form of "inclusion bodies" in kidney cell nuclei may be linked to its carcinogenic effects (CD, p. 12-225).

Epidemiological studies of lead-exposed workers and children suggest that lead may induce chromosomal aberrations that may be associated with certain forms of cancer (Grandjean et al., 1983; Dalpra et al., 1983). Little can be reliably concluded from the conflicting occupational findings on kidney tumor incidence and excess cancer mortality (Cooper and Gaffey, 1975; Kang et al., 1980; Baker et al., 1980; Lilis, 1981; Cooper 1981; McMichael and Johnson, 1982; Selevan et al., 1984), although the significant elevations in respiratory and digestive tract cancer in workers exposed to lead and other agents warrant concern (CD, p. 12-225). These latter findings should not be over-interpreted given differences in age distributions among the populations studied and inadequate controls for factors such as smoking, diet, ethnicity, and geographical location. Furthermore, these studies provide no specific information on the long-term lead exposure levels or the lead compounds to which workers were exposed. Lead emissions from other smelters and refineries include lead sulfate and oxides of lead while windblown dust from stored ore concentrate and contaminated soil is predominantly lead sulfide (Jennett et al., 1977). Exposure to even relatively insoluble lead compounds (e.g. lead sulfide) however, could account for the observed gastrointestinal

and respiratory cancers (CD, p. 12-206).

The criteria document concludes that:

> "Since lead acetate can produce renal tumors in some experimental animals, it seems reasonable to conclude that at least that particular lead compound should be regarded and treated as a human carcinogen (as per recommendations of the International Agency for Research on Carcinogenicity). However, this statement is qualified by noting that lead has been seen to increase tumorigenesis rates in animals only at relatively high concentrations, and therefore does not seem a potent carcinogen. In vitro studies further support the genotoxic and carcinogenic role of lead, but also indicate that lead is not potent in these systems" (CD, p. 12-268).

It is important to note that the IARC recommendations were published in 1980 and do not reflect findings from several recent experimental and occupational studies cited in the criteria document that suggest that other inorganic lead compounds besides lead acetate may be carcinogenic. It appears, therefore, that there is some need for caution and further research on the carcinogenicity of lead compounds,other than lead acetate, that are present in the atmosphere and other exposure media.

7. Effects on the Immune System

Lead interferes with host immune defense mechanisms as indicated by increased susceptibility to infectious agents (CD, Table 12-22), endotoxins (Cook et al., 1974), and increased incidence of tumors (CD, Section 12.8.2.2), in lead-exposed animals. There is suggestive evidence that human resistance to infection may be lowered by elevated lead exposure (Sachs, 1978; Ewers et al., 1982), although no dose-response information is available. Lead-induced immunosuppression, possibly through direct interference with macrophage function (Lawrence, 1981) occurs at low-level exposures in animals (PbB levels of 20-40 µg/dl) (CD. p. 12-268). Although these effects do not induce overt toxicity, they, nevertheless, may be detrimental to health and lead's immunosuppressive capabilty "should be carefully considered" (CD, p. 12-241).

8. Effects on the Hepatic System

The metabolic breakdown by the liver of some pharmacologically active substances (e.g., drugs, hormones, environmental toxins) depends on the availability of the hemoprotein, cytochrome p-450 and consequently, the synthesis of heme (Remmer et al., 1966). Lead exposure impairs the detoxification capabilities of experimental animals, while drug metabolism and liver function in children appear to be affected at fairly high exposures (>40 µg/dl) (Alvares et al., 1975; Saenger et al., 1984). As discussed in Appendix D.1(b), in the absence of conclusive data it must be assumed that any indication of significantly altered heme biosynthesis (e.g., elevated EP) may also indicate a possible inhibition of liver detoxification function.

9. Effects on the Gastrointestinal System

Typical gastrointestinal signs and symptoms caused by lead intoxication include constipation or diarrhea, abdominal pain, nausea, indigestion, and anorexia. Mild symptoms have been associated with PbB levels in the 50 to 70 µg/dl range, and as low as 30 µg/dl (Haenninen et al., 1979; Fischbein et al., 1980). There is insufficient information, however, to establish a clear dose effect relationship for the general population at ambient exposure levels (CD, p. 12-247).

10. Effects on the Endocrine System

Relatively high level lead exposures affect various endocrine processes (e.g., impaired thyroid function) (Sandstead and Galloway, 1967; Sandstead et al., 1969, 1970). Apart from the previously discussed alterations in vitamin D hormone metabolism that is secondary to interference with heme synthesis, endocrine processes do not appear to be impaired by lead at PbB levels below 30 µg/dl.

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As with other parameters of neuropsychological performance, there have been mixed findings regarding lead's association with children's scores on standardized IQ tests, which measure some combination of literacy, information, academic capacity, and intelligence (Flynn, 1984). Several well-controlled studies have found effects that are clearly statistically significant whereas others have found "non-significant" but borderline effects. It is important to note that: 1) the definition of "statistical significance" ($p < 0.05$) is somewhat arbitrary and should not be used to totally exclude results that may have important public health implications; and 2) given the likely subtle nature of the behavioral or neural effects probable at low levels of lead exposure, the differential maturation patterns and sensitivities among different brain processes, and the many other factors that play a larger role in an individual's developmental trajectory, one would not expect to find striking differences in every study, especially in those that use standardized but non-specific measures of intelligence or academic capacity.

The general indication from the better investigations is that PbB levels persistently elevated in the range of 50-70 µg/dl tend to be associated, on average, with about a 5 point reduction in IQ, even among asymptomatic children and after controlling for potentially confounding variables (de la Burde and Choate, 1972, 1975; Rummo, 1974; Rummo et al., 1979). A 5 point decrease in children's average IQ score, given the normal curve of distribution of intelligence, would be associated with a doubling in the number of children with IQ's below 70 (the level used to define mental retardation), as well as a reduction in the number of children with IQ's above 125 (Rutter, 1980). Thus, while any individual child's IQ score may fluctuate over time, the implications of a 5 point average deficit among children are serious.

Considerable uncertainty exists regarding lead's impact on IQ scores of children with PbB levels below 40 µg/dl. This uncertainty largely stems from the complex interaction between lead exposure over time, social factors, and intelligence scores, and from the statistical and methodological limitations of cross-sectional studies to untangle these variables, and the range of interpretations that result from these studies. For example, Ernhart (1983, 1984) reanalyzed previously-published data on a group of children whose average PbB level dropped from 35.2 to 26.9 µg/dl over 5 years (Perino and Ernhart, 1974; Ernhart et al., 1981) and found that after partialling out the effects of sex, parental IQ, and parental education (but not socio-economic status), the proportion of variance explained by lead was no greater than 5% on any one of the IQ measures. With the exception of General Cognitive Index and Verbal Scale scores, the effects of early lead exposure on IQ scores appeared to be neither statistically significant nor persistent throughout childhood. It is possible, as with other studies, that by controlling for one variable such as parental IQ, which may be affected by lead exposure, the effects of lead on children's IQ is diminished. Ernhart (1983) concluded that although these data do not support an inference for an association between neuropsychologic deficits and lead exposures at the levels experienced by the children in this study, the rather low statistical power of the reanalyses does not allow for a definitive conclusion of "no-effect", either. Nevertheless, the results from these analyses are reasonably consistent with those from other investigators; namely that PbB levels above 30 µg/dl, compared to lower levels, show a small, but significant association with some measures of IQ after controlling for confounding variables.

The criteria document concluded from the Needleman et al. (1979) study and subsequent re-analyses (Needleman, 1984) that, after controlling for

confounding variables including pica, average IQ decrements of about 4 points appear to be associated with PbB levels in the 30-50 µg/dl range (CD, p. 12-74 to 12-80). Needleman et al. (1982) calculated that a 4 point decrement in the mean IQ of a normal population distribution would be associated with a three-fold increase in the number of children with severe deficits (IQ < 80) along with a 5% reduction in the number of children who attain superior function (IQ > 125). It is of interest to note that two pilot studies (Yule et al., 1981; Winneke et al., 1982a) that included children with PbB levels below 30-35 µg/dl (Rutter, 1983) living near lead smelters in Europe found IQ deficits (4.5 to 7 points) similar to those observed by Needleman et al. (1979) between high and low exposure groups after correction for confounding variables. However, the relatively crude controls for social variables provided in these latter two pilot studies prevent conclusive interpretation of the observed associations (CD, p. 12-86).

Studies of European children with lower lead exposures (mean PbB ≈ 8-15 µg/dl) have generally found only 1-2 point, and statistically non-significant differences in various IQ scores at PbB levels in the 15-30 µg/dl range after controlling for confounding variables (Smith et al., 1983; Harvey et al., 1983, 1984; Yule et al., 1983; Yule and Landsdown, 1983; Winneke et al., 1983, 1984). Smith et al. (1983) commented that if differences exist in neuropsychological performance attributable to lead at the levels they studied (<25 µg/dl), then the sensitivity of psychological tests and other currently available measures and statistical procedures do not allow these differences to be detected with any degree of certainty.

An important finding from several of these studies that tested for interactive effects (Yule and Landsdown, 1983; Winneke et al., 1983; Harvey et al., 1983) was that neurobehavioral deficits associated with

lead were enhanced in, or even largely confined to, socially disadvantaged children compared to those from more middle class backgrounds. These findings suggest that low level lead exposure, in combination with other factors associated with low socio-economic status (e.g., undernutrition) may predispose a child to psychological impairment. Further research is needed to investigate the possibility that the effects of low levels of lead (PbB < 30 µg/dl) on IQ are due, not to some "pure" form of permanent damage to the brain, as much as to the effects of lead as part of a more complex set of interacting influences including social and nutritional factors.

5) Electrophysiological Effects

As discussed earlier, in addition to its varied effects on neuronal development and chemically-mediated synaptic transmission, lead impairs peripheral nerve conduction velocities, at levels possibly as low as 30 µg/dl (Appendix D.2.a). Similarly, lead exposure affects brain morphology and metabolism, interferes with neurotransmission in central nervous system tissue (e.g., cerebellum, retina) (Palmer et al., 1981; Fox and Sillman, 1979; Sillman et al., 1982), and depresses conduction velocities in the visual pathways of rats accompanied by persistent decreases in visual acuity and spatial resolution (Fox et al., 1977; Cooper et al., 1980; Winneke, 1980; Impelman et al., 1982; Fox and Wright, 1982). Consistent with these findings are those from neurological assessments of children and adult workers which provide consistent findings indicating that a wide range of lead levels are associated with impaired function in the visual-motor and auditory systems (Repko, 1979; Haenninen et al., 1978; Needleman et al, 1979; Winneke et al., 1983).

It has also been demonstrated that electrical activity in the brain itself, determined by electroencephalograms (EEG), is disrupted in animals and humans suffering from lead intoxication (Cooper et al., 1980). More subtle abnormalities in EEG patterns (increased delta/decreased alpha activity) were detected in a subset of children from the Needleman et al. (1979) study with high tooth lead levels (Burchfiel et al., 1980). The lower amounts of alpha activity in the high lead children (PbB levels ≈ 30-50 µg/dl; CD, p. 12-92) might signify that brain maturation was somewhat delayed by lead since such activity tends to increase with age in children (Beningnus et al., 1981).

The brain wave patterns (indexed by slow cortical potentials elicited by classical conditioning) of 1-6 year old children varied as a linear function of PbB (ranging from 6-59 µg/dl) with no evidence of a threshold, although the slope changed systematically with age (Otto et al., 1981). Slow wave voltage tended to be positive in children less than 5 years old and negative in children over 5 years. Neurophysiological evidence suggests that slow surface-positive potentials in very young children may reflect axodendritic inhibitory processes (Otto and Reiter, 1984). Rostron (1982) has speculated that these findings suggest a decrease in attentiveness with increased PbB levels, perhaps lending support to findings of greater distractability in children with elevated lead levels (Needleman et al., 1979; Winneke et al., 1983; Yule et al., 1984). The relative amplitude of synchronized electrical activity between the left and right hemispheres of the brain varied as a cubic function of PbB levels in these children, with inflection points at 15 µg/dl and 40 µg/dl (Beningnus et al., 1981). Increased synchrony and relative amplitude of the EEG at these points could indicate an increase in the amount of information being

processed and, perhaps, that an increased effort is required to assimilate this information (Rostron, 1982).

In a subsample of these children assessed 2 years later, slow-wave voltage during sensory conditioning again varied linearly with PbB with no apparent threshold over a range of 11-39 µg/dl (Otto et al., 1982). This relationship was constant whether PbB levels from the initial or follow-up study were analyzed, suggesting a change that persisted over time despite a substantial decline in mean PbB from 32.5 to 21.1 µg/dl. In a five-year follow-up on a subset of the same children, significant associations were found between PbB levels and increased latencies in brainstem auditory evoked potentials (Otto et al., 1984). The authors stated that while the functional significance of slow wave changes associated with Pb exposure is uncertain, the slowing of nerve conduction in the auditory pathway has been unambiguously related to pathological lesions and non-specific demyelinating diseases such as multiple sclerosis; therefore the latter effects on brainstem auditory evoked potentials are clearly indicative of neurological impairment (Otto et al., 1984).

Interpretation of these data must be tempered by uncertainties regarding: 1) the clinical and functional significance of many of the electrophysiological measures used that are presently considered experimental; 2) the PbB levels actually associated with the observed effects; 3) several inconsistent correlations between PbB and derived EEG measures within the population over time; and 4) the representativeness of the data since only 43 children were initially studied, and 28 subsequently evaluated in the follow-up studies.

Nevertheless, the criteria document concludes that these findings "provide clear evidence of altered CNS functioning associated with relatively low level lead exposure at PbB levels in the 15-30 µg/dl range, and

perhaps, below" (CD, p. 12-95).

3. Effects on the Cardiovascular System

Symptoms consistent with cardiac disease, such as degenerative changes in heart muscle (Kline, 1960), abnormal electrocardiograms (ECG) (Silver and Rodriquez-Torres, 1968) and increased cerebrovascular mortality (Dingwall-Fordyce and Lane, 1963) have been associated with high human lead exposures. Cardiotoxicity has been reproduced in experimental animals acutely exposed to high concentrations of lead. Effects include depression in contractility, increased susceptibility to norepinephrine-induced arrhythmias (exaggerated in neonates), and decreased cardiac protein phosphyrlation (Kopp et al., 1980b; Williams et al., 1977 a,b). It appears that effects may persist in immature rats even after cessation of lead exposure (Williams et al., 1977b).

Chronic administration of lead resulting in PbB levels as low as 40 µg/dl caused structural changes in the myocardium of mice, and ECG abnormalities that are likely due to nerve conduction disturbances (Khan et al., 1977, Kopp et al., 1980 a,b). Besides affecting cardiac output, low levels of lead exposure have produced increased vascular responsiveness to contractile agents such as noradrenaline, and significant elevations in systolic blood pressure in rats with PbB levels around 40 µg/dl (and possibly lower) (Webb et al., 1981; Victery et al., 1982; Perry and Erlanger, 1979; Kopp, 1980a). These changes may be linked to reduced energy availability due to heme synthesis inhibition (Kopp, 1980a) or to altered nerve transmission caused by changes in calcium availability (Webb et al., 1981), and suggest possible mechanisms by which lead may contribute to hypertension in humans.

Excessive amounts of mobilizable lead have been measured in patients with hypertension (and renal impairment of unknown cause) (Batuman et al., 1983) and evidence of increased hypertension has been found among men occupationally exposed to high levels of lead (Inglis et al., 1978; Lilis et al., 1977), although there have been contrasting findings in similar populations (Richet et al., 1966; Cramer and Dahlberg, 1966;). Lower levels of exposure as indexed by PbB or urinary Pb levels, have been associated in some adult populations with hypertension prevalence (Beevers et al., 1976; Kromhout and Coulande, 1984) and blood pressure (Moreau et al., 1982; Pocock et al., 1984), but not in others (Staessen et al., 1984). Pocock et al. (1984) considered the weak (but statistically significant) correlation between lead exposure and hypertension at levels above 37 µg/dl to be of minor importance given the lower PbB levels typically found in British men. However, an unpublished EPA reanalysis of the grouped data reported by Pocock et al. (1984) indicates that blood lead is a significant predictor of blood pressure in their data, both before and after adjusting for covariates, when a regression of blood pressure is performed versus the log of blood lead for their reported group averages (U.S. EPA, 1985c). Furthermore, the regression coefficient indicated that the size of the effect was significant, suggesting a blood pressure increase of 3 mm Hg as blood lead increases from 5 to 15 µg/dl.

Recent analyses of NHANES II data have demonstrated significant associations between blood pressure (systolic and diastolic) and PbB levels among males (not females) aged 12 to 74 years independent of other, potentially confounding variables (e.g., nutrition) (Harlan et al., 1985). Further analyses were conducted on white males aged 40 to 59 years to avoid the collinearity between blood pressure and blood lead evident at lower ages and because data relating cardiovascular disease to blood pressure are

less extensive for non-whites (Pirkle et al., 1985). PbB levels were a significant predictor of blood pressure in this subgroup after including in the multiple regression analyses all known factors previously established as correlated with blood pressure and also when the relationship was tested against every dietary and serologic variable measured in the NHANES II survey (Pirkle et al., 1985). Including both curvilinear transformations and interaction terms had little effect on the blood lead coefficient. A threshold below which blood lead was not significantly related to blood pressure could not be found across a range of adjusted PbB levels between 7 and 34 µg/dl. It is of interest to note that the dose-response relationships found by Pirkle et al. (1985) suggest a large initial effect, leveling off at higher PbB levels, which is consistent with the biphasic blood pressure response to PbB levels found in rats (Victery et al., 1982) and which may account for the inconsistent epidemiologic findings in persons with mild to moderate elevations of blood lead.

Because of the complex inter-relationships among the multiple environmental, dietary, medical, socio-economic, and genetic factors that influence blood pressure, all of which may not be measurable, results from even the recent studies that employed thorough and extensive analyses and high quality data, must be interpreted cautiously. Nevertheless, the suggested relationships between blood lead and blood pressure among adults, even at PbB levels below 30 µg/dl, should continue to be carefully studied and be considered to have potentially important public health implications in terms of increased incidence of hypertension and more serious cardiovascular disease. Pending review of the most recent papers in the criteria document, their results are not reflected in the assessment of health risks associated with different PbB levels in determining an acceptable PbB level.

4. Effects on the Kidney

Lead at high concentrations is concentrated in the kidneys by high affinity binding proteins (which form intranuclear inclusion bodies) and causes numerous types of changes in a variety of physiological processes associated with the kidney. At low dosages, lead affects renal mitochondrial structure (e.g., swelling) and function (e.g., altered respiratory rates, oxidative phosphorylation and synthesis of heme, proteins, nucleic acids and vitamin D hormone) (Goyer, 1968; Fowler et al., 1980, 1981 a,b; Silbergeld et al., 1982; Rosen and Chesney, 1983). Lead's interference with these biochemical processes in the kidney, particularly energy metabolism, might account for the transient decreases in renal tubular reabsorptive processes, as indicated by hyperaminoaciduria, glycosuria, and hyperphosphaturia, at PbB levels ranging from 40 to more than 100 µg/dl, and possibly as low as 30 µg/dl (See CD, Sections 12.5.2 and 12.5.3; p. 12-170). Irreversible kidney damage (e.g., interstitial nephritis) appears to require prolonged high exposure, with PbB levels probably exceeding 70 µg/dl in adults although lead chelation is necessary to detect cumulative body stores that may contribute to the gradual development of this disease (Lilis et al., 1968; Cramer et al., 1974; Wedeen et al., 1979). It should be noted that the effects of chronic, low-level lead exposure on renal dysfunction in children have not been adequately studied.

There is limited evidence that elevated lead absorption contributes to renal disease in association with gout and hypertension (Emmerson, 1973; Batuman et al., 1981; Wedeen, 1982). The mild hypertension observed with chronic low-level lead exposure however, may be related to lead's ability to directly alter vascular reactivity (Webb et al., 1981; see Appendix D.3) and any contribution of lead-induced renal impairment to this

disorder, at low exposure levels, remains to be determined.

5. Effects on Reproduction and Development

Lead compounds have been used as an abortifacient and lead poisoning has been shown to be accompanied by reduced fertility, miscarriages and stillbirths (Oliver, 1911). Little research has been directed however, at whether subtoxic levels affect fertility or cause fetal injuries in humans. In female animals, relatively low-level lead exposure has been shown to affect pubertal progression and hypothalmic-pituitary-ovarian-uterine functions, as evidenced by ovarian abnormalities (Hilderbrand et al., 1973; Der et al., 1974), and delays in vaginal opening (Grant et al., 1980; Kimmel et al., 1980) and first conception (Maker et al., 1975). In addition, the ability of the placenta to support fetuses is compromised in mice exposed to relatively low lead levels (Maisin et al., 1975; Jacquet et al., 1976).

It is of particular concern that placental transfer of lead begins as early as the 12th week of gestation and continues to accumulate in the fetus throughout pregnancy (Barltrop, 1969) resulting in comparable PbB levels in the mother and newborn child (Alexander and Delves, 1981; Rabinowitz and Needleman, 1982). Newborn rodents whose mothers were exposed to lead during pregnancy showed compromised growth (Reiter et al., 1975), congenital malformations in the spinal cord (Carpenter and Ferm, 1977; Jacquet and Gerber, 1979) and delayed development of the CNS (e.g., cortical connections) and its functions (e.g., motor function, size discrimination) (Klein et al., 1978; Crofton et al., 1980; Grant et al., 1980; Overmann et al., 1981; Winneke et al., 1977; 1982b; Schlipkoter and Winneke, 1980; Fox et al., 1977, 1982; McCauley et al., 1982).

Pregnant women who lived in homes with excessive drinking water lead concentrations (>800 ppm) bore a significantly higher proportion of retarded infants (Beattie et al., 1975). Children of women who had worked and lived near a smelter during pregnancy had lower birthweights and an increased frequency of single and multiple malformations although the cause is unclear given the possible exposures both of the mothers and presumably, the fathers, to high concentrations of arsenic, mercury, cadmium, sulfur dioxide, as well as lead (Nordstrom et al., 1978; 1979a,b).

An increased incidence in the overall number of minor congenital anomalies, such as benign tumors and cysts and minor skin defects, was reported in newborn children with mildly elevated umbilical cord lead levels (> 6.3 µg/dl) after controlling for other covariates, although no single anatomic defect was individually associated with lead (Needleman et al., 1984). This suggested to the authors that lead may interact with other teratogenic risk factors to enhance the possibility of an abnormal outcome. No association was found between cord PbB levels and increases in major congenital anomalies. Further investigation of lead's possible interactions with other teratogens at low levels is needed before definitive conclusions can be made.

More subtle effects on the fetus and newborn, such as inhibited heme synthesis, may also be important consequences of maternal lead exposure below 30 µg/dl and transplacental transfer (Hubermont et al., 1976; Hayashi, 1983a,b; Gerber and Maes, 1978).

Several mechanisms can explain lead's teratogenic activity: a) disturbance of DNA synthesis and cell proliferation; (Choie and Richter, 1974a; Sirover and Loeb, 1976); b) chromosomal aberrations; (CD, Table 12-20); c) interference with embryonic nutrition through competition with calcium, iron, and zinc (Mahaffey and Michaelson, 1980); and d) interference with embryonic energy

control apparently in an attempt to compensate for the diminished production of heme due to lead's interference (Maxwell and Meyer, 1976).

ii. In the second step of the pathway, the zinc-requiring enzyme delta-aminolevulinic acid dehydrase (ALA-D), catalyzes the condensation of two molecules of ALA to form porphobilinogen. ALA-D is inactivated by lead without any apparent threshold, and in erythrocytes, its activity appears to be markedly reduced at a PbB around 15 µg/dl in both adults and children (Hernberg and Nikkanen, 1970; Wada et al., 1976; Nieberg et al., 1974; Secchi et al., 1974; Roels et al., 1975b). Based on several of these studies, Zielhuis (1975) calculated that the fraction of children with 40% reduction of ALA-D activity increases from about 10 to about 90% as PbB rises from 10 to 30 µg/dl.

The combination of increased ALA-S and decreased ALA-D activity accounts for the marked accumulation of ALA in the plasma and body fluids, and excess excretion of ALA in urine. The rate of ALA excretion accelerates above a PbB of 40 µg/dl in adults and children (Cramer et al., 1974; Moore et al., 1980; O'Flaherty et al., 1980). Several studies indicate a continuous correlation between urinary ALA (ALA-U) and PbB down to levels around 20-25 µg/dl (Meredith et al., 1978; Selander and Cramer, 1970; Lauwerys et al., 1974; Chisolm et al., 1976). In light of conflicting findings from studies using different measurement techniques, it remains to be established whether increases in ALA-U are preceded by elevations in circulating levels of ALA in plasma at PbB levels below 40 µg/dl (Meredith et al., 1978; O'Flaherty et al., 1980). The criteria document concludes that despite a positive bias in absolute ALA values due to measurement contamination by aminoketones not correlated with blood lead, the relative changes in blood ALA detected by Meredith et al. (1978) "appear

to provide the most plausible basis for the observed correlations with PbB levels as low as 18 µg/dl" (CD, p. 12-19).

While blood indicators of erythropoietic effects of lead may be more accessible, they are not the only, nor necessarily the most sensitive indicators of heme biosynthesis derangement in other organs (CD, p. 12-26). At roughly comparable lead levels associated with such changes in blood ALA and ALA-D, inhibitions of ALA-D and elevations in ALA are observed in the liver, kidneys, and spleen of adult rats and humans, and to a greater degree in the developing brain of young, compared to adult rodents (Millar et al., 1970; Secchi et al., 1974; Gerber et al., 1978; Silbergeld et al., 1982). The impact that elevated ALA may have on the neurological system is discussed in Appendix D.1(d).

It is important to note that because lead is preferentially deposited in bone (Appendix A), the concentrations of lead in the marrow will be significantly greater than in the blood during red blood cell formation and hemoglobin synthesis in the bone marrow (Albahary, 1972), and the developing red blood cells in the marrow will be particularly affected.

iii. Another effect of lead on heme biosynthesis is its interference with the last step of this chain, i.e., insertion of iron into protoporphyrin. This is mediated by the enzyme ferrochelatase, which is located in the inner matrix of the mitochondria of most cells (Moore et al., 1980). Lead impairs the transmitochondrial transport of iron and instead of producing heme, the mitochondria accumulate its precursor, protoporphyrin, which lacks iron and is incapable of performing its essential respiratory function. As a result of lead intoxication in newly forming erythrocytes, protoporphyrin (referred to as erythrocyte protoporphyrin or EP) takes the place of heme in the specific pocket of the hemoglobin molecule. As the red blood cells

remain in the circulation, zinc is rapidly chelated at the center of the molecule in the site normally occupied by iron (Piomelli et al., 1982). The resulting zinc protoporphyrin (ZPP) is tightly bound in the available heme pocket for the life of the erythrocyte, normally 120-130 days (Lamola et al., 1975). Thus, the content of protoporphyrin in circulating red blood cells represents what has accumulated during red blood cell maturation and consequently describes an effect that took place in the bone marrow, with a time lag of 3-4 months (Sassa et al., 1973).

With increasing blood lead, there is a rapid exponential increase of protoporphyrin, with significant accumulations over baseline at PbB levels of approximately 15 µg/dl in infants and children (Roels et al., 1976; Piomelli et al., 1977, 1982; Hammond et al., 1984; Rabinowitz et al., 1985) and 25-30 µg/dl in adults (Roels et al., 1975b; Grandjean and Lintrup, 1978; Odone et al., 1979; Herber, 1980). The population dose-response relationship between EP and blood lead in children aged 10-15 years indicated that EP levels were significantly higher (> 2 standard deviations) than the reference mean in 50% of the children at a PbB level of 25 µg/dl (Roels et al., 1976). A study of 2004 children found that EP levels increased exponentially above a PbB of 18 µg/dl and that PbB levels of 29.9 and 35.2 µg/dl corresponded to EP elevations of more than 1 and 2 standard deviations, respectively, in 50% of the children studied (Piomelli et al., 1982).

The health significance of EP or ZPP accumulation is attributed to the fact that it is evidence of impaired heme and hemoprotein formation in many tissues that results from lead's entry into mitochondria (CD, p. 12-46). Besides its role in the erythropoietic system in forming hemoglobin, heme is active in liver function, vitamin D metabolism, and the nervous system. These interactions, and lead's impact on them, are depicted back in Figure 7-1 and discussed below.

a) Effects of Lead on Heme and Hemoglobin Synthesis and Erythrocytes

Anemia is often the earliest manifestation of chronic and acute lead poisoning. It is defined as a hemoglobin concentration depressed below some clinically accepted level, usually about 9.5-11.0 grams of hemoglobin per dl blood. The symptoms of anemia in young children can include pallor, sallow complexion, fatigue, irritability, and decreased play activity.

The anemia of lead poisoning is related to some combination of decreased heme and hemoglobin production and increased rate of red blood cell destruction. In addition to its inhibitory effects on heme synthesis, lead disturbs the biosynthesis of globin, the protein component of hemoglobin, disrupts enzymatic activities necessary for erythrocyte membrane stability and ultimately, cellular survival (e.g., pyrimidine nucleotidase, ATPase), and causes oxidative damage to the red blood cell membrane (White and Harvey, 1972; Dresner et al., 1982; Gelman et al., 1978; Secchi et al., 1973; Valentine and Paglia, 1980; Angle and McIntire, 1978; Moore et al., 1980; Levander et al., 1975). Although these effects on enzyme activity and globin synthesis are detectable at PbB levels as low as 10 and 20 µg/dl, respectively, their role, if any, in reduced hemoglobin synthesis and shortened erythrocyte survival at such levels is uncertain.

In determining a PbB level of concern for anemia, it is important to distinguish the effects of lead from iron deficiency, which is prevalent in young children and could increase an individual's sensitivity to lead toxicity. Unfortunately, the available data do not provide sufficient information to separate this potentially confounding factor. In children with no obvious iron deficiencies, the incidence of anemia (defined as a hemoglobin concentration below 11 g/dl) rose sharply as the PbB levels increased from 37 to 100 µg/dl (Betts et al., 1973). At PbB levels below 36 µg/dl, 14% of the children were anemic, compared to 36% with levels

between 37 and 60 µg/dl. The criteria document cites a threshold PbB for anemia in children of 40 µg/dl (WHO, 1977) and 50 µg/dl in adults (CD, p. 12-28). However, until additional dose-response information on large groups of children is available, with appropriate controls for iron deficiency, this "threshold" should not be considered definitive.

b) Heme Synthesis and Liver Function

A major fraction of heme synthesized in the liver is used in the hemoprotein, cytochrome P-450. This hemoprotein is the terminal oxidase of the microsomal mixed function oxidase system that is involved in the metabolism of a variety of drugs and foreign toxins, as well as endogenous substrates such as steroid hormones (Granick et al., 1978). Decreases in liver cytochrome P-450 content and in drug detoxification rates have been observed following acute and chronic lead administration in animals and in lead-poisoned children and occupationally-exposed adults (Scoppa et al., 1973; Alvares et al., 1975, 1976; Meredith et al., 1977; Chow and Cornish, 1978). Lead-induced alterations and diminished cytochrome P-450 function are also believed responsible for the decreased excretion of 6 Beta-Hydroxy-cortisol (6, β-OHF), a metabolite of cortisol, in young children with moderate elevations of blood lead (46 µg/dl)(Saenger et al., 1984).

Because of children's vulnerability and exposure to drugs and foreign chemicals, and their high metabolic rates, these findings suggest that in the absence of conclusive data it should be assumed that any indication of significantly altered heme biosynthesis (e.g., elevated EP) may also indicate a possible inhibition of liver detoxification function.

c) Heme and Vitamin D Metabolism

Renal 1-hydroxylase, another heme-requiring cytochrome P-450 mediated mitochondrial enzyme system, converts 25-hydroxyvitamin D (which is formed in the liver from vitamin D) to the hormonal metabolite 1, 25-dihydroxy-

vitamin D (1,25-$(OH)_2$ D) in the kidney. 1,25-$(OH)_2$ D is the major active form of vitamin D in: 1) orchestrating the differentiation and turnover of cells in bone mineralization (CD, p. 12-41); 2) stimulating intestinal absorption of calcium and phosphorous (Sorell et al., 1977; Rosen et al., 1980); 3) maintaining extra- and intra-cellular calcium homeostasis essential for cellular integrity and function (including responses to hormonal and electrical stimuli, modulation of cyclic nucleotide metabolism, and regulation of several enzyme systems) (Cheung, 1980; Rasmussen and Waisman, 1983; Rosen and Chesney, 1983; Rosen, 1983); 4) mediating the activation of various immunoregulatory processes (Provvedini et al., 1983; Bhalla et al., 1983; Tsoukas et al., 1984); and 5) mediating pancreatic function and insulin secretion (Clark et al., 1981; Kadowski and Norman, 1984a,b).

In addition to its reliance upon heme, the biosynthesis of the vitamin D hormone is controlled largely by the functional integrity of the renal mitochondria, by the ionic (calcium, phosphorus) environment of the exracellular fluid, and by the active uptake of calcium by mitochondria (CD, p.12-38). Given lead's toxic effects on mitochondria, cellular energetics, and cytochrome P-450 function, and the fact that ferrochelatase activity in kidneys is inhibited by lead just as it is in red blood cells (Fowler et al., 1980), it is not surprising that lowered 1,25-$(OH)_2$ D levels occur at PbB levels corresponding to those associated with the onset of EP accumulation in erythropoietic tissue. For example, a strong negative correlation between children 1,25-$(OH)_2$D and PbB levels was found over a range of 12-120 µg/dl (Rosen et al., 1980). In children with PbB levels over 33 µg/dl, the reductions in 1,25-$(OH)_2$ D were comparable to those observed in children with severe renal insufficiency lacking two-thirds of normal renal function, as well as in those children with a variety of in-borne metabolic disorders such as vitamin D-dependent rickets, oxalosis, and

hypoparathyroidism (Rosen and Chesney, 1983; Chesney et al., 1983).

Several other points should be made regarding the significance of lead-induced reductions in blood serum levels of 1,25-$(OH)_2$ D: (1) Mahaffey et al. (1982) noted the possibility of a feedback mechanism by which lead-induced reductions in 1,25-$(OH)_2$ D interfere with intestinal lead absorption, or that normal bone mineralization permits lead to be sequestered in bone. Recent experimental data in rats (Smith et al., 1981), however, indicate that: dietary intake of vitamin D does not affect blood lead concentration; low 1,25-$(OH)_2$ D levels can inhibit calcium transport thereby enhancing lead absorption; and reduced 1,25-$(OH)_2$ D levels do not protect target organs (e.g., kidney) by sequestering lead in bone. (2) Although chelation of children with elevated PbB levels results in a rapid (within 2 days) return to normal 1,25-$(OH)_2$ D levels (Rosen et al., 1980), the vitamin D system's ability to recover only after lead levels are reduced does not necessarily imply that the system is operating as a normal biological feedback mechanism. (3) Decreased calcium levels and increased parathyroid hormone (PTH), along with impaired bone mineralization -- conditions that typically accompany severe vitamin D deficiency (as e.g., in rickets) -- are not evident in children with PbB levels below 62 µg/dl (Rosen et al., 1980). However, PTH and serum calcium levels typically are normal even in children with [illegible]

The varied biological roles of 1,25-$(OH)_2$ D in the body, including extra- and intracellular calcium homeostasis, cell differentiation/maturation, immunoregulatory function, and pancreatic function, e.g., insulin secretion (Kadowski and Norman, 1984a,b,; Clark et al., 1981) are becoming increasingly evident. Impairment of these activities that results from lead's depression of circulating 1,25-$(OH)_2$ D levels may underlie many of the diverse effects of lead. The criteria document concludes that "It appears likely that lead-induced reductions in heme underlie the effects seen in the vitamin D-endocrine system. This origin would account for the similarities in "thresholds" for the effects of lead on both EP accumulation and decreases in levels of 1,25-$(OH)_2$ D. It also typifies a cascade of biological effects among various organ and physiological systems of the body, a cascade that can ultimtely encompass the entire organism" (CD, p. 12-37) and "that impaired production of 1,25-$(OH)_2$ D can have profound and pervasive effects on tissues and cells of diverse type and function throughout the body" (CD, p. 12-49).

d) Heme Synthesis and the Nervous System

The nervous system, both central and peripheral, is recognized as a target of critical importance in the toxicity of lead. Behavioral, electrophysiological, morphological, and biochemical investigations have demonstrated alterations in brain function at relatively low levels of exposure
when

(i) Interference with neurotransmission by the heme precursor, ALA

The excessive accumulation of ALA is believed to be linked to the clinical and biochemical similarities (e.g., paralysis, psychiatric disturbances, nerve demyelination) of lead intoxication and "porphyria", conditions in which elevated tissue concentrations of porphyrin precursors result from genetic or acquired deficiencies (Dagg et al., 1965; Moore et al., 1980). Excessive ALA levels in the brain may be responsible for some neurological dysfunctions associated with more mild lead exposure as well, since low levels of ALA in vitro can interfere at the neuromuscular junction or spinal cord with normal neurotransmission by γ-aminobuityric acid (GABA), which ALA closely resembles (Nicoll, 1976; Brennan and Cantrill, 1979; Silbergeld et al. 1980, 1982). Interference with GABA-ergic function by exposure to lead is consistent with such clinical and experimental signs of lead neurotoxicity as excitability, hyperactivity, hyperreactivity, and in severe cases, convulsions (Silbergeld and Lamon, 1980).

(ii) Heme deficiency and altered neurochemical synthesis

Litman and Correia (1983) have reported that lead treatment of rats was associated with an inhibition of the hepatic heme-requiring enzyme system, tryptophan pyrrolase, and resulted in significantly elevated brain levels of tryptophan, 5-hydroxyindoleacetic acid, and the neurotransmitter, serotonin. With infusion of heme, these increases were reversed. Elevated levels of tryptophan and its metabolites have been associated with human hepatic encephalopathy and with neurohistological and symptomatic changes seen in victims of acute porphyria attacks (e.g., alteration of brain neurons, axonal wasting, psychomotor disturbances) (Litman and Correia, 1983). It remains to be resolved, however, whether changes in this heme-dependent enzyme system alone can account for observed low-level lead neurotoxicity.

(iii) Impairment of heme availability in neural tissue

Heme biosynthesis appears to be inhibited in nervous system tissues at dose ranges comparable to those which are toxic in erythroid and liver cells (Whetsell et al., 1978; Sassa et al., 1979). Co-administration of heme and lead prevented most of the neuro-morphological effects caused by lead alone, namely destruction of myelin and Schwann cells and structural alterations of neurons (Whetsell and Kappas, 1981; Whetsell et al., 1984). These results are suggestive of heme's possible role in neurotoxicity, but again, firm conclusions must await further research.

(iv) Impairment of cytochrome function in brain energy metabolism

Another possible heme-mediated mechanism of lead neurotoxicity is suggested by findings that production and operation of the electron transport cytochrome C respiratory chain in the developing cerebral cortex are impaired when neonatal rats are chronically exposed to low levels of lead (Holtzman and Shen Hsu, 1976; Bull et al., 1979). Disruption of energy metabolism has been implicated in developmental delays in the metabolically active nervous system of young animals exposed to relatively low levels of lead (McCauley et al., 1979; Crofton et al., 1980).

These linkages between the biochemical effects of lead on heme synthesis and neurological function are primarily based on animal or in vitro experimental data. As such, it is difficult at this time to determine a lead exposure level of concern for heme-related neurological impairments in humans. Nevertheless, the common biochemical processes operating across neurological and hematological systems in mammalian species suggest that the abnormalities in heme synthesis caused by low level lead exposure in humans may also indicate some risk of neurobehavioral impairments.

2. Neurological Effects of Lead

a) Acute Effects and Peripheral Nerve Damage

The effects of lead on the nervous system are both structural and functional, involving various regions of the brain and spinal cord (i.e., the central nervous system) as well as the motor and sensory nerves leading to specific areas of the body (i.e., the peripheral nervous system). These effects can result in deterioration of intellectual, sensory, neuromuscular, and/or psychological functions.

Acute encephalopathy (degenerative brain disease) is the most severe consequence of lead intoxication. Early features of the syndrome include lethargy, sporadic vomiting, irritability, loss of appetite, dizziness, poor attention span, muscular tremor, and memory loss. These signs can abruptly progress to delirium, convulsions, coma, and ultimately death (Cumings et al., 1959). Acute encephalopathy in adults usually is manifested at PbB levels of approximately 100-120 µg/dl (Chisolm and Harrison, 1956; Chisolm, 1965); scattered evidence (Gant et al., 1938; Smith et al; 1938; Bradley et al., 1956; Bradley and Baumgartner, 1958; Cumings, 1959; Rummo et al., 1979) suggests that this syndrome may be associated with PbB levels between 80 and 100 µg/dl in the most susceptible children (CD, p. 12-62).

Severe lead poisoning with or without encephalopathy has permanent effects on the behavior and intellectual functioning of children, even if subsequent lead exposure is minimized. Such sequelae range from mental retardation and cerebral palsy to sensorimotor deficits, short attention span, and optic atrophy (Byers and Lord, 1943; Chisolm and Harrison, 1956; Perlstein and Attala, 1966; Chisolm and Barltrop, 1979).

While encephalopathy occurs primarily in children, peripheral nerve damage (neuropathy) due to high lead exposure is more commonly found in adults occupationally exposed to lead. Overt symptoms such as muscle tremor, palsy (e.g., "wrist drop") or weakness, muscle and joint pain, and gastrointestinal complaints have been observed in workers with PbB levels exceeding 40 µg/dl (Lilis et al., 1977; Spivey et al., 1979; Baker et al., 1979; Haenninen et al., 1979; Zimmerman-Tansella et al., 1983). Small reductions in nerve conduction velocities have been observed in some apparently asymptomatic workers with PbB levels as low as 30-50 µg/dl (Seppalainen et al., 1975, 1979; Araki and Honma, 1976; Melgaard et al., 1976; Ashby, 1980; Bordo et al., 1982; Johnson et al., 1980; Seppalainen and Hernberg, 1980, 1982; Singer et al., 1983; Triebig and Nottbohm, 1983). These observations were primarily on peripheral arm nerves that are responsible for the conduction of tactile and positional information, and information about painful stimuli and temperature.

Overt, lead induced peripheral neuropathy has been documented in children with PbB levels above 60 µg/dl (Erenberg et al., 1974), and in some cases possibly as low as 40 µg/dl (CD, p. 12-95). Although more subtle signs of possible advancing neuropathy (i.e., slowed nerve conduction velocities) have been observed in children across a wide range of increasing PbB levels, (Landrigan et al., 1976), no clear threshold for abnormal function can be determined from the available data.

In interpreting the effects of lead on the peripheral nervous system, it is important to note that: 1) Because these are chronic effects and PbB levels do not accurately reflect the long-term accumulation of body lead, it has not been determined if peak exposures prior to the time of study are responsible for the dysfunction, or the length of time that PbB

must remain above a certain level to cause impairment; 2) The range of nerve conduction velocities in humans is great, even when measured by a single investigator and, in almost all studies, most velocities among individuals are well within the range of normal values (although a statistical reduction in a population does indicate the need for reducing lead exposure; Seppalainen et al., 1975); and 3) Because peripheral nerves are able to regenerate, there is some dispute as to whether the observations of slowed nerve conduction velocities reflect mild, reversible impacts of lead (Buchtal and Behse, 1981) or are early warning signals of progressively more serious peripheral neuropathies that are important in the diagnosis of otherwise unrecognized toxic lead effects (Feldman et al., 1977; Seppalainen and Hernberg, 1980).

The criteria document concludes "nevertheless it is clear that these effects represent departures from normal neurologic functioning and their potential relationship to other more serious effects argues for prudence in interpreting their potential health significance." (CD, p. 12-61)

b) Effects Associated with Chronic Low-Level Exposures

Besides the severe pathophysiological changes observed in the central nervous system associated with childhood lead intoxication, various maladaptive behaviors, neuropsychological deficits, and neuro-anatomical changes may be associated with chronic exposures to relatively low concentrations of lead. Below is a summary of the numerous biochemical, morphological, and functional effects of lead at low dosages and exposures that have been found in developing nervous systems. No single mechanism appears sufficient to account for the diverse effects of lead on neurological function, and it is more likely that lead acts at several cellular and sub-cellular sites. Although neurochemical changes may preceed observable

effects on electrophysiology, morphology, and behavior in terms of dose, they are not separate from functional changes at higher levels. In those systems that have been examined pharmacologically in vitro (e.g., inhibition of adenyl cyclase, acetylcholine release, and Na,K-ATPase), a continuous dose-response relationship is suggested, best fitted by smooth curves with either no threshold or thresholds in the nanomolar range (Silbergeld, 1983).

It should be noted that the findings from in vitro or animal studies cannot be directly extrapolated to estimate PbB levels associated with changes in pediatric neurological functions because: a) the relatively short lifespans of experimental animals alters the relationship between dose and duration assumed for humans; b) significant species differences exist for absorption, retention, and internal compartmentalization of lead; and c) with some exceptions, the measurements of neurotoxicity are not comparable to those possible in studies of children (Silbergeld and Goldberg, 1980; Winneke et al., 1982b). However, in assessing the more overt effects reviewed in the next section, it is important to note this continuum of lead neurotoxicity starting with biochemical changes at the lowest observed dose levels.

1) Brain Development

Lead readily enters the brain and appears to be selectively deposited in the hippocampus and cortex as well as in non-neuronal elements (e.g., glial cells, endothelial cells of brain capillaries) that are important in the maintenance of "blood-brain barrier" functions (Fjerdingstad et al., 1974; Grandjean, 1978; Stumpf et al., 1980). Once deposited, lead is retained in the brain for long periods of time even after external exposure ceases and PbB levels decline (Mykkanen et al., 1979; Goldstein et al., 1974). These spatial and temporal patterns of brain lead accumulation

correspond to the following neurobehavioral and morphologic abnormalities associated with lead exposure: 1) pathologic studies of exposed animals and encephalopathic humans that indicate changes of a primarily vascular (e.g., endothelial and glial cell) nature (Michaelson and Sauerhoff, 1974); 2) animal studies that show effects on neuronal populations in the hippocampus and cortex and behavioral changes indicative of hippocampal and cerebellar dysfunction (Campbell et al., 1982; Petit and Alfano, 1979; Bushnell and Bowman, 1979); and most importantly 3) electro-physiological and behavioral changes associated with lead exposure measured in young animals and children that persist long after exposure is reduced or ceases (Brown, 1975; Otto et al., 1982).

The sensitivity of the brain during the period of maximal brain growth and differentiation in the first 2 years of life tends to magnify the severity of the long-term consequences of any toxin encountered during that period (Dobbing, 1974). The immaturity of specific brain tissues (i.e., hippocampus, cerebellum and neocortex) at birth and their relatively late development suggests that post-natal lead exposure could interfere with mitosis, cellular migration, differentiation of dendritic and axonal processes, synaptogenesis, and myelin production, as well as exerting biochemical and cytotoxic effects (Campbell et al., 1982). While the developing nervous system may possess considerable reserve for functional compensation (involving plasticity, regeneration, and redundancy of neural pathways), specific processes affected by lead apparently may not be reversed, either because lead is not removed from brain cells (Silbergeld, 1983) or because of interruption or damage to neurostructural components undergoing rapid development at the time of the lead insult.

Rat pups exposed to low levels of lead during the pre-natal or neonatal period show retarded development in cerebral energy metabolic pathways, delayed cerebral cortex synaptogenesis, and reductions in hippocampal morphometric, dendritic, and axonal development (Bull et al., 1979, 1983; McCauley et al., 1979, 1982; Petit and Alfano, 1979; Alfano and Petit, 1982; Petit and LeBoutillier, 1979; Campbell et al., 1982). These biochemical and morphological disruptions are paralleled by delays in the development of exploratory and locomotor activity, and by learning and behavioral deficits in young, lead-exposed animals (Bull et al., 1979, 1983; McCauley et al., 1979, 1982; Brown, 1975, Overmann, 1977; Bushnell and Bowman, 1979; Rice and Willes, 1979; Petit et al, 1983).

The effects of in utero or post-natal lead exposures on human infant neurological development have begun to be investigated. Mentally retarded children in Scotland were more likely by a factor of 1.7 to come from homes in which high levels of lead in drinking water (> 800 ppm) were present during pregnancy compared to controls (Beattie et al., 1975). PbB levels in a sample of these children at 2 weeks of age were 25.8 $\pm$ 8.9 µg/dl compared to 20.9 $\pm$ 7.9 µg/dl in normal children (Moore et al., 1977). Although these are provocative findings, their quantitative value is uncertain given that the children were limited to those known to health care services (and hence not necessarily representative), the matching was imperfect, and the PbB levels were available for only about 50% of the children.

Preliminary results from recently initiated prospective studies suggest that low to moderate lead exposure (mean PbB $\approx$ 15 µg/dl) during the first two years of life may have a small impact on early sensorimotor and mental development (Bellinger et al., 1984; Dietrich et al., 1984). Assessment of

the medical significance and persistence of these effects, if any, must await follow-up testing and replications from other longitudinal studies.

2) Motor Coordination and Reflexes

Pre- and post-natally lead-exposed rats tend to show developmental delays in their ability to orient properly and respond to selected reflexive stimuli (Overmann, 1977; Overmann et al., 1979, 1981; Grant et al., 1980). Impaired performance was observed in rats with PbB levels as low as 35 µg/dl at 11 days of age although no significant effects have been found at higher exposures in some studies using somewhat different measures of motor coordination and reflexes (Overmann et al., 1979; Zenick et al., 1979; Grant et al., 1980). These contrasting results can probably be attributed to differences in body weight, age at testing, and in the test apparatus and procedures (Zenick et al., 1979).

Lead-induced abnormalities in motor ability may be linked to preferential concentration of lead in the cerebellum where posture and movement is regulated, or to lead's damaging effects on peripheral nerves and at the neuromuscular junction (Cooper and Manalis, 1974; Silbergeld et al., 1974).

Small deficits in perceptual motor integration and fine motor coordination have been reported in children with PbB levels of 50-60 µg/dl, and possibly as low as 30-40 µg/dl (de la Burde and Choate, 1972, 1975; Landrigan et al., 1975; McBride et al., 1982; Needleman et al., 1979; Winneke et al., 1982a), or lower (Winneke et al., 1983). No significant lead-related deficits in psychomotor performance have been found at comparable PbB levels (i.e., 30-60 µg/dl) (Rummo, 1974; Rummo et al., 1979; Perino and Ernhart, 1974) and at PbB levels below 25 µg/dl (Winneke et al., 1984). No differences in fine motor scores were found in another study, although the mean PbB levels for the control group (26 µg/dl) may have been too

high to detect any effect in the exposed group (PbB ≈ 38 µg/dl) (Kotok, 1972; Kotok et al., 1977). These conflicting results are analogous to those found in animal experiments in which somewhat different measures of motor coordination and reflexes were also used. Nevertheless, any deficits in perceptual motor and fine motor coordination that are, in fact, related to lead may be functional evidence of lead-induced decrements in motor nerve function. This has been noted in children and in adults who exhibit conduction deficits in distal-extremity nerves at PbB levels above 30 µg/dl (See Appendix D.2.a). Similarly, the findings of perceptual inaccuracies associated with lead exposure have been interpreted in terms of lead-induced attentional deficits which are discussed below (Winneke et al., 1983).

3) Hyperactivity and Other Behavioral Disorders

Since Byers and Lord (1943) reported hyperactivity as a possible sequel for children who had recovered from lead poisoning, there has emerged a large and controversial data base concerning possible associations between lead and hyperactivity and other behavioral disturbances. Hyperactivity is a complex syndrome with respect to both cause and manifestation. Attention deficit disorder is generally thought to be the most salient manifestation of the condition (American Psychiatric Association, 1980). This disorder occurs with and without hyperkinesis, which refers more to inappropriate and/or random activity than it does to an increase in activity, although the latter is sometimes seen (David et al., 1983). Other symptoms frequently present are impulsivity, low frustration tolerance, hyperexcitability, and disturbances in conduct (Wender, 1971; David et al., 1983).

Inconclusive findings of hyperkinesis have been reported in neonatally lead-exposed rodents (CD, Table 12-2). Attempts to collate these data are

hampered by variability in the species, dose of lead, length and route of exposure, age, the methodology for activity testing and the presence of growth retardation. It has been proposed that a) the apparently discrepant findings on hyperkinesis are consistent with an explanation in terms of lead-induced, situation-specific, emotional or behavioral over-reactivity rather than hyperactivity per se (Hastings et al., 1977; Winneke et al., 1982b; Kishi et al., 1983); b) these behavioral disturbances are consistent with previously described disruptions in hippocampal morphology and function (Petit et al., 1983); and c) these behavioral effects may contribute to learning deficits observed in lead-exposed animals (see Appendix D.2(b)5).

Despite these interesting analogies between some of the changes in developmental animal behavior and hyperactive abnormalities, it would be premature to extrapolate from simple animal models to this complex clinical syndrome in children. Multiple etiologic factors including genetic influences, perinatal complications, covert cerebral insult, irregular brain maturation, maldevelopment and perhaps, most importantly, psychosocial factors can play a role in hyperactivity (David et al., 1983). Some studies that have attempted to control for these etiological factors and pica (which may be a consequence rather than a cause of hyperactivity) have found consistently higher lead levels in hyperactive children (Baloh et al., 1975; David et al., 1976; Gittleman and Eskenazi, 1983), while other studies have not (Rummo, 1974; Milar et al., 1981). Because of methodological limitations, conclusions from these studies are also limited.

In a more carefully controlled study, David et al. (1983) found that reductions in hyperactive children's PbB levels (from 29.3 to 19.5 µg/dl) as a result of chelation therapy with penicillamine were associated with marked symptomatic and behavioral improvements, as assessed by teachers,

parents, and treating physicians. Hyperactive children given a therapeutic drug to treat the syndrome, but whose PbB levels remained approximately the same, showed some similar improvements while children given a placebo exhibited no significant changes in behavior ratings or PbB levels.

The criteria document concludes that the above data are at best qualitatively suggestive and that if lead is indeed causally involved in the etiology or exacerbation of the behavioral abnormalities associated with hyperactivity, it is currently impossible to state with confidence the levels, durations or critical periods of lead exposure that may have been important (CD, p. 12-89).

There is somewhat more convincing evidence that low PbB levels may contribute to some other behavioral disorders such as attentional deficits and distractibility in essentially normal children not diagnosed as hyperactive. Several analyses of classroom behavior have failed to adequately account for the influence of social class although they have produced consistent dose-response relationships in which teachers' ratings on several behavioral measures (e.g., "distractability", "not persistent", low overall functioning) increase parallel with tooth and PbB levels (de la Burde and Choate, 1972; Needleman et al., 1979; Yule et al., 1984). As is the case for several other general population studies (Landrigan et al., 1975; Winneke et al., 1983), hyperactivity was noted in very few children and was generally not associated with lead levels. After adjusting for socio-economic and other potentially confounding factors, behavioral and attentional deficits as rated by teachers (e.g., disordered classroom activity, restless, easily distracted, not persistent, does not follow directions, low overall functioning) were significantly associated with children's tooth and PbB levels (Winneke et al., 1983). The criteria document

has interpreted this study, which also assessed lead-induced deficits in IQ and other psychometric tests, as showing overall neurobehavioral deficits at PbB levels possibly below 30 µg/dl (Winneke et al., 1983).

In addition, lead levels in young children have been consistently associated, following appropriate adjustments, with deficits in reaction time under varying intervals, which is an index of attentiveness (Needleman et al., 1979; Winneke et al., 1983; Yule and Landsdown, 1983; Hunter et al., 1983), and with reaction behavior (Winneke et al., 1984). The criteria document concludes that these findings appear to argue for probable effects of lead on attention and vigilance functions at PbB levels extending below 30 µg/dl, and possibly, down to as low as 15-20 µg/dl (CD, p. 12-84).

4) Auditory and Language Processing

Central nervous system damage caused by severe childhood lead poisoning is often associated with motor-speech and language disorders (Byers and Lord, 1943; Mellins and Jenkins, 1955). There is conflicting evidence on whether subtle cerebral injury associated with chronic low-level lead absorption is manifested in impaired verbal behavior and auditory processing. Several studies have found no statistically significant lead-related differences on verbal subtests of standardized intelligence tests in children with PbB levels across a range from below 10 to above 60 µg/dl (de la Burde and Choate, 1975; Landrigan et al., 1975; Kotok et al., 1977; Yule and Landsdown, 1983; Yule et al., 1984; Smith et al., 1983; Winneke et al., 1982a, 1983, 1984), while other studies have (Kotok, 1972; Rummo et al., 1979; Needleman et al., 1979; Yule et al., 1981). Significant associations, however, have been detected between children's lead levels (possibly as low as 30-50 µg/dl PbB) and a more extensive battery of measures, including motor-speech behaviors, language comprehension, formulation behaviors (Needleman et

al., 1979; 1984) and auditory processing tasks (de la Burde and Choate, 1975; Needleman et al., 1979). In addition to more specific measures of language and auditory function, these findings of lead-associated decrements may be attributable to samples drawn from among children with relatively early exposures to lead.

Although no conclusions can be drawn from these findings, it is clear that further research on low level lead effects in children should include sensitive measures of motor-speech behaviors and communication impairments. Because maturation of the auditory cortex, which plays a vital role in language processing, and the onset of competence in speech and language occurs within the second year of life (Shaheen, 1984), such research should include assessments of the effects of lead absorption in children prior to their second birthdays.

5) Cognitive Function

In addition to deficits in behavioral functions, fine motor control, and auditory, language and speech development, there is evidence that low levels of lead may be associated with effects on some complex cognitive functions including learning, visual-perception skills, and IQ scores. In studies not confounded by nutritional or litter effects (a common problem in behavioral assays), rats exposed to lead in utero and/or through early development, resulting in PbB levels below 30 µg/dl and as low as 20 µg/dl, display alterations in learning task performances (visual discrimination, shock avoidance, operant conditioning) (Winneke et al., 1977, 1982b; Cory-Slechta and Thompson, 1979; Gross-Selbeck and Gross-Selbeck, 1981). Monkeys exposed for one year after birth to achieve PbB levels between 30 and 50 µg/dl were significantly retarded in their ability to learn spatial and discrimination tasks (Bushnell and Bowman, 1979) and in

their ability to alter their behavior under changed learning conditions (Rice and Willes, 1979). After lead dosing ceased, the lead treated monkeys at 2-3 years of age (PbB ≈ 20 µg/dl) had higher response rates than controls to reinforced stimuli (Rice et al., 1979), and deficits in spatial memory persisted in these monkeys at 4-5 years of age when PbB levels had stabilized at 5 µg/dl (Levin and Bowman, 1983). PbB levels are presented for comparative purposes only and should not be extrapolated to human dose-response relationships.

In considering these effects, it should be noted that performance in a learning task is based on a number of functional processes, such as motor functions, emotional-motivational conditions, sensory functions, and cognitive functions (namely memory and/or learning processes, i.e., the formation and retention of stimulus-response associations) (Bornschein et al., 1980; Winneke et al., 1982b).

It has been suggested that the above findings, which include "improved" performance in lead-treated animals on some learned tasks where success was measured by rapid response, indicate an underlying tendency to respond excessively or a behavioral "over-reactivity," whether or not such response is appropriate (Winneke et al., 1982b). This interpretation corresponds to some extent to lead-induced increases in locomotor activity and response-disinhibition (Overmann, 1977; Winneke et al., 1977; Schlipkoter and Winneke, 1980). Taken together, these data indicate that lead exposure during early development is disruptive in attention-demanding, difficult discrimination learning and complex neuropsychological performance and reduces responsiveness to contingencies in the environment, but this exposure facilitates active avoidance and other simple learning tasks (Overmann, 1977; Winneke et al., 1982b). Although these results cannot be quantitatively extrapolated to

children, they are in agreement with findings from recent studies that lead at low doses may be associated with a spectrum of alterations in children's behavioral, academic, and possibly intellectual development (see below).

These studies on children have attracted controversy because of difficulties associated with attributing subtle deficits in child development to lead exposure rather than to effects due to genetics, nutrition, medical history, access to education, and parental and social influences, all of which interact in potentially complex ways to mold an individual (Pearson and Dietrich, 1985). Untangling these different sources of behavioral variance is complicated by the necessary focus on children from lower socioeconomic areas where lead exposure is elevated and learning and caregiving conditions often are not ideal.

Other difficulties encountered in the conduct and interpretation of childhood lead studies include: 1) accurately classifying exposure since PbB is an index of recent, but not necessarily historical, lead exposure, and because the relationship between tooth and PbB levels is uncertain; 2) inappropriate measurement covariates (e.g., social class as an index of parental care and intellectual stimulation) that can bias regression analyses; 3) incomplete assessment of complex behavioral and intellectual processes; and 4) possible non-representativeness of study samples since most studies relied on information from either pre-selected clinic groups along with a selected "match" sample, or volunteers from the general population who may be more altruistic, interested, or better informed (Smith et al., 1983).

Based on five methodological criteria (adequate markers of lead exposure, sensitive measures of neurobehavioral function, appropriate subject selection, control of confounding covariates, and appropriate statistical analysis), the criteria document has identified a group of neurobehavioral studies that "were conducted rigorously enough to warrant at least some consideration here" (CD, p. 12-65).

parts of the body, particularly in the brain of the developing organism (Bjorklund et al., 1981; Momcliovic and Kostial, 1974).

Despite the limitations, blood lead has been the most widely used index of exposure because of the ease and relative safety of its collection and measurement. In future research there should be increased use of serial blood measurements in combination with tooth lead analysis, or other indices that reflect changes in tissue lead burdens with changes in exposure.

APPENDIX B. ESTIMATES OF LEAD UPTAKE

For each of the numbered lines in Table 5-1 in the integrated lead uptake/biokinetic model, the assumptions and estimates used in calculating average lead uptake for children from the various exposure pathways are discussed in the correspondingly numbered paragraphs below.

1. Outdoor air lead: For purposes of this analysis, it is assumed that each air lead concentration analyzed is maintained at a constant level and therefore represents the maximum average (e.g., either quarterly or monthly) allowable under any given concentration. The possible impact of daily variations in air concentrations on uptake is assumed to be small given the equilibration period for lead in blood (2 months in adults), the relatively small contribution direct inhalation of lead has on total exposure, and the modulation of lead levels after deposition and integration of lead particles in the environment. It is also necessary to address potential differences between lead levels monitored by stationary samplers and actual exposures of children to airborne lead. Such differences arise from various vertical and horizontal dispersion patterns of lead over complex micrometeorological conditions (e.g., urban street canyons). For instance, lead levels decrease significantly with distance and with height near roadways and point sources (Huntzicker et al., 1975; Landrigan et al., 1975; PEDCo, 1977, 1981). Short- and long-term roof-top lead levels in New York City were about 60-80% of street level readings (Lioy et al., 1980; Bauman et al., 1982). Despite such spatial gradients and inter-site variability, it is assumed that the currently designed lead monitoring network will adequately differentiate pollutant variability and instances of significant excursions, and that given the relatively small contribution of inhaled outdoor airborne lead to total exposure to atmospheric lead, the level monitored by a fixed sampler is a reasonable representation of outdoor, inhalable lead exposure.

2. Indoor air lead: The penetration of atmospheric lead into residential structures depends on the size of the lead particles, meteorological conditions, and the permeability of the windows, doors, and walls of the home. A range of indoor/outdoor ratios has been found (0.3-0.8) for different cities and structures (Yocom et al., 1971; Yocom, 1982; General Electric Company, 1972; Moscheandras et al., 1981; Halpern, 1978; Berk et al., 1981; Tosteson et al., 1982) and is applied to the urban situation. Near point sources where large particles predominate and infiltration into homes is low, the ratio appears to be closer to 0.3 (Cohen and Cohen, 1980).

3. Time spent outdoors: The amount of time spent between indoor and outdoor environments varies among young children depending on their stage of development (i.e., infant, toddler, pre-school), season, geographical location, and family behavior. For present purposes a range of 2-4 hours per day spent outdoors (and therefore 20-22 hours spent indoors) is considered a reasonable average (CD, p. 7-42).

4. Time weighted air lead concentrations for each level is estimated by: [(outdoor concentration x time spent outdoors) + (indoor concentration x time spent indoors)] ÷ 24 hours.

5. The volume of air breathed each day is dependent on age, body size, lung capacity, altitude, and activity of the child. For instance, ventilatory volume can increase three-fold during strenuous exercise (Cotes, 1979). There are few data for young children and the estimates of 4.6 m^3/day (ICRP, 1975), 6 m^3/day (Nutrition Foundation, 1982), and 10 m^3/day (CD, p. 7-39) for 2-year olds have been used to construct a range of average ventilation rates.

6. The range of total lead intake by inhalation for each air lead level is computed by multiplying both the estimated upper and lower bound

time-weighted average concentrations of air lead by upper and lower bound estimates of the volume of air respired per day.

7. Respiratory deposition and absorption: Only a portion of inhaled lead is deposited in the lungs and subsequently absorbed into the bloodstream. The deposition efficiency of lead particles depends primarily on their size and the physiology and rate of breathing of the individual. In Appendix A (Section 1a), a respiratory deposition/absorption rate of 25 to 50% is calculated for young children living in typical urban/rural areas, while a rate of 50 to 75% is calculated for those living near point sources.

8. Total lead uptake from the air is the product of total intake and the lung deposition/absorption factor.

9. Average dietary lead consumption: In deriving these estimates, it is necessary to make several generalized assumptions that do not account for spatial and temporal variations in the addition of atmospheric lead to the diet. For example, with the exception of self-sufficient households, most food is raised, packaged, and consumed in different locations, thereby blending the effects of different atmospheric lead levels from around the country. Furthermore, there may be a time lag between lead's introduction into the atmosphere and its incorporation into, and ingestion via the diet. Nevertheless, it is clear from the most recent data that deposition on and absorption into crops by lead throughout the country serves as a significant route of animal and human exposure to atmospheric lead (CD, Table 7-18). The recent EPA revisions to the gasoline lead content phasedown schedule (EPA, 1985b) whereby the standard is reduced from 1.10 grams per gallon of leaded gasoline (gplg) to 0.10 gplg, effective January 1, 1986, can be expected to eventually reduce dietary lead consumption in relation to reduced

atmospheric lead deposition nationwide.

Given the wide spat[illegible] distribution of atmospheric lead over time to different populations [illegible] the food pathway, it is difficult to reliably estimate dietary co[illegible]butions of lead under alternative air lead levels in the future. Esti[illegible]es of current mean dietary lead intake levels are, however, provi[illegible] in the criteria document (CD, Table 7-25). By applying FDA data on [illegible] content of various foods both before and after processing, packagin[illegible] preparation, and on dietary patterns (Beloian and McDowell, 1981; [illegible]ek, 1982; National Food Processors Association, 1982, Pennington, 19[illegible]inik et al., 1983; U.S. FDA, 1984), the CD estimates that, on the [illegible]e, 25.8 µg of dietary lead are ingested daily by a 2-year old child that 10.2 µg of that can be attributed to atmospheric deposition of [illegible]ead on vegetation or soil surfaces. The remaining 15.6 µg/day is attributed to lead solder and to undetermined sources. It is likely that further research will show that the lead estimated to be from undetermined sources is part atmospheric in origin and part from industrial metals (CD, p. 7-42).

Because the U.S. FDA, in conjunction with the National Food Processors Association, is actively pursuing programs to further reduce lead in foods, the CD estimates that lead in canned foods should eventually decline by 70% (CD, p. 7-48). The mean value of 15.6 µg/day currently attributable to lead solder and undetermined sources is therefore adjusted by an intermediate factor of 35% to 10.1 µg/day.

The remaining lead in the diet is apportioned to atmospheric lead deposition. Most crops are grown, and most animals are raised, in rural areas where atmospheric lead has been primarily attributable to gasoline [illegible] is necessary therefore to estimate the impact of the recent revi[illegible] phasedown schedule so that dietary lead consumpt

under alternative air lead levels can be estimated to represent future trends. By 1990, the average maximum quarterly value due only to mobile source impacts for population-oriented or neighborhood scale monitoring sites is estimated under the revised phasedown program to be approximately 0.01 to 0.02 $\mu g/m^3$ (Battye, 1985b). Projected remote or rural monitoring values were not analyzed. Based on the projections for neighborhood scale monitors, it is clear that regardless of what the lead NAAQS is, the average air lead levels in areas away from point sources (where food is generally grown and raised) in the U.S. will be below current rural air lead levels. Assuming that major point source emissions have predominately local impacts, it is estimated that the average air lead level in areas where food is grown and raised will be approximately 0.01 $\mu g/m^3$. In comparison, the CD's estimated mean atmospheric contribution to the diet of 10.2 µg/day CD is derived primarily from data on foods from crops grown or animals raised in the U.S. since 1979; during this period, maximum quarterly average air lead levels in non-urban areas have generally been below 0.45 $\mu g/m^3$ in non-urban areas and below 1.0 $\mu g/m^3$ in urban areas (CD, Table 7a-3; EPA, 1984).

It is, therefore, assumed that for average air lead levels of 0.25, 0.50, 0.75, and 1.0 $\mu g/m^3$, the contribution of atmospheric lead to the diet will be reduced by roughly a factor of 10 from that estimated under current conditions, i.e., 10.2 to 1.0 µg/day.

For an air lead level that is constantly maintained at 1.25, 1.50 and 1.75 $\mu g/m^3$, it is assumed that some non-automotive emissions of lead will cause a small effect on dietary lead consumption such that the average atmospheric contribution will be reduced approximately five-fold, from 10.2 to 2.0 µg/day.

The total average dietary lead intake for alternative air lead levels can then be calculated by adding the atmospheric contribution to the estimated lead intake from solder and undetermined sources.

10. Gut absorption: Only a portion of ingested lead is absorbed into the bloodstream. As discussed in Appendix A, the percentage of absorption of lead varies greatly depending on the contents of the gut and the nutritional status of the child. A range of absorption rates between 42 and 53% (Ziegler et al., 1978; Alexander et al., 1973) is assumed for children.

11. Daily dietary lead uptake is obtained by multiplying rows 10 and 9.

12. and 13. Dust/soil concentrations: As discussed in Section IV, the accumulation of lead in street and household dusts and soils appears to be directly related to the volume of traffic, and inversely related to distance from neighborhood streets and roads, distance from lead painted and brick houses and buildings, and distance from lead smelters and other point sources. Despite these observations, there is little information on the relationship between different air lead levels and dust levels over time. Predicting such a relationship would require the inclusion of many complex variables such as deposition rates, chemical and physical characteristics of the lead particles and soils, topographic and meteorological conditions, frequency of street washings and precipitation, background dust concentrations, and information on transport of dust and soil into homes and buildings. Given current data, there would be an extremely large amount of uncertainty surrounding any one of these variables for different locations. In order to predict outdoor and indoor dust concentrations under alternative air lead concentrations, reliance is placed on available studies that include measurements of both air levels and dust and/or surface soil concentrations (see Table B-1). These data

Table B-1. Summary of Environmental Lead Measurements from Various Locations

Average Air Lead ($\mu g/m^3$)	Average Outdoor Soil/ Dust Lead ($\mu g/g$)	Average Indoor Dust Lead ($\mu g/g$)	Location/Reference
0.20	43	70	Various Sites in U.K.
0.40	336	190	(DOE, 1983)
0.28	518	565	Derbyshire, U.K. (lead mining
0.34	4,881	1,803	area) (Barltrop et al., 1975)
0.40	81	211	Omaha (Angle and McIntire, 1978)
0.68	339	300	
0.82	262	479	
0.95[a]	-	500	New Haven (Stark et al., 1982)
1.6 - 2.0	1,200	11,000	Hartford (Lepow et al., 1975)
			Near non-ferrous smelters in:
0.27	631	412	Bartlesville
0.255	398	424	Anaconda
0.278	438	331	Palmerton
0.19	81	80	Ajo (Hartwell et al., 1983)
0.30	112	-	Rural area, Brussels, and near lead
0.45	114	-	smelter, Belgium (Roels et al.,
0.8	466	-	1978, 1980)
3.67	2,560	-	
0.41	690	1,239	Near Arnheim lead smelter, Holland (Brunkreef et al., 1981; Diemel et al., 1981)
0.82	924	713	Near Toronto lead smelters and in
3.01	2,416	1,550	city (Roberts et al., 1974)
1.3	427	1,479	Near El Paso lead smelter (Morse
2.7[b]	948[c]	8,623[c]	et al., 1979)
0.5	700	1,700	Near Silver Valley lead smelter
0.5	337	3,900	(Yankel et al., 1977; Idaho Dept.
0.7	2,200	3,400	Health and Welfare, 1977)
3.0	1,300	3,300	
6.6	1,200	2,400	
14.2	3,000	10,400	
16.8	7,474	11,700	

[a]Estimated from SAROAD monitoring data

[b]Geometric annual mean of air lead levels measured within 5 km of smelter

[c]Geometric mean of dust and soil lead levels within 6.4 km of smelter

are limited in that samples were collected only once from a small number of locations. It is assumed, however, that both the air and dust measurements were representative of lead levels in those areas and that the studies employed comparable sampling and analytical techniques.

Because of historical accumulations of relatively large lead particles near primary and secondary lead smelters and other point sources, outdoor soil and dust lead concentrations, and consequently potential exposures, are significantly greater in these areas, regardless of ongoing emission controls. Therefore, separate exposure estimates for individuals living near point sources under alternative air lead levels are required. Data collected near lead smelters where emissions were comparable to current situations will be used to develop outdoor soil/dust lead levels for point sources meeting different air lead concentrations.

Three of the studies not used to develop relationships require comment: a) Barltrop et al. (1975) surveyed a rural district in England with minimal air pollution, but with high natural soil lead levels as well as being contaminated by nearly 1900 years of mining activity. Thus, lead deposition on soil surfaces had probably been low for some time, in contrast to the other studies in which surface contamination was ongoing or had been recently reduced; b) Eight of the ten homes sampled by Lepow et al. (1975) were built prior to 1940 and apparently had significant sources of leaded paint that had been "corrected" for previous to the study. In addition, some of the homes were located close to heavily trafficked roadways, where street level air concentrations ranged between 2.2 and 7.7 $\mu g/m^3$, thus lending uncertainty to a dust/air relationship from this study based on annual average air lead levels measured at centrally located monitors distant from the dust sampling sites; c) The smelter studied by

Yankel et al. (1977) operated for several years with severely limited air pollution control capacity due to a baghouse fire in 1973. The very high soil and dust lead concentrations measured near the smelter then would not be expected today with normally controlled emissions. In addition, the high indoor dust lead levels measured by Brunekreef et al. (1981) and Diemel et al. (1981) near the Belgian smelter were probably due, in part, to extremely high lead content (up to 40% by weight) in peeling paint in old houses (built around 1900; the children in these houses were excluded from analysis of blood lead levels).

With these exceptions, the studies listed in Table B-1 appear to have sampled a broad spectrum of homes (e.g. both low and middle class, old and modern, with and without leaded paint) and neighborhoods that can be considered fairly representative of current U.S. conditions in urban and point source areas. Although far from conclusive, the available data suggest the generalized relationships between air lead and dust lead concentrations presented in Table B-2. The ranges represent boundaries that encompass the majority of observed and interpolated values and are used to estimate street dust/soil lead and indoor dust lead concentrations under alternative air lead levels.

Interpolations were necessary because of the limited amount of data. For instance, Angle and McIntire (1978) and DOE (1982) report outdoor soil/ dust lead concentrations in urban areas with an average air lead level of approximately 0.4 $\mu g/m^3$ to be 81 and 336 ppm (µg Pb/g soil or dust), respectively. One of the rural control areas studied by Roels et al. (1978) had an outdoor soil/ dust lead concentration of 114 ppm corresponding to an air lead level of 0.45 $\mu g/m^3$. The range of 80-350 ppm is thus estimated based on these data. For indoor dust, the former two studies report concentrations

Table B-2. Generalized Relationships Between Lead Concentrations in Air and in Dusts and Soil[1]

Air Lead ($\mu g/m^3$)	Outdoor Soil/Dust Lead ($\mu g/g$)		Indoor Dust Lead ($\mu g/g$)	
	General	Near Point Source	General	Near Point Source
0.2	40-150	80-375	70-100	80-400
0.3	60-250	200-600	70-150	200-600
0.4	80-350	250-700	140-200	350-650
0.5	100-450	350-800	220-300	450-700
0.6	200-600	450-1000	250-500	550-750
0.7	250-650	550-1150	300-625	600-800
0.8	300-950	650-1300	450-700	650-900
1.0	500-1150	750-1450	525-875	800-1150
1.25	600-1250	850-1600	625-1000	1050-1400
1.5	700-1400	1000-1750	750-1150	1200-1700
1.75	775-1450	1075-1950	800-1200	1350-1900

[1]Derived from environmental surveys in Table B-1. The ranges of dust and soil concentrations for each air lead level reflect differences in emission sources, distance of measurement sites from these sources (within 5 km for point sources) and characteristics of the homes (e.g., permeability, paint condition, etc.), and other variables assumed to be representative of real world conditions. Values that are underlined represent actual data (rounded off where necessary) listed in Table B-1, while the remainder are interpolations using the most representative and plausible data in Table B-1 and an assumption that there is a directly proportional relationship between air lead and lead in soil and dust (both indoors and outdoors).

of 190 and 211 ppm; these were chosen as an upper bound estimate for 0.4 $\mu g/m^3$ while the lower bound of 140 ppm was derived by multiplying by two the lower bound estimate for an urban/rural area with an air lead level of 0.2 $\mu g/m^3$ (70 ppm from DOE, 1982). Outdoor soil/dust lead concentrations near point sources that can reasonably be associated with 0.4 $\mu g/m^3$ were derived from Brunekreef/Diemel et al., 1981 (690 ppm) and by interpolating the levels measured by Hartwell et al. (1983) concurrently with average air lead levels of around 0.25 - 0.28 $\mu g/m^3$. The resulting estimate is 624 to 630 ppm and, when combined with the Brunekreef value, results in an upper bound estimate of 700 ppm. The lower bound estimate of 250 ppm is assumed based on the levels of 80 ppm observed by Hartwell et al. at 0.2 $\mu g/m^3$, 466 ppm seen at 0.8 $\mu g/m^3$ by Roels et al., and 337 ppm seen at 0.5 $\mu g/m^3$ by Yankel et al. This brief example at 0.4 $\mu g/m^3$ only superficially illustrates the limitations of the available data and the judgments necessary to fill in gaps using various assumptions, such as the assumption of a direct and roughly linear relationship between air lead and surface deposition. It must be emphasized that there is a great deal of uncertainty in these estimates. For instance, assuming that a decrease in air lead from 1.0 to 0.8 $\mu g/m^3$ would result in reduced soil and dust lead concentrations may overestimate the impact that such a decrease in lead emissions would have on children's exposure, particularly via outdoor soil which tends to retain lead for long periods of time. Dust lead levels would likely respond relatively more contemporaneously to reduced air emissions, but the necessary length of time is difficult to estimate.

14. Time weighted concentrations of lead in dust and soil that a child is exposed to is computed by: [(outdoor soil/dust lead concentration

x time spent outdoors) + (indoor dust lead concentration x time spent indoors)] ÷ 24 hours.

15. Amount of dirt ingested: Hand to mouth activity (e.g., thumb sucking and finger licking) and immature dietary habits (i.e., the retrieval and subsequent consumption of food from dusty surfaces or soil), which are normal behavorial characteristics of children up to five years of age (Lin-Fu, 1972), make soil and dust major sources of ingested lead for children (Charney et al., 1983). There is little information on the amount of dirt a child eats in the normal course of a day. Based on a small number of direct measurements, Day et al. (1975) estimated that under average urban conditions (and after 30 minutes of normal playground activity), 5 to 50 mg of dirt from a child's hands can be transferred to a typical "sticky sweet". A small child playing in dirt easily ingests 10 mg of soil/dust with each episode of hand to mouth activity (Drill et al., 1979). Ten hand-mouth activities per day (or ingestion of 2 to 20 "sweets"; Day et al., 1975) would thus result in the ingestion of 100 mg (0.1 g) of dust and soil per day (Lepow et al., 1975). This estimate has been used in several documents (Drill et al., 1979; NAS, 1980; CD, Table 7-23) and will be used here as well. Children with pica who display patterns of repetitive hand-to-mouth activity or delibertely ingest paint, plaster, paper and other non-food items including dirt may be exposed to considerable amounts of lead compared to children who only inadvertantly ingest foreign subsances. Future reductions in airborne lead emissions are not likely to significantly alter their exposure to lead over the next few years. Regulatory alternatives to protect these children are discussed in Section VII.

16. Lead intake from dust and soil is computed by multiplying the time weighted concentration of indoor and outdoor soil/dust concentrations by 100 mg.

17. Gut absorption of dirt: As discussed in Appendix A, an absorption rate of 30% is assumed for ingested lead in dust and soil.

18. Total lead uptake from dust and soil is obtained by multiplying rows 16 and 17.

19. Total lead uptake is the sum of rows 8, 11, and 18.

APPENDIX C. UPTAKE AND BLOOD LEAD CONCENTRATION

Several studies are available that provide the necessary linkages to relate the exposure/uptake estimates calculated under different air lead levels in the integrated uptake model (See Section V.A.1) to children's PbB levels. The results of these studies are summarized in Section V.A.2 and are discussed below.

a) Dietary Lead Ingestion Studies in Infants

Studies that have measured dietary lead intake concurrently with PbB levels among infants and toddlers are compared in the criteria document (Table 11-49). Although precise estimates of dietary lead consumption can not be assumed, these studies (U.K. Central Directorate, 1982; Sherlock et al., 1982; Ryu et al., 1983) have several advantages: 1) careful control and analysis of dietary intake; 2) minimal lead exposure to sources other than the diet as the study population (infants) is relatively immobile; and 3) the impact of total lead exposure (i.e., from all sources) on blood lead can be estimated by applying intake/blood lead relationships because tracer studies (Chamberlain et al., 1978; Rabinowitz et al., 1976) show no differences in the distribution of lead to tissues whether taken up from lung or gut.

Both the U.K. Central Directorate and the Sherlock et al. studies involved infants with relatively high PbB levels and high intakes. Because the PbB levels (< 20 µg/dl) and lead intakes of the Ryu infants are more relevant, the criteria document concludes that the slope from this study is the best available estimate (CD, p. 11-126). The relationship between lead intake and infants' blood lead, derived by EPA's analysis of Ryu et al. (1983) is: PbB = A + 0.16 PbD, where "PbD" represents dietary lead intake and "A" represents non-dietary lead. Applying the gastrointestinal absorption rates (42-53%) used in Section V.A.1 to convert dietary intake levels

into uptake and assuming a background PbB of 4 µg/dl, based on a study of blood lead and lead intake in Boston infants (Rabinowitz et al., 1984b), yields two possible lead uptake/PbB relationships depending on the absorption rate. These relationships are illustrated in Figure 5-1 in the summary of uptake/PbB relationships.

b) Application of Chamberlain and Heard Analysis

An attempt to relate blood lead and absorbed lead was made by Chamberlain and Heard (1981) using epidemiological and clinical data on adult men (Williams et al., 1969; Kehoe, 1961; Nordman, 1975; Zurlo and Griffini, 1973; Fugas and Saric, 1979). Total dietary and airborne lead uptake was estimated using calculations similar to those presented in the integrated lead uptake model in Section V.A. The resulting eye-fitted curve is shown in Figure C-1. The dashed curve is that previously derived in a NAS (1972) report. The straight line is the increase in blood lead to be expected from an increase in lead uptake based on the assumptions given in Chamberlain et al., (1978): a) a fraction, 0.55, of the uptake becomes attached to red blood cells; b) the biological half-life of lead in blood is 18 days; c) a factor, 1.3, is to be allowed for long-term resorption and re-entry into blood of some of the lead which is stored in bone; and d) the mass of blood is 5400 grams With these assumptions:

$$\frac{\Delta \text{ PbB}}{\Delta \text{ Uptake}} = \frac{0.55 \times 18 \times 1.3}{54 \times 0.693} = 0.34 \text{ µg/dl per µg/day}$$

In order to apply this equation to children, several adjustments are required. For example, the mass of blood in young children is estimated to fall between 800 and 1500 grams (Wintrobe, 1979). It has been suggesteed that the half-life of lead in children's blood is shorter than in adults (Duggan, 1983) although no direct measurements have been taken to allow a reliable estimate.

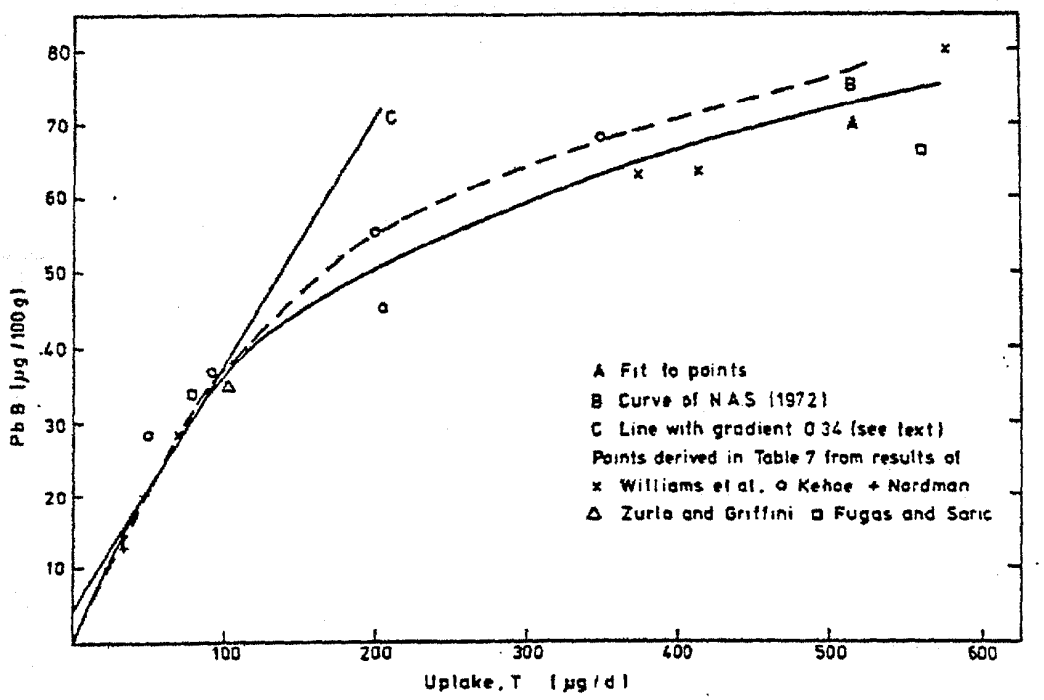

Figure C-1. Relationship between daily lead uptake and blood lead in adult men. From Chamberlain and Heard (1981).

Because there is no information available on appropriate factors to adjust this specific equation to children, the derived relationship from adult data illustrated in Figure C-1 is illustrated in Figure 5-1 only for comparative purposes.

c) Lead Balance Studies: Compartmental Models

To demonstrate a causal relationship between lead in the body and a biological change, it would be ideal to know the amount of lead present at the site and time of the effect. For instance, if lead is suspected to induce neuropsychological changes, a measure of the lead level present in nerve cells when the change occurred would be desirable. Living tissues can rarely be sampled, and data obtained at necropsy cannot reveal the variations in exposure throughout the individual's life. For analytical simplicity, these tissues can be grouped together on the basis of lead distribution characteristics and body burdens of lead represented as a limited number of distinct, homogenous, and well-mixed pools or physiological compartments with similar kinetic properties. Mathematical biokinetic models have been fitted to data obtained in long-term balance studies and to lead isotope tracer experiments that estimate the rates of input to, transfer between, and excretion from the different compartments (Rabinowitz et al., 1976, 1977; Batschelet et al., 1979; Bernard, 1977; Mallon 1983; Harley and Kneip, 1985). Differences in the predictive lead models have been discussed by Bernard (1977) and Batschelet et al. (1979).

Two models are shown schematically in Figure C-2. Compartments as defined kinetically are not necessarily congruent with specific tissues or organ systems; the three pool model of Rabinowitz et al. (1976) considers blood, the most labile soft tissues, and bone marrow (M. Rabinowitz, personal communication) as part of the central compartment where exchange takes place continuously with the second (soft tissues and labile bone) and

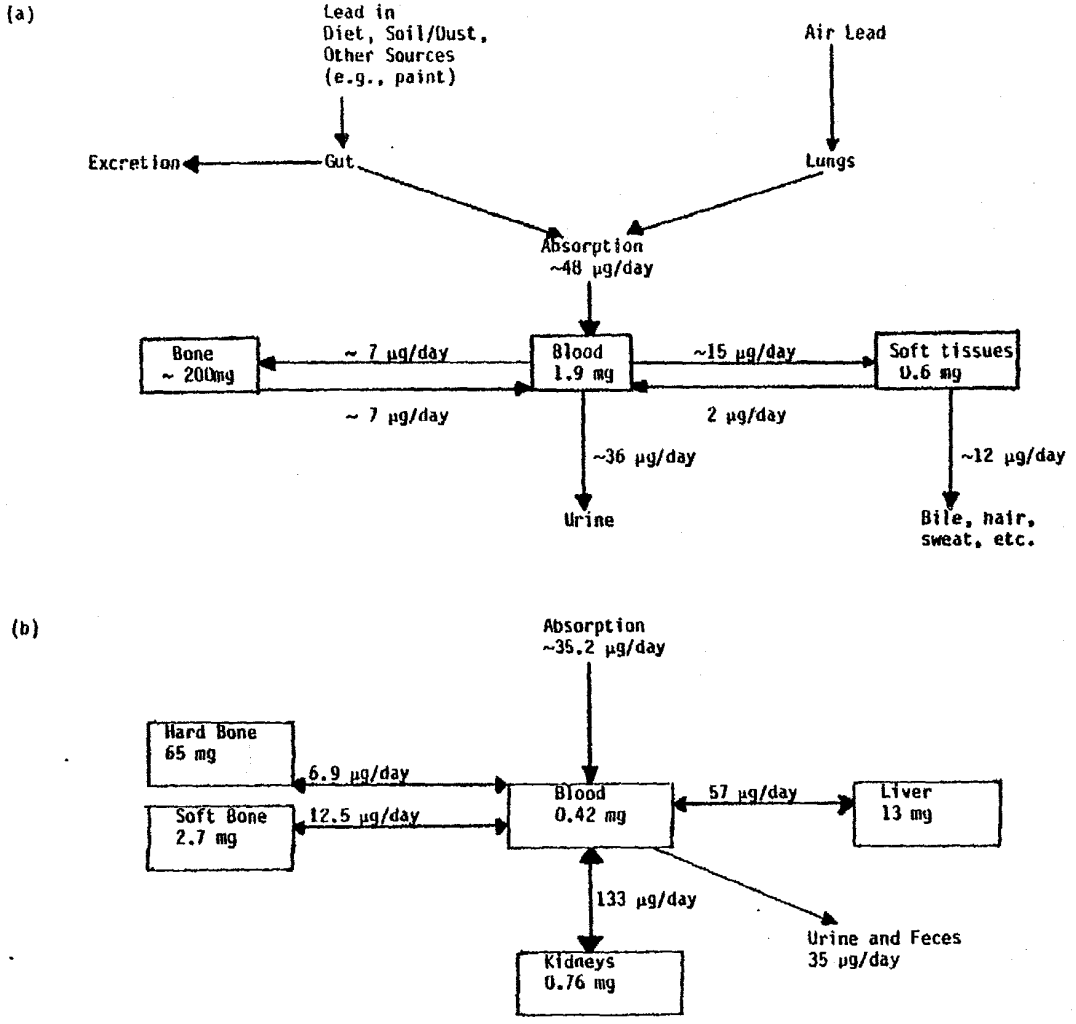

Figure C-2. Schematic models of lead metabolism in adult men described by (a) Rabinowitz et al., 1976 and (b) Bernard, 1977. The amounts of lead in each compartment, exchanging daily between compartments, and excreted daily are shown for steady state conditions of continuous exposure to inhaled and ingested lead. The amounts of lead shown entering the central compartment are the amounts that were assumed to be absorbed daily into the systemic circulation from all sources (Hammond et al., 1981).

third (immobile bone lead) pools. The five-compartment model proposed by Bernard (1977) consists of pools that are mainly blood, liver, kidney, and soft and hard bone.

The choice of pools or level of aggregation in a model depends on the available experimental data, the appropriate time scale, and the predictive uses of the analysis, and is a compromise between accuracy and complexity. For example, blood can be broken down into plasma and erythrocytes and then further into plasma protein-bound lead, diffusible lead, extracellular fluid lead, and erythrocyte proteins. Soft tissues can be broken down into brain (hippocampus, medulla, etc.), kidneys, liver, hair, and so on. The hard tissue pools can be separated into compact (cortical) and cancellous (trabecular) bones, and teeth; within each of these, separate components may be needed to model distinct diffusion time scales (Marcus, 1985). Because the skeletal system in young children is rapidly developing and is both large and kinetically active, it is especially important to model bone lead in children. Until such refinements are further tested, a relatively simple 3 - 5 pool model should provide a framework for predicting lead distributions in children.

These models are helpful in predicting total body burden or equilibrium levels of lead over time in any of the presumed kinetic compartments under different exposure conditions. The basic assumption of the models is that the mass of lead in each of the compartments changes according to a system of coupled first-order linear differential equations with constant fractional transfer rates. Such models predict that when the lead intake changes from one constant level to another, there is a directly proportional change in the mass of lead in each compartment and the attainment of a new equilibrium.

The rates and magnitudes of these changes are dependent upon the rates of lead flux in the tissues and can theoretically be calculated from a compartmental model of the appropriate parameters. Support for a first order kinetic model for lead metabolism is demonstrated by calculations, using first order models of soft tissue and bone concentrations of lead, and other elements (calcium strontium, radium), that fit human measurements as well as by using more complex ones (Johnson and Myers, 1981; Mallon, 1983).

PbB levels in adults after exposure for 5 and 19 years have been computer simulated by Hammond et al. (1981) based on predictions of the Rabinowitz and the Bernard models. The amount of lead absorbed each day into the systemic circulation was entered into the computer program as a single unit. This daily increment was allowed to be distributed and excreted in accordance with the magnitudes of the model rate constants. Table C-1 gives the predicted PbB levels at the end of the specified exposure periods expressed as functions of the total amount of lead absorbed each day from all sources.

It is assumed that these linear mathematical models with distinct rate constants for each lead compartment are, in general, valid for relatively low to moderate lead exposures (CD, p. 11.A-2). The studies that have experimentally determined compartmental models in humans have used a very small number of subjects, however, all of whom were adult males, with a limited range of exposure conditions. Given the physiological and metabolic differences between children and adults, the projected PbB levels calculated in Table C-1 have limited applicability and are used for comparative purposes only.

A four-compartment biokinetic model of lead metabolism has been developed from data obtained in controlled single dose and chronic lead exposures of

Table C-1. IMPACT OF DIFFERENT LEVELS OF LEAD UPTAKE ON BLOOD LEAD AS PREDICTED BY 2 COMPARTMENTAL MODELS AND COMPUTED BY HAMMOND ET AL. (1981, 1982)

Total Pb Absorbed (µg/day)	PbB Predicted by Bernard Model (µg/dl)		PbB Predicted by Rabinowitz Model (µg/dl)	
	After 5 yr.	After 19 yr.	After 5 yr.	After 19 yr.
35.2	13.5	16.5	13	14
70.4	30.5	34.2	26	36
105.6	48.4	52.4	39	45
140.8	66.7	70.9	52	60
176.0	85.2	89.6	65	76
211.2	103.9	108.3	78	91

infant (9 months) and juvenile (22 months) baboons (Mallon, 1983; Kneip et al., 1983). Dynamic blood measurements and steady state blood and organ lead measurements were accurately fitted to predict concentrations of lead in blood, liver, and kidney, and bone (the four compartments in which 95% of total body lead is contained) (Heard and Chamberlain, 1984). Human metabolism and growth patterns were applied in a computer simulation of the model that was then successfully validated using human autopsy data.

The model parameters were revised using measured metabolic data for each organ (e.g., bone turnover rates) for children and were used to simulate lead organ burdens and concentrations in children with constant lead exposures from birth (Harley and Kneip, 1985). Although complete model validation is not possible, the revised model is consistent with experimental data on blood lead accumulation following dietary lead uptake among infants (Ziegler et al., 1978), and skeletal lead accumulation following controlled exposures in adults (Heard and Chamberlain, 1984), and, given the available data it appears to provide the best estimates of PbB levels in children with continuous lead uptake.

Table C-2 presents PbB levels predicted by the model for male children under different exposures, or lead uptake levels. No differences were found between the sexes except at older ames, and predicted PbB levels were highest among 2-3 year olds, consistent with results of NHANES II and the New York City screening program (Billick et al., 1979). These results are applied to estimates of the integrated lead uptake model in Section VII.C.2(a) so that children's PbB levels can be estimated under alternative air lead levels.

d) Empirical Relationships Between Blood Lead and Lead in Individual Exposure Media

One of the modeling approaches presented in Section V, and applied in

Table C-2.

Predicted Equilibrated Blood Lead Levels Over Time Among Children with Constant Lead Uptakes[a]

Age	Lead Uptake (µg/day)							
	10	20	30	40	50	60	70	80
1	3.0	5.9	8.9	11.9	14.8	17.8	20.8	23.8
2	4.0	8.1	12.1	16.2	20.2	24.2	28.3	32.3
3	3.7	7.3	11.0	14.6	18.3	22.0	25.6	29.3
4	3.5	7.0	10.5	14.0	17.5	21.0	24.5	28.0
5	3.6	7.3	10.9	14.5	18.1	21.8	25.4	29.0
6	3.5	6.9	10.4	13.8	17.3	20.7	24.2	27.6
7	3.3	6.5	9.8	13.0	16.3	19.5	22.8	26.0
8	2.5	5.0	7.4	9.9	12.4	14.9	17.4	19.9
9	2.3	4.6	6.9	9.3	11.6	13.9	16.2	18.5
10	2.6	5.2	7.8	10.4	13.0	15.6	18.2	20.8

[a]From Harley and Kneip (1985).

Section VII.C.2, to estimate PbB levels in children exposed to various air lead levels is referred to as the "disaggregate" model. In this model, for each exposure medium to which children are exposed to airborne lead (i.e., air, dust, soil, diet) separate empirical relationships derived from controlled experimental, observational of community studies, are applied so that a combined exposure function can be estimated under various air lead levels. The disaggregate model developed in the CD (Table 13-6) and presented here in Table 7-10 relies on the most relevant and reliable of the available mathematical relationships. The relationship (≈1.97 μg/dl per $\mu g/m^3$) between children's blood lead and inhaled air lead (derived from Angle and McIntire, 1979; Roels et al., 1980; and Yankel et al., 1977) has already been discussed in Section V. The studies used to derive the remaining relationships in the disaggregate model, between children's blood and lead in diet, soil, and dust, are summarized in the following tables.

Table C-3. STUDIES RELATING BLOOD LEAD LEVELS (μg/dl) TO DIETARY INTAKES (μg/day)

Study	Analysis	Model	R^2	Model D.F.	Estimated Blood lead at 0 H_2O Pb	Predicted blood lead contribution (μg/dl) for a given dietary intake (μg/day)			Slope from 100 to 200 μg/d., μg/dl per μg/d.
						100	200	300	
Sherlock et al. (1982) study of 31 adult women in Ayr	Sherlock et al. (1982)	$PBB = -1.4 + 3.6 \sqrt[3]{PBD}$	0.52	2	-1.4	16.7	21.1	24.1	0.034
Sherlock et al. (1982) study of infants in Ayr combined with U.K. Central Directorate Study	Sherlock et al. (1982)	$PBB = 2.5 + 5.0 \sqrt[3]{PBD}$	-	2	2.5	23.2	29.2	33.5	0.060
U.K. Central Directorate (1982) Study of infants in Glasgow	U.K. Central Directorate on Environmental Pollution (1982)	$PBB = 17.1 + .056(PBD)$ or $PBB = 3.9 + 4.6 \sqrt[3]{PBD}$	0.39 0.43	2 2	17.1 3.9	5.6 21.4	11.2 26.9	16.8 30.8	0.056 0.053
Ryu et al. (1983) study of infants	EPA	$PBB = A + .16PBD$	-	1	-	16.0	32.0	48.0	0.16

Source: CD, Table 11-49..

Table C-4. ESTIMATES OF THE CONTRIBUTION OF SOIL LEAD TO BLOOD LEAD

Study	Range of soil lead values (µg/g)	Depth of sample	Estimated slope ($X10^3$)	Sample size	R^2
Angle and McIntire (1982) study of children in Omaha, NE	16-4792	2"	6.8	1075	.198
Stark et al. (1982) study of children New Haven, CT	30 - 7000 (age 0-1)	½"	2.2	153	.289
	30 - 7600 (age 2-3)		2.0	334	.300
Yankel et al. (1977) study of children in Kellogg, ID	50 - 24,600	3/4"	1.1	860	.662
Galke et al. (1975) study of chilren in Charleston, SC	9 - 7890	2"	1.5	194	.386
Barltrop et al. (1975) study of children in England	420 - 13,969 (group means)	2"	0.6	82	NA*
Neri et al. (1978) study of children in British Columbia	225-1800 (group means, age 1-3)	NA	7.6	87	NA
	225-1800 (group means, age 2-3)	NA	4.6	103	NA

*NA means Not Available. Source: CD, Table 11-63.

Table C-5. ESTIMATES OF THE CONTRIBUTION OF HOUSEDUST TO BLOOD LEAD IN CHILDREN

Study	Range of dust Lead values (µg/g)	Age range in years	Estimated slope ($X10^3$)	Sample Size	R^2
Angle and McIntire (1979) study in Omaha, NE	18-5571	1-18	7.18	1074	.198
		6-18	3.36	832	.262
Stark et al. (1982) study in New Haven, Ct	70-7600	0-1	4.02	153	.289
	40-7600	2-3	1.82	334	.300
	9-4900	4-7	0.02	439	.143
Yankel et al. (1977) study in Kellogg, ID	50-35,600	0-4	0.19	185	.721
		5-9	0.20	246	.623

Source: CD, Table 11-64.

APPENDIX D. HEALTH EFFECTS OF LEAD

This appendix discusses and evaluates the information on the various human health effects associated with lead exposure. The discussion is broken down into the major health effects areas of primary concern and is intended to support the assessment in Section VII.C(1) of health risks associated with various blood lead (PbB) levels for purposes of determining an appropriate lead NAAQS.

1. Heme Biosynthesis and Related Functions

Under normal circumstances, heme biosynthesis is a highly efficient and coordinated pathway, which produces only sufficient amounts of intermediates and, ultimately, heme to service requirements for hemoglobin -- the blood pigment responsible for transporting oxygen to the tissues -- as well as a multitude of functions mediated in most cells by heme-containing proteins. These hemoproteins include myoglobin, the hemoglobin of muscle, and the mitochondrial respiratory pigments, cytochromes, responsible for cellular energetics. Moderately elevated lead exposure has been demonstrated to disturb the biosynthetic sequence so as to produce large quantities of redundant intermediates that must then be excreted; more severe lead intoxication may result in the development of anemia. Lead's interference at susceptible stages of the biosynthetic pathway (illustrated in Figure D-1) may have important implications for a multitude of organs and systems, especially in the growing child, and is briefly reviewed below.

i. The initial step of the heme synthetic pathway, the formation of delta-aminolevulinic acid (ALA) from succinyl-CoA and glycine by the mitochondrial enzyme delta-aminolevulinic acid synthetase (ALA-S), represents the control point of the pathway. During lead exposure, the activity of this rate-limiting enzyme is increased through feedback

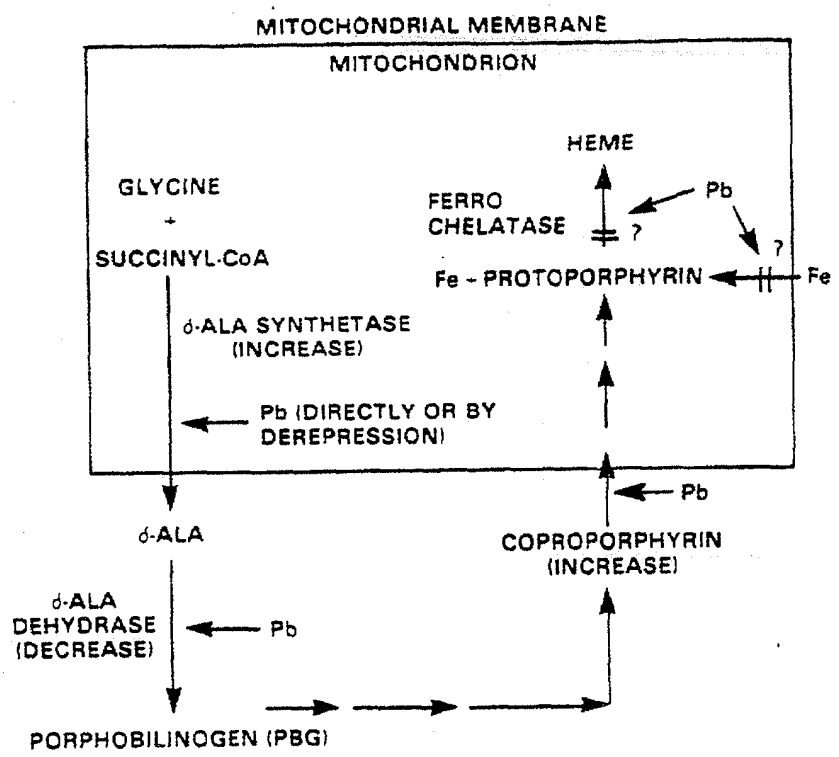

Figure D-1. Lead effects on heme biosynthesis, from CD, Figure 6-1.

$\mu g/m^3$ that are just at attainment would be made using only the aggregate epidemiological model. However, the aggregate epidemiological model and the integrated uptake/biokinetic model predict that at higher air lead levels somewhat greater protection may be provided compared to the disaggregate model. For example, according to the uptake/biokinetic model a level possibly as high as 1.0 $\mu g/m^3$ would be sufficient to protect children living near point sources from exceeding PbB levels of 25 $\mu g/m^3$, and that 1.0 $\mu g/m^3$ may protect 99.5% of children living away from point sources from PbB levels above 20 $\mu g/m^3$ if the air levels were just met, assuming a constant GSD between 1.34 and 1.39. If only the least conservative parameter values are assumed in the aggregate epidemiological model, an air lead level that is just attained at the current standard level of 1.5 $\mu g/m^3$ may protect 99.5% of children from exceeding 25 $\mu g/m^3$, while a level just attained at 1.25 $\mu g/m^3$ may be protective against PbB levels above 20 $\mu g/m^3$. In order to protect against PbB levels above 15 $\mu g/dl$, an air lead level that is just attained at no higher than 0.5 $\mu g/m^3$ would be required, regardless of which model is accepted, assuming GSDs in the range of 1.34 and 1.39.

Finally, if the percentage of the population to be protected is changed from 99.5% to 99.0% or 99.9%, for example, or the GSD value that is used changes to 1.47 to reflect the overall value for a heterogeneous population the above calculations would be revised accordingly.

e) Alternative Statistical Approach to Estimate Blood Lead Distributions

The three exposure models used in this section to predict the PbB levels associated with various air lead levels were designed to estimate mean blood lead levels of hypothetical populations given the available data and assumptions used in each of the models. In general, these models did not attempt to account for changes in PbB levels among children exposed to very high levels

of lead, typically from lead in paint. Given a population geometric mean PbB, the 99.5 percentile of each of the blood lead distributions for these populations was then calculated using geometric standard deviations (GSDs) derived from NHANES II in order to estimate the degree of protection against alternatively considered individual PbB levels determined to be associated with some health risk (i.e., 10 to 25 µg/dl).

This approach has been questioned in that the distribution of PbB levels in children is really the sum of two distributions, one from general exposure to air lead, food lead, etc., and one from very high exposure to lead paint or other high concentration sources (Schwartz, 1985). Given that the sum of lognormal distributions is not lognormal, errors could be introduced by trying to fit a distribution at high levels using one overall GSD. Since one would not expect the PbB levels of highly exposed children to fall proportionately as the mean PbB level falls, the underestimate of the "fatness" of the tail would be expected to increase as the mean PbB level fell (Schwartz, 1985).

This theoretical point is supported by the CDC and NCHS analysis of NHANES II data in which the sample was divided into two periods, before and after the increase in the rate of change of PbB levels (Annest et al., 1983). For the second period, the GSD of both black and white children's PbB levels was approximately 1.43. However, the GSD that correctly predicted the percent of children above 30 µg/dl was 1.54, i.e., the extreme tail is fatter than predicted by the GSD that best fits the entire distribution. Moreover, the difference in these GSDs was larger in the second period, when mean PbB levels were lower than it was in the first period, indicating that the error increases as the mean PbB level falls (Schwartz, 1985). Thus, it is possible that by using a constant GSD for an entire

distribution in setting a lead NAAQS, the number of children in the tail of the cumulative distribution function at high PbB levels would be underpredicted, and that the errors associated with estimating their PbB levels would change with the mean PbB level.

An alternative approach that has been proposed relies on a logistic regression analysis of how the percentages of children in NHANES II who were above 15 µg/dl, 20 µg/dl, and 25 µg/dl varied with the mean of the log of children's blood leads for each study quarter (Schwartz, 1985). This approach makes no assumption about the shape of the distribution curve, but merely fits the tail area at the appropriate cutoff (e.g., 20 or 25 µg/dl) and thereby avoids the problem of using a constant GSD as well as incorporating the actual NHANES II data on children above those alternative target levels. The results are shown in Table 7-13. Using the results of this analysis, it is possible to calculate the mean PbB level that corresponds to a given choice of critical lead level and a given fraction of the population to be held below that critical level. For example, if the critical level is 20 µg/dl and the critical fraction is 99.5% of the children, the following equation is used:

$$\ln (p/1-p) = -15.506 + 5.246 \text{ mean } \ln (\text{lead})$$

for the 99.5% level, $p = 0.005$ and $p/(1-p) = 0.005025$ yielding

$$-5.2933 = -15.506 + 5.246 \text{ mean } \ln (\text{lead})$$

which can be solved for the geometric mean PbB level. Table 7-14 compares estimated mean PbB levels using this regression analysis to those presented in Table 7-6 derived by using the range of constant GSDs presented in the CD and derived from NHANES II for each critical target PbB, assuming that 99.5% protection is the goal.

As discussed, the three modeling approaches presented earlier in this section estimated the population mean PbB levels predicted under

Table 7-13. RESULTS OF LOGISTIC REGRESSION ANALYSIS OF NHANES II DATA

Probability of being over:	Coefficient Intercept/Mean Ln (Lead)	Standard Error Intercept/Mean Ln (Lead)	t-Statistic Intercept/Mean Ln (Lead)
10 µg/dl	-[a]	-[a]	-[a]
15 µg/dl	-13.418 / 4.998	0.818 / 0.304	9.22 / 7.94
20 µg/dl	-15.506 / 5.242	1.123 / 0.409	13.81 / 12.33
25 µg/dl	-16.202 / 5.053	1.757 / 0.636	16.40 / 16.44

[a]Given the limited sample size, a stable estimate could not be calculated.

Source: Schwartz, 1985.

Table 7-14. POPULATION MEAN BLOOD LEAD LEVELS (µg/dl) REQUIRED TO PREVENT 99.5% OF U.S. CHILDREN FROM EXCEEDING SPECIFIED BLOOD LEAD LEVELS ESTIMATED FROM ALTERNATE TECHNIQUES

	Maximum Acceptable Blood Lead Level (µg/dl)			
	25	20	15	10
Logistic Regression[a]	8.7	7.0	5.1	-[b]
Constant GSD[c]				
1.39	10.7	8.6	6.4	4.3
1.34	11.8	9.4	7.1	4.7

[a]From results in Schwartz, 1985 based on analysis of NHANES II data.

[b]Given the limited sample size, a stable estimate could not be calculated.

[c]Derived from analyses of homogenous populations sampled by NHANES II (CD, p. 11-30).

various air lead levels, and the PbB levels at the 99.5 percentile were calculated for each mean PbB and assuming a constant GSD (either 1.34 or 1.39) (See Table 7-12). For example, the criteria document "disaggregate" model estimates that at an average air lead level of 0.5 $\mu g/m^3$, the population mean PbB level among children would be approximately 8.5 µg/dl which corresponds to keeping 99.5% of children from exceeding a PbB level of 18.1 or 19.9 µg/dl (depending on which GSD is assumed). In contrast, according to results of the Schwartz (1985) regression analysis, a population mean PbB level of 8.7 µg/dl would correspond to preventing 99.5% of children from exceeding a PbB level of 25 µg/dl. Obviously, significantly different impacts would be predicted under various air lead levels using either of these two statistical techniques to characterize the tail of a cumulative distribution of PbB levels while relying on the same three exposure models presented previously by this paper. Another illustration, using the aggregate epidemiological model, indicates that an air lead level of 0.75 $\mu g/m^3$ would result in a population mean PbB level around 7.4 µg/dl, assuming blood/air lead slopes of 4 and a non-air PbB contribution of 4.4 µg/dl. This mean PbB level corresponds to preventing 99.5% of children from exceeding either 15.7 or 17.3 µg/dl for GSDs of either 1.34 or 1.39, respectively. In contrast, according to the Schwartz (1985) regression analysis, a mean PbB level of 7.0 µg/dl would correspond to 99.5% of children from exceeding PbB levels above 20 µg/dl; i.e., an air lead level of 0.75 $\mu g/m^3$, using the same exposure model, would be significantly less protective based on the Schwartz (1985) analysis compared to the analysis using constant GSDs of 1.34 to 1.39. It appears that the proposed approach by Schwartz (1985), by more fully accounting for children in the tail end of the distribution, focuses on how those excessively exposed to sources of lead not affected by atmospheric emissions, such as paint lead, are

affected by incremental changes in air lead. Because of the significantly different predictions possible under these alternative approaches, the staff seeks CASAC guidance on the appropriate techniques for estimating the tail end of PbB distributions under alternative air lead levels and estimated population mean PbB levels.

D. Summary of Staff Conclusions and Recommendations

The major staff conclusions and recommendations made in Section VII, A-C are briefly summarized below:

1) The quarterly averaging period used for the current lead standard allows significantly elevated monthly average concentrations, and repeated monthly excursions above a quarterly standard level may produce PbB levels elevated over those that would be predicted unless the standard was exceeded. Because such elevations may be associated with some increased health risk, the staff recommends that consideration be given to a monthly average since it would be more protective of children's health than the current quarterly standard. Guidance is requested from CASAC on whether the added protection provided by a change to a monthly standard would warrant a revision of the current quarterly averaging period. The staff also requests comment on whether the available information suggests the need for an averaging period less than a month. Should a monthly average lead NAAQS be chosen, it would be necessary to revise the current one in six day air lead sampling schedule. Analyses are underway to determine the most appropriate sampling schedules under a monthly standard.

2) The primary lead NAAQS should be expressed in a statistical form rather than the current deterministic form. The decision on the statistical approach to be adopted, with possibly more frequent sampling, should be made in conjunction with establishing a level for the standard.

3) Lead affects many different organ systems and biochemical/physiological processes across a wide range of exposure levels. These effects range from biochemical changes in energy metabolism, neurotransmission, and blood enzyme activity detectable at very low dosages with no apparent threshold on a subcellular-molecular level, to severe, irreversible central nervous system damage manifested by mental retardation, encephalopathy and possibly death at PbB levels above 80-100 µg/dl.

4) Based on recent studies, the PbB level of 30 µg/dl used as the maximum safe level for an individual child in setting the 1978 lead NAAQS contains little or no margin of safety for children from several adverse health effects. Based on an assessment of the available health effects data, the staff concludes that a child with a PbB of 25-30 µg/dl is at risk of significant alterations in heme synthesis (as indicated by elevated EP), depression in vitamin D metabolism, and possibly neurobehavioral disturbances, which collectively may represent impaired functioning and depleted reserve capacities of many different tissues and organs. Below 25-30 µg/dl, the risk associated with observed reductions in heme and vitamin D hormone synthesis, as well as altered brain wave activity and small decrements in cognitive function and behavior have not been fully determined. The CDC has revised the PbB level used to identify children with excessive lead exposure in the lead poisoning prevention screening program from 30 to 25 µg/dl, a medical "intervention" level that represents a compromise between the amount of tolerable risk and the practical limits of effectively implementing the existing screening program. The staff concludes that a PbB for an individual child of 25 µg/dl appears to contain little or no margin of safety from significant risks of multi-organ impairments and possible neurological dysfunction.

5) Fairly consistent results were provided by the three modeling approaches used to estimate PbB levels among children under alternative air lead concentrations assumed to be maintained at constant levels: the integrated lead uptake/biokinetic model, the aggregate epidemiological blood lead/air lead slope approach, and the disaggregate epidemiological approach presented in the criteria document. Calculations were performed on the assumption that the geometric standard deviation (GSD) for the child population is constant and in the range of 1.34 to 1.39 as cited in the CD. Based on this premise, all three models predicted that in order to prevent 99.5% of children from exceeding 25 µg/dl, an air lead level constantly at attainment, no higher than the current standard level would be required, and possibly no higher than 0.75 $\mu g/m^3$, depending on the assumptions and calculations used in the different models. Should a PbB of 20 µg/dl be determined to be the maximum acceptable safe PbB level and assuming a goal of 99.5% protection, GSDs between 1.34 and 1.39, and an air level that is constantly maintained, then a level no higher than 0.5-0.75 $\mu g/m^3$ would be required - unless the least conservative aggregate epidemiological model alone is considered, in which case, a level of 1.25 $\mu g/m^3$ may be sufficient. A level that is maintained at 0.5 $\mu g/m^3$, and possibly as low as 0.25 $\mu g/m^3$, would be required to prevent 99.5% of children from exceeding PbB levels above 15 µg/dl, depending on which model is considered, and assuming a constant GSD between 1.34 and 1.39.

Calculations were also performed based on a different characterization of the tail end of the distribution of children's PbB levels. This alternative statistical approach indicates that somewhat different average air lead levels would be required for equivalent health protection using the same three exposure modeling approaches. For example, the criteria

document "disaggregate" model estimates that at an average air lead level of 0.5 $\mu g/m^3$, the population mean PbB level among children would be approximately 8.5 µg/dl which corresponds to keeping 99.5% of children from exceeding a PbB level of 18.1 or 19.9 µg/dl (depending on which GSD is assumed). In contrast, according to results using the alternative statistical approach (which is based on a logistic regression analysis of NHANES II data), a population mean PbB level of 8.7 µg/dl would correspond to preventing 99.5% of children from exceeding a PbB level of 25 µg/dl.

Further information and CASAC guidance is sought on: a) whether these modeling approaches are valid given the available data and how they can be improved; b) appropriate values of specific parameters within the various models, e.g., blood/air lead slope, non-air PbB contribution; and c) the appropriate statistical technique to characterize the tail end of the blood lead distribution under alternative air lead levels as predicted by the various models, i.e., should a "constant" GSD be used to represent the entire distribution of children's blood lead levels (and if so, what the appropriate GSD value is), or whether the alternative approach based on logistic regression analysis of NHANES II data would be an improvement.

VIII. CRITICAL ELEMENTS IN THE REVIEW OF THE SECONDARY STANDARD

This section includes a discussion of information drawn from the criteria document that appears most relevant to the review and possible revision of the current secondary NAAQS for lead. It focuses on field and laboratory studies that identify potential effects of lead in biota of terrestrial and aquatic ecosystems at levels of exposure relevant to natural habitats. Within each category, the section presents 1) a brief summary of the relevant scientific information; 2) an evaluation of the potential quantitative relationships between lead and effects; and 3) an evaluation of the quantitative relationships between levels of lead in the natural habitat and biologically available lead. A preliminary staff recommendation is also presented, recognizing the major uncertainties in the available data, that consideration be given to making the secondary standard equivalent to the primary standard in all respects.

I. Terrestrial Ecosystems

Anthropogenic emissions of lead deposit on terrestrial ecosystems via wet and dry deposition. After initial deposition on vegetation and other surfaces, the migration and distribution of lead in the soil reservoir depend on a number of environmental factors that influence the immobilization of lead via precipitation, surface adsorption and ion exchange reactions (Zimdahl and Skogerboe, 1977; Miller & McFee, 1983; Camerlynck & Kiekens, 1982). Once in the soil reservoir, lead is relatively insoluble and immobile (NAS, 1980; Nriagu, 1978) and is not readily removed by such mechanisms as leaching and stream run-off (CD, p. 8-7, 8-13). As a result, lead accumulates in the soil reservoir even when the deposition rate is relatively low.

A. Mobility and Bioavailability of Lead

Zimdahl and Skogerboe (1977) identified soil pH and cation exchange capacity (CEC) as primary determinants of a soil's capacity to bind lead. Based on their empirically derived equation, the binding capacity for lead for various soil types was estimated. Although the reliability of this equation to predict soil binding capacity is questionable (due to its linear form which may not be appropriate for high CEC's), this analysis suggests that while the capacity of certain soils to immobilize lead is large, it is finite.

When examining the potential impact of lead on terrestrial ecosystems, a distinction must be made between total soil lead content and the available or potentially available fractions. The fraction of soil lead that may be biologically available includes the potentially available lead (exchangeable forms determined by chemical extraction) and the actually available water soluble forms (lead in soil moisture) (CD, p. 6-29). The generally low solubility of lead and the apparently small percentage (1-12%) of total soil lead that is exchangeable (Camerlynck and Kiekens, 1982; Miller and McFee, 1983; Hughes, 1981; Atkins et al., 1982) suggest that the bioavailability of this pollutant is quite limited. The potential effect of acid precipitation to increase the relative mobility of lead in soil (Tyler, 1978; Hutchinson, 1980) is of clear concern as a mechanism that may increase the bioavailability of this heavy metal.

Given the varying capacity of different soil types to immobilize lead under different environmental conditions and the limited usefulness of chemical extraction studies to provide reliable estimates of exchangeable soil lead fractions, it is difficult to predict the percentage of total soil lead that is biologically available (actual or potential). As a result, it is difficult to predict the magnitude of increase in total soil lead concentration that

results in a soil moisture lead concentration associated with levels of biologically available lead that may cause adverse effects.

B. Effects in Terrestrial Biota

This section, based on the scientific literature summarized in the criteria document, includes a review of the effect of lead in components of the terrestrial ecosystem, i.e., flora, microbes and fauna. The lowest levels of exposure at which effects have been observed in field and laboratory studies are emphasized. The biological or ecological significance of certain lead-induced effects is unclear. This is primarily due to the difficulty in determining the long-term significance of subtle changes in ecosystem structure and function. Given the available data, it is difficult to assess the extent to which lead-induced effects constitute short or long-term, adverse environmental impacts.

1. Flora

a. Exposure, Uptake and Translocation

Plant exposure to lead occurs via root uptake from the nutrient medium (soil moisture) (CD, p. 8-14). Although 90% or more of lead taken up via the roots may remain tightly bound in the roots (Koeppe, 1981), field and laboratory studies provide evidence that some lead is translocated to physiologically active tissues in vascular plants (CD, p. 8-15 to 8-17).

Recent isotopic and mass balance studies suggest the mechanism of foliar uptake as another route of exposure of plants to lead (Facchetti and Geiss, 1982; Lindberg and Harriss, 1981). While the relative significance of foliar uptake has not been clearly determined, it is potentially quite high since surface deposition of lead is estimated to account for 90% of total plant lead (CD, p. 8-38). Elevated lead burdens in plants near smelters and along roadsides, for example, have been attributed

primarily to surface deposition (Getz et al., 1977; Nriagu, 1978; Smith, 1976). Taken together, these studies suggest that deposition on vegetative surfaces and foliar uptake may be of greater importance than previously thought.

b. Experimental Data from Hydroponically Grown Plants

Experimental data on lead-induced effects in plants are available primarily from laboratory studies of agricultural plants grown in artificial nutrient media (i.e., hydroponic solution). These studies (Table 8-1) report that at relatively low concentrations, ranging from 2-10 μg Pb/g solution, inhibition of photosynthesis, alteration in enzyme activity and reduction in growth can occur. While the physiological and biochemical changes observed in these studies are biologically significant, the results cannot be readily extrapolated to the varied conditions present in natural habitats. Such factors as length of treatment (exposure), chemical form of lead, level of nutrients in solution, and age and species of plant can influence the experimental results (Koeppe, 1981; Paivoke, 1979) and limit the extrapolation of controlled experimental results to the natural habitat. The absence of data to clearly define the quantitative relationship between soil moisture lead and total soil lead further limits the usefulness of laboratory studies of hydroponically grown plants for environmental impact prediction. Due to the absence of data, it is difficult to accurately assess the potential effect of lead in terrestrial flora. Lead-induced effects have been evaluated for a limited number of plant processes (CD, p. 8-17) and the data base on effects in non-agricultural plants and trees (Smith, 1981) is inadequate.

c. Experimental Data of Plants Grown in Lead-Amended Soils

Studies involving the artificial addition of lead salts to soil have evaluated lead-induced changes in plants at specified soil lead concentrations.

Table 8-1. LEAD-INDUCED EFFECTS IN HYDROPONICALLY GROWN VASCULAR PLANTS

Effect	Species	Lead concentration (µg Pb/g solution)	Species of Lead Salt	Length of Treatment	Reference
Inhibition of germinating root elongation	Rye grass seedlings	< 2.5	Lead nitrate	14 days	Wong and Bradshaw (1982)
50% reduction root growth		1.7			
Absence of root growth		5			
Inhibition of carbon fixation pathway	Tomato chloroplasts	10.35	Lead nitrate Lead chloride	-	Miles et al. (1972)
Reduction in elongation	Wheat seedlings	10	Lead nitrate	48 hours	Lane et al. (1978)
Inhibition of ATP content	Kidney bean seedling leaves	1 - 10	Lead nitrate	15 days	Sung and Yang (1979)
	Buckwheat seedling leaves				
Reduction in synthesis chlorophyll-a chlorophyll-b	Oat seeds	10	Lead chloride	72 hours	Hampp and Lendzian (1974)
60% increase in acid phosphatase at 6 days, followed by decrease at 12 days	Pea seedlings	2	Lead acetate	12 days	Paivoke (1979)
Inhibition of root growth		2	Lead chloride	12 days	
Inhibition of root growth	Barley seedlings	2	Lead nitrate	10 days	Garland and Wilkins (1981)

In general, high concentrations of total soil lead are necessary before physiological effects in plants are observed. Khan and Frankland (1983) report significant growth reduction in radish plants with exposure to 1000 µg Pb/g soil and complete growth inhibition at 5000 µg Pb/g soil. These total soil lead concentrations are found in certain high lead environments, i.e., near roadsides and smelters (Wheeler and Rolfe, 1979; CD, p. 7-30; Atkins et al., 1982). It is unclear, however, whether lead-induced effects would occur under natural soil conditions where the availability of lead is influenced by nutrient levels, organic matter content, CEC, and pH of the soil (Koeppe, 1981).

d. Field Evidence of Lead-Tolerance

Further indication of the effect of lead is provided by the identification of lead tolerant plant communities near roadsides and point source emissions (CD, p. 8-38; Antonovics et al., 1971; Atkins et al., 1982). Potential changes in species composition in these areas have implications for the long-term effect of lead on ecosystem function and stability. At relatively low total soil lead concentrations (112 µg Pb/g soil), Atkins et al. (1982) suggest that selection pressure due to soil lead resulted in the evolution of lead tolerance in a roadside grass.

2. Microbes

Available data suggest that the impact of lead in terrestrial ecosystems may be evident first in the components of the soil and litter microcosm (e.g., fungi, bacteria and algae) (Tyler, 1972) that play a critical role in the decomposition of organic matter and in nutrient cycling (Doelman and Haanstra, 1979a; Doelman, 1978).

a. Experimental Studies of Lead-Induced Effects

Experimental studies provide evidence of lead-induced effects in

soil microbes at soil lead concentrations as low as 750-5000 µg Pb/g soil (Table 8-2). In the presence of lead (1500 µg Pb/g soil), the composition of microbe communities may shift to more lead-tolerant populations (Doelman and Haanstra, 1979b) and, at soil lead concentrations found near roadways and point sources (750-2000 µg Pb/g soil), soil microbial activity may be sufficiently reduced to inhibit the decomposition and nitrification processes (Smith, 1981; Doelman and Haanstra, 1979a; Liang and Tabatabai, 1978). Inhibition of growth and activity in soil microbes has occurred at lead concentrations in solution of 10-50 µg Pb/ml (Table 8-2).

While these data suggest that certain soil microbes can be affected by lead at soil lead concentrations found near roadsides and point sources, the data are inadequate to draw any general conclusions about the tolerance of soil microbes to lead (Doelman, 1978) and lead's effect on this ecosystem component as a whole. The inhibitory effect of lead appears to vary with different types of microbes (Johnson et al., 1982; Martin and Coughtrey, 1981). In addition, because microbes exhibit a diversity of functions that interact in ways that are not well defined (Swift et al., 1979; CD, 8-22, 8-23), a broader data base, encompassing various taxonomic groups, is required for environmental impact prediction. Even drawing quantitative conclusions about the microbes studied in these experiments is constrained by experimental conditions that influence the bioavailability of lead and result in uncertainties associated with extrapolating laboratory results to the natural habitat. The long-term significance of lead-induced changes in soil microbial populations is unclear and depends on whether the ecosystem has the ability to compensate for such perturbations. The critical role of soil microbes in terrestrial ecosystem processes

Table 8-2. EXPERIMENTAL EVIDENCE OF LEAD-INDUCED EFFECTS RELATING TO SOIL MICROBIAL ACTIVITY

Effect	Microbe	Lead Concentration	Reference
Possible inhibition of decomposition	Bacteria	2000 - 5000 µg Pb/g soil	Smith (1981)[a]
Delay and inhibition of decomposition of organic compounds	Bacteria	750 - 1500 µg Pb/g soil Lead chloride	Doelman and Haanstra (1979a)
14% inhibition of nitrification	Bacteria	1000 µg Pb/g soil Lead acetate	Liang and Tabatabai (1978)
Change in composition of microflora after 3 years (Selection of tolerant strains)	Bacteria	1500 µg Pb/g soil Lead chloride	Doelman and Haanstra (1979b)
Inhibition in 50% of microbial strains	Fungi Bacteria Actinomycetes	50 µg Pb/ml[b] Lead acetate	Williams et al. (1977c)
Inhibition of growth	Fungi	10-50 µg Pb/ml[b] Lead nitrate	Babich and Stotzky (1979)

[a]As cited in Criteria Document, p. 8-22
[b]Note lead concentration in solution

(decomposition and nutrient cycling) suggests, however, the serious nature of the potential inhibition of microbial activity by lead and indicates the need for additional research to more clearly define the effect of lead in this ecosystem component.

b. Field Evidence of Altered Microbial Activity

Reduced abundance and altered composition of microflora populations have been observed in the vicinity of point source emissions of lead and in an area contaminated with metal mine waste. Corresponding to these changes, the accumulation of litter and alterations in soil parameters have been reported. Lead was the predominant heavy metal contaminant in these areas (Jackson and Watson, 1977; Bisessar, 1982; Williams et al., 1977c).

Although these field observations suggest the inhibitory effect of lead on microbial activity in certain heavily contaminated areas, their usefulness in assessing the environmental impact of lead is limited for the following reasons:

1) the inability to isolate the effect of lead from the confounding effects associated with other components of point source emissions and other heavy metals; and
2) the lack of quantitative information concerning the effect of other environmental factors that influence the decomposition rate, i.e., temperature and moisture conditions (Smith, 1981).

3. Fauna

a. Exposure

The principal pathway of exposure for fauna is through dietary intake (CD, p. 8-26). Fauna of the grazing food-chain are affected most directly by deposition of lead on vegetation. Others, such as predators, are affected more indirectly by lead moving through the food-chain, thus

raising concerns about the potential accumulation and biomagnification of lead at higher trophic levels. While biomagnification (biological concentration of lead from one trophic level to the next) has not been observed in vertebrate food-chains (NAS, 1980; Williamson and Evans, 1972), available data suggest that the biomagnification of lead does occur in invertebrate food-chains (NAS, 1980; Getz et al., 1977; Wade et al., 1980; Watson et al., 1976). Thus, non-toxic levels of lead taken up and accumulated by invertebrates may produce toxic effects in their predators. Although support for this potential route of exposure is provided (Bull et al., 1983a; Getz et al., 1977; Gish and Christensen, 1973), the occurrence of lead burdens in prey high enough to cause toxic effects in predators is variable (Wade et al., 1980).

b. Field and Laboratory Evidence of Lead-Induced Effects

The available data on lead-induced effects in invertebrates are very limited and are not sufficient to establish quantitative relationships. Decreased soil invertebrate abundance, suggesting potentially significant alterations in soil decomposition processes, has been observed, however, in the vicinity of point source emissions of lead and in the area of a metal mine waste site (Watson et al., 1976; Williams et al., 1977c; Bisessar, 1982). Due to the presence of other pollutants and heavy metals in these areas, it is not possible to attribute the observed reductions to lead alone.

Very few field studies reporting lead exposures, body burdens and associated effects in wildlife are available. Unusually high lead exposures resulting in toxic effects have occurred primarily in waterfowl and livestock. Sources of these exposures have typically included lead wastes, paint and spent lead shot (unrelated to airborne lead emissions), and contaminated

forage near lead smelters (NAS, 1980; Forbes and Sanderson, 1978). With the exception of cattle and waterfowl, incidence rates of lead poisoning in terrestrial fauna are generally unavailable (Forbes and Sanderson, 1978; Botts, 1977) and difficult to verify.

Although lead burdens in mammals are elevated relative to natural background levels (CD, p. 8-29, 8-30), with burdens positively correlated with proximity to roadways (Williamson and Evans, 1972; Quarles et al., 1974), it is uncertain if exposures are resulting in animal burdens high enough to be of concern. This uncertainty results from a limited data base of field observations that report conflicting findings. Body burdens of lead that have been identified to cause effects in animals have not been observed in certain high lead environments, i.e., roadsides and smelter areas (Forbes and Sanderson, 1978; Getz et al., 1977). Other studies, however, indicate that elevated lead burdens associated with effects may occur in livestock grazing near smelters and in small mammals in areas adjacent to highways, mining sites and smelters (NAS, 1980; Clark, 1979; Quarles et al., 1974).

When assessing the effects of lead on domestic animals and wildlife, it is important to consider the more subtle effects that are not readily discernible in field observational studies. Drawing on animal toxicological studies discussed in the CD and referred to in Appendix D, it is clear that lead can affect a wide range of critical functions such as heme synthesis, neurobehavioral function, and reproduction and development. Investigation of these effects has been limited, however, primarily to laboratory animals. In part because of species differences in susceptibility (Forbes and Sanderson, 1978) and a lack of sufficient quantitative exposure/uptake/response data in natural habitats, results from controlled

animal studies have not been extrapolated to animals in natural environments.

While current analyses and understanding of the potential effects of lead in domestic animals and wildlife species are considerably less definitive than for humans, the available data strongly suggest that animals may be at risk. When assessing much of the same data in 1980, the Committee on Lead in the Human Environment of the National Academy of Sciences concluded that animal sensitivity to lead might equal or exceed that of man (NAS, 1980).

II. Aquatic Ecosystems

A. Behavior of Lead in Water and in Sediments

The capacity of surface waters to retain lead in solution at equilibrium is dependent upon the physical and chemical water quality parameters of the particular aquatic environment (NAS, 1980). In addition to physical and chemical parameters that determine lead's solubility, biological conditions can influence the behavior of lead in aquatic systems (Rickard and Nriagu, 1978), and, hence, its availability and potential impact in aquatic biota. Although lead is readily complexed in natural water systems (CD, p. 6-33), concentrations exceeding 100 µg Pb/l (lead in solution) have been reported for surface waters receiving urban runoff and sewage and industrial effluents (NAS, 1980).

Due to the lack of major exports of lead from freshwater ecosystems, these systems function as potential sinks for lead loading (McNurney et al., 1977; Getz et al., 1977), with the sediment as the primary sink for lead similar to soil in terrestrial ecosystems (Rickard and Nriagu, 1978). The sedimentation of lead depends on a number of environmental factors (CD, p. 8-13), and the retention of this heavy metal within the sediment is influenced by the substrate type (McNurney et al., 1977;

Wershaw, 1976; Newman and McIntosh, 1982). Over the past century, a trend of increasing deposition of lead in the sediments of freshwater systems has been observed (CD, p. 5-1, Figure 5-1), with elevated lead concentrations observed in sediments draining urban areas relative to rural areas (McNurney et al., 1977; Getz et al., 1977).

As a result of the accumulation of lead in the sediments of freshwater systems, the soluble fraction comprises only a small percentage of the total lead burden (Rickard and Nriagu, 1978; Wershaw, 1976). Because of potential regeneration, however, the reservoir of lead in the sediment can become a source of soluble lead even after the discontinuation of lead inputs (Wershaw, 1976). The significance of this mechanism to increase the availability of waterborne lead to aquatic biota may be most pronounced in water bodies in which complexed lead in the sediment remains at the water-sediment interface. Field observations indicate that this situation does occur (Getz et al., 1977).

B. Effects in Aquatic Biota

This discussion of the effects of lead in aquatic biota focuses on vertebrates (fish) because this component of aquatic ecosystems appears most sensitive to this heavy metal and, relative to other taxonomic groups, a more extensive data base is available. There is some evidence, however, of effects of lead in other aquatic biota at low concentrations of waterborne lead. Although the data are limited, lead-induced effects (e.g., increased mortality, impaired reproduction) in certain aquatic invertebrates have been reported at concentrations as low as 19 - 30 µg Pb/l (CD, p. 8-33, 8-34; Borgmann et al., 1978; Biesinger and Christensen, 1972).

Hematological and neurological changes have been observed in fish exposed under laboratory conditions to waterborne lead concentrations between

8-120 µg Pb/l (Table 8-3). While the hematological system of fish may be capable of compensating for lead-induced changes, the neurological effects, black tails (an early indicator of spinal deformity) and spinal curvature (which increases mortality and prevents successful reproduction) are of clear concern (Hodson et al., 1978a). These findings are conservative because sensitivity to lead is species-specific and trout exhibit increased susceptibility to lead relative to other fish (Wong et al., 1978), and the effects observed at the lower limits of the concentration range may have been enhanced by the relatively soft water conditions used in the experiments (Davies et al., 1976).

Extrapolating these results to natural systems is constrained by the many factors that influence the toxicity and bioavailability of lead, i.e., form of lead, route and length of exposure, pH, hardness and temperature of water, and life stage of organism (Hodson, 1979; Hodson et al., 1978b, 1979; Wong et al., 1978). Decreased pH level appears to increase the uptake of waterborne lead by fish although the precise mechanism of action is unclear (Hodson et al., 1978b). These data suggest that lead will have its greatest effect on fish in soft water, low pH aquatic systems because these systems have a greater capacity to retain lead in solution at equilibrium before reaching chemical saturation (Hem, 1976), and the adverse effects of lead in fish are closely related to dissolved lead content (Hodson et al., 1978b; Wong et al., 1978).

III. Staff Conclusions and Recommendations

The available laboratory and field data indicate that at concentrations at or below those found in certain high lead environments, lead can: 1) affect certain plants (e.g., inhibition of photosynthesis, reduced growth, changes in composition), microbes (e.g., reduced abundance), and

Table 8-3. EFFECTS OF WATERBORNE LEAD IN AQUATIC VERTEBRATES (FISH)

Effect	Fish	Exposure Conditions	Water Parameters	Reference
Neurological changes, enzyme activity inhibition, behavioral changes[a]	Trout, sunfish, goldfish	Variable exposure to 10-100 µg Pb/l	Variable[b]	Wong et al. (1978)
Neurological changes (Black tails, spinal curvature)	Rainbow trout (eggs)	Chronic exposure to 8 µg Pb/l	Hardness 28 mg/l as $CaCO_3$ (soft water) pH 6.7-7.3	Davies et al. (1976)
Neurological change (Black tails)	Rainbow trout (eggs and young fish)	30 week exposure to 22 µg Pb/l	Hardness 135 mg/l as $CaCO_3$, pH 8.2	Hodson et al. (1979)
Neurological change (Black tails, spinal curvature)	Rainbow trout (young fish)	30 week exposure to 120 µg Pb/l	NR	Sippel et al. (1983)
Hematological changes (increased number red blood cells (rbc), decreased rbc volume, decreased rbc ALA-D activity)	Rainbow trout (young fish)	Up to 32 week exposure to 13 µg Pb/l	Hardness 136 mg/l as $CaCO_3$, pH 7.7	Hodson et al. (1978a)
Neurological change (Black tails)		32 week exposure to 120 µg Pb/l		
Hematological changes	Brook trout (young fish)			
Decreased glutamic transaminase activity (GOT)		2 week exposure to 34 µg Pb/l	NR	Christensen et al. (1977)
Decreased hemoglobin		2 week exposure to 58 µg Pb/l		
Decreased GOT activity		8 week exposure to 58 µg Pb/l		

[a]Compilation of several sources.
[b]Limited information indicates soft water conditions (< 50 mg/l hardness as $CaCO_3$).
NR -Not reported.

fish (e.g., neurological changes); and 2) alter the composition of microbial communities and inhibit invertebrate activity resulting in delayed decomposition, reduced nutrient supply, and altered soil properties (e.g., lower organic content). With respect to domestic animals and wildlife, a qualitative assessment of the available field studies and animal toxicological data suggests that animals may be as susceptible to the effects of lead as humans.

The available data also raise concern about the continuing accumulation of lead in the soil reservoir that functions as a finite sink of undefined capacity. Due to the persistence of lead in the environment, such accumulations are expected to continue as long as inputs exceed outputs. Thus, even at relatively low deposition rates lead could affect the ecosystem over the long-term.

The available data are limited, however, and do not permit any definitive findings with respect to concentration-response functions associated with the observed effects or provide clear quantitative relationships between concentrations of lead in the natural habitat and biologically available lead. Data are not available to determine quantitative relationships between ambient concentrations of lead and effects in the biota of terrestrial and aquatic ecosystems. These limited data do suggest, however, that effects of lead on these ecosystems can be significant, although poorly defined, particularly with respect to their long-term implications.

The effects of lead on ecosystems are probably more closely related to the deposition and long-term accumulation of lead than to current ambient air quality levels. This suggests that a secondary standard for lead in the form of a deposition rate may be more appropriate than one expressed as an airborne concentration level. Such a deposition standard

is conceptually appealing because it could be a more effective method to provide protection against the welfare impacts of lead. Its application at this time is constrained, however, by practical considerations such as the absence of sufficient data to develop appropriate deposition targets and the lack of reliable methods for measuring both wet and dry deposition.

Although quantitative relationships are not well enough developed to specify the most appropriate secondary standard, the key question is whether the range of alternative air quality levels discussed in Section VII would provide adequate welfare protection. While this question cannot be answered definitively, all but one of the air quality levels discussed in Section VII would likely reduce current ambient lead loading. These reductions, coupled with reductions achieved by the continued phase-down of lead in gasoline (gasoline consumption accounts for 85-90% of total airborne lead emissions), would likely mitigate the potential risks of lead-induced ecosystem effects occurring in most areas of the country. In urban centers, along roadsides, and in the immediate vicinity of major point sources that have experienced a long-term, historical accumulation of lead, and where the natural soil sinks for lead may be approaching or have exceeded their capacity to bind lead, the more sensitive components of the ecosystem (e.g., soil microbes) may remain at some risk that is difficult to quantify at present. The level of the primary standard chosen from air quality ranges discussed in Section VII could, however, provide adequate protection from ambient-related exposures for most, if not all mammals both domestic and wild. Therefore, given the available data along with their major uncertainties, the staff recommends that consideration be given to making the secondary standard equivalent to the primary standard in all respects.

APPENDIX A. LEAD METABOLISM AND PHYSIOLOGICAL MEASUREMENT

1. Lead Absorption

Environmental lead compounds can be absorbed into the bloodstream from the lung after inhalation, from the gastrointestinal tract after ingestion, or to a limited extent from direct dermal contact. In addition, fetuses absorb lead through the placenta. Some lead that is inhaled or ingested passes out of the body before being absorbed, and some lead that is absorbed from the lungs or the gut is removed from the blood and excreted.

The absorption kinetics for each pathway are dependent upon a number of factors, including the physical and chemical nature of the lead compounds at the time of exposure and the presence of other modifying agents (e.g., dietary constituents, other pollutants). Once inorganic lead is abosrbed into the bloodstream it is readily transported to other locations in the body and does not normally retain any characteristics associated with its exposure or absorption route. Dermal absorption is potentially significant only for high organic lead exposure in occupational settings or other special circumstances. This route, therefore, will not be addressed further.

a) Respiratory Absorption

Although lead aerosols in ambient air can encompass a broad size range depending on proximity to sources and meteorological conditions, most urban and rural airborne lead mass is associated with submicron particles, with a distinct peak of large particles in the upper end of many of the size distributions (Davidson and Osborn, 1984). Particle size distributions of airborne lead mass, collected from various urban, rural and point source areas were combined with recent lung deposition data (Chan and Lippmann, 1980) to estimate the mass fraction deposited in each compartment of a

mouth-breathing adult's respiratory tract (Davidson and Osborn, 1984). Based on these calculations, it is estimated that on average, about 26 to 42% of airborne lead particles in these different locations are capable of deposition into the respiratory tract of adults. This is generally consistent with deposition data on lead particles generated in laboratory chambers (Kehoe, 1961; Gross, 1981; Nozaki, 1966; Chamberlain et al., 1978) and near a highway (Chamberlain et al., 1978) in resting adults breathing through mouthpieces. It is estimated that 10-26% of these submicron particles deposit in the alveolar region (Davidson and Osburn, 1984) where absorption into the bloodstream appears to be rapid and nearly complete, regardless of the inhaled lead particles' chemical form (Chamberlain et al., 1978; Rabinowitz et al., 1977; Morrow et al., 1980; Barry, 1975). The remaining 16% of the lead particles, mainly in the coarse mode (>2.5 μm) is estimated to deposit in the extrathoracic and tracheobronchial compartments of the respiratory tract. Clearance of most of this material to the esophagous may be rapid, except for non-hygroscopic particles lodged in the tracheobronchial region. From the esophagous, the lead particles are either expectorated or swallowed. Lead absorption into the blood through the gut is about 40% by mass of coarse-mode inhaled particles (MMED ~ 2.9 μm) (Kehoe, 1961).

Total respiratory absorption of inhaled lead particles for adults can be calculated by adding the products of deposition and absorption rates for each region of the respiratory tract. Thus, (10 to 26% x 100%) for the alveolar region is added to (16% x 40%) for the combination of extrathoracic and tracheobronchial regions, yielding an estimate of 16-32% for total respiratory absorption of inhaled lead particles among adults in various U.S. atmospheres.

Given that particles larger than 1 to 3 μm which predominate near lead smelters (within 2-5 km) and other stationary sources (Jennett et al., 1977; Davidson and Osburn, 1984) are likely to deposit in the respiratory tract with increasing efficiency as particle size increases (Chan and Lippmann, 1980), the above estimates may underestimate respiratory deposition and absorption of lead particles in these areas. For example, it is estimated that 15-55% of 5 μm particles by mass deposit in the alveolar region and 8-45% deposit in the tracheobronchial region of mouth-breathing adults (Chan and Lippman, 1980). The upper bounds of these ranges are 2 - 3 times higher than those estimated for airborne lead particles in various urban, rural, and point source atmospheres, previously discussed. In the absence of extensive lead particle size data around lead point sources that would allow a separate analysis to calculate respiratory deposition and absorption for these areas specifically, it is assumed that for adults, total respiratory absorption of inhaled lead particles is approximately twice as efficient (i.e., 30-60%) around point sources compared to the general case representing typical urban and rural areas.

Because atmospheric particle size distributions and individual deposition characteristics (e.g., mouth versus oronasal breathers) as well as other factors (e.g., ventilation rates) vary widely, the above discussion may not address potentially important exposure/deposition cases. This is especially true for children, whose respiratory deposition and absorption characteristics have not been studied experimentally. Age-dependent differences in respiratory geometry, air flow conditions, metabolism, and body compartment weight must be applied to make projections from adult data.

The criteria document cites a model that accounts for some of these differences in estimating that submicron particles deposit in the respiratory

tract of a 10-year child 1.6 - 2.7 times more efficiently than in an adult (James, 1978). Although the author states the model should yield a "reasonable approximation" for younger children whose lungs are not fully developed, Hoffman et al. (1979) calculated significantly higher alveolar retention rates for submicron nuclide aerosols in 2-8 year old children compared with 10 year olds. Another limitation of the James model is its assumption of uniform deposition throughout the entire lung surface, ignoring enhanced deposition in airway bifurcations and other "hot spots" in large bronchi (Schlesinger and Lippmann, 1978; Martonen, 1983). This may be an important factor even for submicron lead aerosols whose toxicity is largely systemic, since clearance from such hot spots will be diminished and because absorption of soluble lead compounds can occur in the upper bronchial airways. Consequently, it is uncertain whether the deposition and absorption factor range of 1.6-2.7 derived from James (1978) is applicable to children, especially those in the age range of our sensitive population.

Assuming that this model is applicable to younger children, the absorption factor becomes: (0.16 to 0.32) x (1.6 to 2.7) = (0.26 to 0.86) for mouth-breathing children in general urban/rural atmospheres and similarly, 0.48 to 1.6 for mouth-breathing children living near point sources. (Obviously, a respiratory deposition/absorption efficiency factor greater than 1.0 is impossible.) Since most people shift to mouth breathing only temporarily during exercise or other activities (e.g., conversation) or during illness (e.g. congestion), these estimates, based on mouth-breathing individuals, likely overestimate total respiratory deposition and absorption over the course of a day. Therefore, daily respiratory absorption rates

of 25 to 50% and 50% to 75% are assumed for children living in general urban/rural areas and near point sources, respectively.

b) Gastrointestinal Absorption

The absorption in the gastrointestinal (GI) tract of lead-containing compounds present in food, water, soil, dust, paint chips, or other materials that a child may ingest is dependent upon the physical/chemical form of the material, the composition of the diet, and the age and physiological status of the individual.

Young children have a higher intake of lead on a body weight basis because of higher requirements for calories, fluid, and air (Mahaffey and Michaelson, 1980). In addition to ingesting more lead, children up to 8 years of age absorb between 42 and 53% of ingested dietary lead compared with 7 to 15% in adults (Alexander et al., 1973; Ziegler et al., 1978; Kehoe, 1961; Chamberlain et al., 1978; Rabinowitz et al., 1980).

These rates do not reflect the wide degree of inter-subject variability observed in the studies nor other factors that influence absorption in children. For example, absorption rates 2 to 4 times higher were observed in adults following fasting periods of 4 to 16 hours (Blake, 1976; Chamberlain et al., 1978; Heard and Chamberlain, 1982; Rabinowitz et al., 1980). Such increases can be expected among children who skip meals, a particular problem among lower income groups (Koh and Caples, 1977). Regular eating patterns do not insure minimized dietary lead absorption, however. Based on several animal studies, clinical investigations, and epidemiological surveys, children with diets deficient in calcium, iron, phosphate, zinc, copper, vitamin D, protein, lipids, or lactose can be expected to absorb and retain lead to a greater degree (Mahaffey and Michaelson, 1980; Rosen et al., 1981; Chilsolm, 1981; Heard and Chamberlain, 1982; CD, Table 10-4).

This phenomenon may partially explain the enhanced neurotoxicity of lead in animals with nutritional deficits (Mahaffey and Michaelson, 1980). The importance of nutritional interactions with lead absorption and possibly toxicity is particularly significant for young children because of their large fluxes in relative nutrient status. These interactions can only be estimated qualitatively with present information, however. Although nutritional deficiencies are more pronounced among lower income children (Mahaffey and Michaelson, 1980; Owen and Lippmann, 1977; Hambidge, 1977), they exist in children of all socio-economic strata (CD, p. 10-41).

The ingestion of non-food items such as dust, soil and dirt through normal hand-to-mouth activities in children constitutes the greatest contribution of atmospheric lead to a typical child's total lead exposure (CD, Table 7-25). Animal experiments indicate that lead of variable chemical form in soil or dust is as available for absorption as food lead (Dacre and Ter Haar, 1977) and in vitro studies demonstrate that the acidity of the human stomach is adequate to extensively solubilize lead assimilated from soil and dust (Day et al., 1979; Harrison, 1979; Duggan and Williams, 1977). Based on these data and the fact that ingestion of such materials occurs other than at mealtimes, allowing for potentially enhanced absorption due to the previously discussed fasting factor, the CD estimates that 30% of the lead ingested in dust and soil is absorbed in a child (CD, p. 10-10).

An inverse relationship was found between particle size and gastrointestinal absorption of lead, especially in the range of 1-100 μm, such that a 6 μm dietary lead particle was absorbed five times as efficiently as a 197 μm particle (Barltrop and Meek, 1975). There is little information to assess whether the conversion in the physical form of atmospheric lead-containing particles once inside the complex geochemical matrix of soil or as dust

would affect their bioavailability and, consequently, toxicity. Thus, all atmospheric lead particles that have deposited are considered to have the same absorption rate (30%) if ingested.

2. Transplacental Transfer

Lead uptake via this pathway occurs rapidly beginning in the twelfth week of gestation and increases throughout development (Barltrop, 1969). Cord PbB levels are slightly lower than maternal levels and are significantly correlated with maternal exposure (Alexander and Delves, 1981; Rabinowitz and Needleman, 1982; Ryu et al., 1978).

3. Physiological Retention, Distribution, and Excretion

The initial uptake of lead from the lungs or gut is to plasma, where it is rapidly distributed to red blood cells, bone, and virtually all of the organs and tissues of the body (Chamberlain et al., 1978). The level of lead at any one site and time is determined by complex, dynamic interchanges among the various tissues and fluids that affect their respective affinities for lead. With consistent exposure for an extended period, a near steady-state distribution within the body is achieved (CD, p. 10-13). A primary goal of more refined lead uptake estimates to be used in conjunction with the biokinetic model discussed in Section V.A.2 will be to assess how short-term exposures superimposed on a long-term uptake pattern affect this steady-state distribution in children.

a) Retention and Excretion

In children, 47 to 58% of ingested lead on average is eliminated in the feces without prior gastrointestinal absorption (Alexander et al., 1973; Ziegler et al., 1978), while at least as great a percentage of inhaled lead particles fail to deposit in a child's respiratory tract, assuming that the previously-discussed James (1978) model is accurate. In adults, 40-60% of the lead absorbed from the gut or lungs into the blood is

excreted in urine with a half-life between 18 and 37 days depending on initial blood lead or dosage (Chamberlain et al., 1978; Rabinowitz et al., 1976; Griffin et al., 1975). This rapidly excreted fraction is estimated to be only 16% of the absorbed lead in infants (CD, Table 10-3, based on Ziegler et al., 1978).

Lead is excreted into the urine by the kidneys, both by glomerular filtration and transtubular flow (Goyer, 1968). Lead-induced renal effects (Appendix D.4; CD, Section 12-5) may compound toxicity by interfering with urinary lead excretion.

Absorbed lead can also pass from the blood through the intestinal wall into the gut and be eliminated with the feces, as is the ingested and inhaled lead that is swallowed and not absorbed (Chamberlain et al., 1978). The excretion rate of this "endogenous" fecal lead appears to be roughly equal in children and in adults (CD, Table 10-3). A small portion of absorbed lead is excreted in sweat and milk, or is stored in tissues that are later shed (e.g., hair, nails, deciduous teeth) (Rabinowitz et al., 1973).

The balance of the absorbed lead is transported to soft tissues and bones where it may be stored for months to years or reabsorbed into the blood. In adults, between 1 and 4% of daily lead intake is retained in the body (Chamberlain et al., 1978; Rabinowitz et al., 1977; CD, Table 10-3) while children (2 months to 8 years of age) are estimated to retain between 18 and 33% (Alexander et al., 1973; Ziegler et al., 1978; CD, Table 10-3).

b) Distribution

Lead that remains in the body can be divided conceptually into separate physiological pools. The largest pool is skeletal (i.e., bones and teeth) which accounts for about 94% of total body lead in adults and about

73% in children under 16 years of age (Rabinowitz et al., 1974; Barry, 1975). The remaining body burden of lead resides in soft tissue and blood. Under typical conditions, more than 99% of blood lead is bound within red blood cells, primarily to hemoglobin (DeSilva, 1981), although it is the very small fraction transported in plasma and extracellular fluid that carries lead to the various body organs (Baloh, 1974).

The selective accumulation of lead in the heart (aorta), kidney cortex, and liver (Barry, 1975, 1981; Gross et al., 1975) may be associated with the sensitivity of these organs to elevated lead exposure. The greater capacity of young animals to retain lead in their tissues, particularly in the brain, may help to account for the persistence of neurotoxic effects of various types in young animals (CD, 12.4.3.1.5) and children (CD, 12.4.2.2.2) long after external lead exposure has ceased and PbB levels have declined to "normal". Furthermore, relative uptake characteristics and distribution patterns of lead among the regions of the brain may be factors in lead neuropathology (Grandjean, 1978; Klein and Koch, 1981).

Within the cell, there is selective uptake of lead into nuclear inclusion bodies and mitochondria (Barltrop, et al., 1971; Castellino and Aloj, 1969), which is consistent with lead-induced interference of normal processes in these organelles such as disrupted energy metabolism and ion transport, and possible genotoxicity (CD, 12.2.1 and 12.7).

4. Kinetics and Physiological Indices of Lead Exposure

Skeletal lead is relatively inactive physiologically, with an approximate biological half-time in normally exposed humans of 17-28 years (Rabinowitz et al., 1976). When lead exposure is reduced or terminated, lead is released from the skeleton so that the declines in blood lead levels and

excretion rates are less than would be predicted for the amount absorbed. This is especially evident in occupationally exposed adults (O'Flaherty et al., 1982). Lead turnover rates in dense cortical bones (e.g., teeth, tibia, femur) are substantially slower than in spongy trabecular bones (e.g. rib, vertebrae) (Steenhout, 1982). Long-term resorption rates of lead stored in the skeleton, though difficult to measure, have been derived from isotopic ratio and radiolabel tracer studies (Chamberlain et al., 1978; Manton, 1977). About 25% of an adult's PbB is estimated to result from eventual re-entry of skeletal lead (Chamberlain et al., 1978). Chamberlain (1983) proposes that the blood lead/air lead ratios discussed in Section V.B. be multiplied by a factor of 1.3 to allow for possible re-entry into the blood of lead transferred to bone or other long-term storage.

The release of lead from the skeleton may be accelerated under some stressful conditions, such as chelation therapy, nutritional deficiencies, hormonal imbalances, bacterial infections, and possibly lactation with subsequent transfer of both lead and calcium from mother to fetus or newborn (Bethea and Bethea, 1975; Rosen and Wexler, 1977; Keller and Doherty, 1980; Gross and Pfitzer, 1974). As a result, children, whose skeletal systems are more prone to some of these demineralizing conditions, are at increased risk of remobilization of skeletal lead.

The lead content of deciduous teeth provides an index of historical exposure over several years since teeth accumulate lead up to the time of shedding or extraction. Tooth lead levels appear to be proportional to exposure (Needleman and Shapiro, 1974; Steenhout and Pourtois, 1981) and to blood lead levels (Shapiro et al., 1978), and are becoming more commonly used as an exposure index in population studies of lead health effects in children (e.g., Needleman et al., 1979; Winneke et al., 1982a, 1983;

Ernhart et al., 1981; Smith et al., 1983). Uniform measurement techniques are required to insure comparability in future studies since the absorption of lead varies depending on the type of tooth (e.g., incisor versus molar) and the constituent matrix within the tooth (e.g., primary and secondary dentine, enamel). Although tooth lead levels are not useful in appraising current exposure, reliable techniques of in situ tooth analysis are being developed such as X-ray fluorescence (Shapiro et al., 1978) which, when combined with serial blood measurements, could provide indices of ongoing uptake of lead in target organs.

While most of the body burden of lead appears to be toxicologically inactive due to its storage in bone and other possibly "protective" pools in soft tissue such as nuclear inclusions and atherosclerotic plaque deposits (Cramer et al., 1974; Barry, 1975), the fraction of mobile lead in soft tissue and blood available to biological sites of action determines the degree of potential toxicity to the organism. The most useful index of this active fraction and of imminent toxicity may be the amount that is excreted in response to administration of a chelating agent, such as EDTA or penicillamine (CDC, 1985; Chilsom et al., 1976; Chilsom and Barltrop, 1979; Saenger et al., 1982; Piomelli et al., 1984). Chelatable lead apparently comprises a fairly large labile body pool made up of soft tissue lead and a mobile compartment within bone (CD, p. 10-25).

In contrast to skeletal lead, turnover in soft tissues and blood is rapid, with a residence time of four to six weeks in adults (Rabinowitz et al., 1976; Griffin et al., 1975), and possibly much shorter in children (Duggan, 1983). Despite this transience, lead added to and removed from these pools reaches equilibrium with relatively constant exposure. A change in lead exposure and absorption shifts the balance to a new

steady state of dynamic equilibrium within about 60 days although changes in PbB levels may be noted immediately (Tola et al., 1973; Rabinowitz et al., 1973; Griffin et al., 1975). The equilibration period in children may be quite different given their accelerated skeletal metabolism and apparently increased lead resorption rates from bone, as well as the shorter half-life of lead in their blood (Duggan, 1983). It does not appear that with continuous dosing lead accumulates in the blood, although it may do so in other tissues (Kehoe, 1961; Purser et al., 1983).

In contrast to tooth lead measurements which reflect lead exposures integrated over years, a single blood lead measurement is limited to reflecting primarily steady state exposures over recent months, although a PbB level may respond to short-term changes in exposure in proportion to the initial PbB content. Under conditions of intermittent exposures and rapid growth, as is the case with children, blood lead provides only a static picture of a dynamic process that includes intake, excretion, storage, and mobilization. A high degree of variability in PbB levels was frequently observed in children sampled semi-annually from birth through two years of age (Rabinowitz et al., 1984a), while older children (4-12 years) display greater stability (David et al., 1982). In addition, blood lead is only an indirect indicator of lead levels at critical sites in the various organs and tissues (Azar et al., 1973; Grant et al., 1980). For instance, levels of mobilizable lead ($CaNa_2$ - EDTA) in 26% of "asymptomatic" children with moderate elevations in blood lead (30-49 µg/dl) were similar to chelatable lead values obtained in children with overt lead toxicity (Piomelli et al., 1984). Again, this limitation of blood lead as an index is especially evident with abrupt changes in exposure because of lead's shorter retention time in blood compared with other

(3) Lead impairs the transmitochondrial transport of iron and instead of producing heme, the mitochondria accumulate its precursor, protoporphyrin which, lacking iron, is incapable of performing its essential respiratory function. As a result of lead intoxication in newly forming erythrocytes, protoporphyrin (referred to as erythrocyte protoporphyrin or EP) takes the place of heme in the specific pocket of the hemoglobin molecule. As the red cells remain in the circulation, zinc is rapidly chelated at the center of the molecule in the site normally occupied by iron (Piomelli et al., 1982). The resulting zinc protoporphyrin (ZPP) is tightly bound in the available heme pocket for the life of the erythrocyte, normally 120-130 days (Lamola et al., 1975). The PbB threshold for elevated EP in children is approximately 15 µg/dl in children with significant elevations (>1 and 2 standard deviations above normal EP mean levels) occurring in 50 percent of children studied at PbB levels of between 25 and 35 µg/dl (Roels et al., 1976; Piomelli et al., 1982).

The health significance of EP or ZPP accumulation is that it indicates that heme or hemoprotein synthesis in many tissues has been impaired as a result of lead's entry into mitochondria (CD, p. 12-46). Previously, EP elevations at PbB levels around 30 µg/dl were of concern based on functional disruptions in hemoglobin synthesis at 40 µg/dl and neurobehavioral effects above 50 µg/dl (EPA, 1977). In setting the current lead NAAQS in 1978, 30 µg/dl was adopted as a maximum safe PbB, allowing some margin of safety relative to levels associated with inhibitions of hemoglobin synthesis or neuropsychological deficits. This PbB level was identical to the Center for Disease Control's (CDC) previous criteria level for undue lead exposure for young children.

Recent data, however, have provided more information on the extensive impact of lead on the body heme pool and associated disruptions of many

physiological processes (see Figure 7-1). With increasing lead exposure, impairment of heme and hemoprotein synthesis intensifies in different organ systems resulting in reductions in oxygen transport, changes in cellular energetics, neurotransmitter function, and in detoxification of drugs and other foreign agents, and impairments in the biosynthesis of important substances such as 1,25-dihydroxyvitamin D (1,25-OH_2-D). Inspection of Figure 7-1 reveals effects that can be viewed as intrinsically adverse as well as those that reduce the body's ability to cope with other forms of toxic stress, e.g., reduced hepatic detoxification of certain drugs and other xenobiotics (as a result of lead-induced impairment of hepatic enzyme systems), and possibly impairment of the immune system (CD, p. 13-30).

Of the functional consequences associated with heme reductions and lead's interaction with those processes, perhaps the best quantitative data is available on the negative correlation between PbB levels (beginning at 12 µg/dl) and circulating levels of the vitamin D hormone, $1,25(OH)_2$ D (Rosen et al., 1980). Highly significant and profound depressions in circulating $1,25(OH)_2$ D levels were found in children whose PbB levels ranged from 33 to 120 µg/dl, with the most striking decreases above 62 µg/dl. The criteria document concludes that it appears likely that lead-induced reductions in heme underlie this association, and that impaired production of $1,25(OH)_2$ D can have profound and pervasive effects on tissues and cells of diverse type and function throughout the body (CD, p. 12-49):

(1) Altered levels of $1,25(OH)_2$ D may impact calcium homeostasis and thus calcium-dependent processes essential to several enzyme systems, the transport of and response to various hormonal and electrical stimuli, and cyclic nucleotide metabolism. In addition, lead may directly affect the role of $1,25(OH)_2$ D in cell differentiation/maturation, immunoregulation, pancreatic

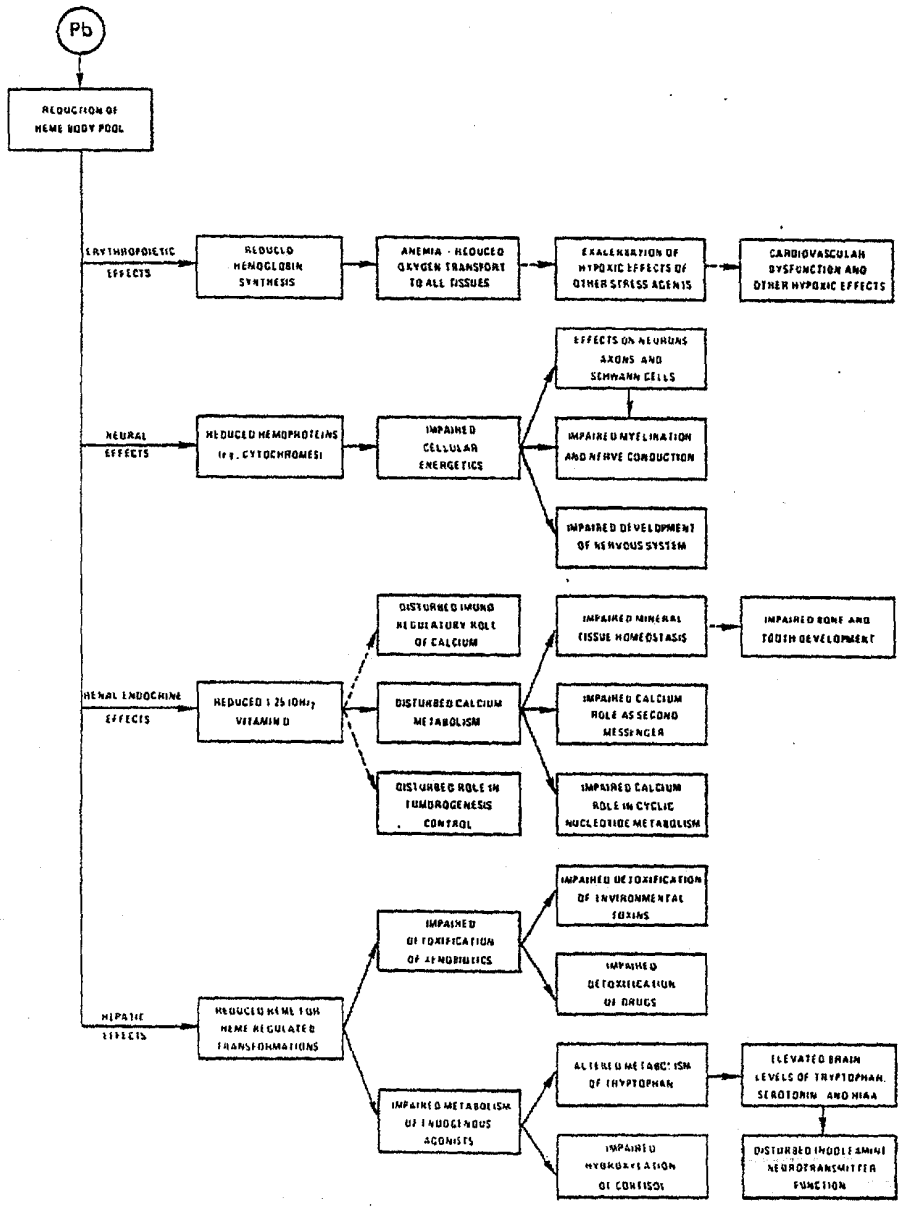

Figure 7-1. Multi-organ impact of reductions of heme body pool by lead. Impairment of heme synthesis by lead results in disruption of wide variety of important physiological processes in many organs and tissues. Particularly well documented are erythropoietic, neural, renal-endocrine, and hepatic effects indicated above by solid arrows (⟶). Plausible further consequences of heme synthesis interference by lead which remain to be more conclusively established are indicated by dashed arrows (- - ➤).

Source: Criteria Document (Figure 13-4).

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function (e.g., insulin secretion), and mediation of tumorigenesis (See Appendix D.1(c); CD, pp. 12-40 to 12-42);

(2) The effect of lead on $1,25(OH)_2$ D is a particularly robust one, with PbB levels of 30-50 µg/dl resulting in decreases in the hormone that overlap comparable decreases observed in children with severe kidney injury lacking two-thirds of normal renal function, as well as in those with various genetic disorders such as vitamin D-dependent rickets and hypoparathyroidism (Rosen et al., 1980; Rosen and Chesney, 1983; Chesney et al., 1983).

At higher levels, lead's interference with heme synthesis and other red blood cell functions (e.g., inhibition of Py-5-N activity which affects membrane stability) may result in anemia. Although this is a serious clinical manifestation, the inhibition of heme synthesis at lower lead levels has much wider implications for a multitude of organs and systems, as described above, especially in the growing child.

The CD concludes that:

> "Given the available evidence indicative of significant effects on neurological functioning and other important physiological processes as PbB levels increase above 15-20 µg/dl and approach or exceed 30-40 µg/dl, the rationale for continuing to view 30 µg/dl as a "maximum safe" PbB level is called into question and substantial impetus is provided for revising the criteria level downward, i.e., to some PbB below 30 µg/dl. At this time, it is difficult to identify specifically what blood-Pb criteria level would be appropriate in view of the existing medical information. Clearly, 30 µg/dl can no longer be seen as affording any margin of safety before PbB levels are reached that are associated with unacceptable risk of notable adverse health effects occurring in some children. This is based on at least two grounds: (1) PbB levels in the 30-40 µg/dl range are now known to "mask" for some children markedly elevated chelatable body lead burdens that are comparable to lead burdens seen in other children displaying overt signs and symptoms of lead intoxication; and (2) PbB levels in the 30-40 µg/dl range are also associated with the onset of deleterious effects in several organ systems which are either individually or collectively seen as being adverse.

> "At levels below 30 µg/dl, many of the different smaller effects reported as being associated with lead exposure might be argued as separately not being of clear medical significance, although each is indicative of interference by lead with normal physiological processes. On the other hand, the collective impact of all of the observed effects (representing potentially impaired functioning and depleted reserve capacities of many different tissues and organs) may, at some point distinctly below 30 µg/dl, be seen as representing an adverse pattern of effects worthy of avoidance with some added margin of safety. The onset of signs of detectable heme synthesis impairment in many different organ systems at PbB levels starting around 10-15 µg/dl, along with indications of increasing degrees of pyrimidine metabolism interference and signs of altered nervous system activity, could be viewed as such a point. Or, alternatively, the collective impact of such effects might be argued as becoming sufficiently adverse to warrant avoidance (with a margin of safety) only when the various effects come to represent marked deviations from normal as PbB levels exceed 20-25 µg/dl and begin to approach the more clearly adverse 30 µg/dl level. Lastly, other arguments have been advanced to the effect that any deviation from normal biochemical levels or physiological functioning in any organ system should be viewed as adverse health effects to be avoided, even at PbB levels below 10 µg/dl." (CD, p. 13-40)

Table 7-5 presents a preliminary staff assessment of the data in the CD that are most useful in determining a safe PbB for protection of the sensitive populations. The table focuses on those effects associated with PbB levels at and below 40 µg/dl. The clearly adverse effects at higher exposures are listed in Table 7-2.

Based on the above discussion, the staff concludes that multi-organ effects resulting from impairments in heme synthesis and vitamin D metabolism are likely between 25-30 µg/dl, and that potentially significant effects on these processes, as well as on the central nervous system may be possible at the lower PbB levels indicated, but the evidence and risks are less certain. In evaluating the health effects in the context of decision-making on an appropriate PbB level of concern, the following considerations are important.

1) There is considerable uncertainty and controversy regarding the nature and degree of lead's impact on neuropsychological function although the weight of the evidence suggests a small but significant association

Table 7-5. STAFF ASSESSMENT OF KEY HEALTH EFFECTS OF LEAD

PbB	Observed Effects	Implications
40 µg/dl	Reduced hemoglobin synthesis; anemia in some children[1] Possible IQ (4-5 point avg.) and behavioral deficits[2] Significant reductions in vitamin D hormone synthesis[3] Possible slowed nerve conduction velocities[4] Subtle alterations in brain electrophysiology[5]	Strong evidence for significant and persistent effects on hematological, neurological, immunological and detoxification systems.
30 µg/dl	Significantly elevated EP[6] Possible IQ (4 point avg.) and attentional deficits[7] Significant reductions in vitamin D hormone synthesis[3] Possible slowed NCVs[3] Subtle alterations in brain electrophysiology[5] Significant Py-5-N activity inhibition[8]	Likely multi-organ effects resulting from heme and vitamin D impairment. Some risk of behavioral/sensory disturbance and effect on cognitive function or academic capacity.
25 µg/dl	Significantly elevated EP[6] Possible IQ (1-2 point avg.) and attentional deficits[9] Reduced vitamin D hormone synthesis[3] Subtle alterations in brain electrophysiology[10]	Likely multi-organ effects resulting from heme and vitamin D impairment. Some risk of behavioral/sensory disturbance and effect on cognitive function or academic capacity.
20 µg/dl	Elevated EP[6] Possible IQ (1-2 point avg) and attentional deficits[9] Reduced vitamin D hormone synthesis[3] Subtle alterations in brain electrophysiology[10]	Some risk of multi-organ effects resulting from heme and vitamin D impairment. Some risk of behavioral/sensory disturbance and effect on cognitive function or academic capacity.
15 µg/dl	Lowest level of elevated EP[6] Possible IQ and attentional deficits[9] Reduced vitamin D hormone synthesis[3] Subtle alterations in brain electrophysiology[10] Reduced ALA-D activity[11]	Small risk of multi-organ impairments resulting from heme and vitamin D impairment, behavioral/sensory disturbance and effect on cognitive function or academic capacity.
5-10 µg/dl	Reduced ALA-D activity,[11] Py-5-N synthesis[8] Subtle alterations in brain electrophysiology[10]	Significant functional effects unlikely.
?	Experimental alterations in neurochemistry and cellular energy metabolism[12]	Effects detectable at low in vitro levels or experimental dosages; corresponding human PbB levels and functional significance difficult to determine

[1]Betts et al., 1973; Rosen et al., 1974; Adenbojo, 1974; Pueschel et al., 1972

[2]De la Burde and Choate, 1972, 1975; Perino and Ernhart, 1974; Ernhart et al., 1981; Ernhart, 1983; Needleman et al., 1979 Needleman, 1984

[3]Rosen et al., 1980; Mahaffey et al., 1982; Rosen and Chesney, 1983

[4]Seppalainen et al., 1979; Seppalainen and Hernberg 1980, 1982; Feldman et al., 1977

[5]Otto et al., 1981, 1982, 1984; Beningnus et al., 1981; Burchfiel et al., 1980

[6]Piomelli et al., 1977; 1982; Roels et al., 1976; Hammond et al., 1984; Rabinowitz et al., 1985

[7]Needleman et al., 1979, 1982; Needleman, 1982

[8]Valentine and Paglia, 1980; Angle and McIntire, 1978; Angle et al., 1982

[9]Smith et al., 1983; Harvey et al., 1983, 1984; Yule et al., 1984; Hunter et al., 1983; Winneke et al., 1983, 1984

[10]Otto et al., 1982, 1984

[11]Hernberg and Nikkanen, 1970; Granick et al., 1973; Roels et al., 1975b; Wada et al., 1976

[12]Bull et al., 1975, 1979; Holtzman and Shen Hsu, 1976; McCauley et al., 1979; Holtzman et al., 1978; Silbergeld and Adler, 1978; Silbergeld et al., 1979, 1982; Purdy et al., 1981; Litman and Correia, 1983

between lead, IQ, and disturbances in sensory/attention processes at levels between 30 and 50 µg/dl and possibly down to 15 µg/dl. It is hoped that improved information will result from ongoing research as well as from the ongoing EPA "risk assessment" that will elicit probabilistic expert judgment on the existing data base regarding lead's relationship to IQ in children.

2) Similarly, there is incomplete information on the medical significance of elevations in EP and the dose-response relationship between lead and hemoglobin decrements. The ongoing risk assessment will hopefully provide useful information on these issues as well.

3) The risks associated with reductions in vitamin D hormone synthesis and altered brain wave activity at PbB levels $\leq$ 30 µg/dl are difficult to determine at present. It is felt that the collective impact of these changes along with other lead-induced effects at low PbB levels should be considered sufficiently important to warrant avoidance.

4) As part of their lead poisoning screening program, the CDC has revised their definition of lead toxicity for individual children from 30 µg/dl to 25 µg/dl PbB, accompanied by an elevated EP level ($\geq$ 35 µg/dl) (CDC, 1985). Detecting these levels identifies a child as requiring immediate medical and environmental intervention. The revisions were based on the recent evidence of neurobehavioral, hematological, and vitamin D metabolism effects of lead cited above, and on evidence that a blood lead concentration may underestimate the body burden of lead in a child. CDC argued that 30 µg/dl provides little or no margin of safety, and that the biologic threshold for lead toxicity as indicated by increasing EP levels, is below 20 µg/dl (CDC, 1985). However, CDC acknowledges that practical considerations must be taken into account in setting this level. An intervention level of 25 µg/dl therefore represents an

accommodation based on a pragmatic decision on the limits of effectively implementing the existing screening program and how much risk is tolerable.

5) The Clean Air Act requires that the air standard be precautionary in nature and that the level should not be based on economic or technological considerations. While the lead NAAQS and CDC's program share the common goal of reducing children's lead exposure, there is an important distinction. The screening program is a form of secondary prevention and is necessary to prevent lead toxicity among susceptible children, but is based in part, on practical, technological, and cost considerations. In contrast, the lead NAAQS is a form of primary prevention to control lead emissions at the source, before opportunities for human uptake and undue risks arise, and is not to be based on cost.

The staff concludes on the basis of the above considerations that the CDC intervention level is not directly an appropriate surrogate for the lead NAAQS and that a PbB level of 25 µg/dl contains little or no margin of safety from potentially adverse effects on heme synthesis, vitamin D metabolism, and possibly neurological and behavioral functions.

2. Predicting Blood Lead Levels under Alternative Air Lead Levels

Three approaches are examined here that can be used to estimate the impact of alternative air lead levels on PbB levels among children. The first is to combine the estimates of daily lead uptake from all routes of exposure for given air lead concentrations with the derived lead uptake-to-blood lead relationships, as presented in Section V.A. The second approach is to directly apply mathematical relationships between air lead and blood lead derived from population studies and appropriate statistical analyses that account for children's exposure to atmospheric lead through pathways other than inhalation such as ingestion of dust and soil (Section

V.B.2). Finally, a hybrid of the first two approaches is provided in the criteria document in which mathematical relationships derived from population studies are applied to estimates of lead concentration in individual media (Section V.B.1). These three modeling approaches are discussed below and the results are presented (in Table 7-12) for consideration in the possible use of one, two, or all three approaches (with any necessary modifications using improved data) in assessing the protection afforded by alternative lead NAAQS.

All three models estimate PbB levels in terms of population mean levels. For purposes of setting a lead NAAQS, it is necessary to determine the blood lead distribution corresponding to a given mean PbB for the population of children such that a specified percentage is protected from exceeding a maximum acceptable PbB level. In determining such a distribution, it is important to recognize that there is significant biological variability within any population, and it is those individuals with the greatest adverse response to any given lead exposure that are of greatest concern in establishing a primary lead NAAQS. A method to consider the most susceptible segment of the population of children is discussed here.

Several epidemiological studies have indicated that the log values of measured individual PbB levels in a uniformly exposed population are normally distributed with a variation, including analytical variation, ranging between 1.3 and 1.4, when expressed as a geometric standard deviation (GSD) (Tepper and Levin, 1975; Azar et al., 1975; Billick et al., 1979). Using standard statistical techniques, it is possible to use the geometric standard deviation to calculate the mean population blood lead level that would place a given percentage of the population below an acceptable maximum PbB for an individual child. The NHANES II study, which provides the best available data in terms of quality control and

sample size, yields estimates of GSDs in the range of 1.34 to 1.39, uncorrected for analytical variation, for various subgroups of young children with comparable sex, age, income, and place of residence (i.e., degree of urbanization) (CD, p. 11-29 to 11-30). By using these GSDs for separate homogeneous populations identified in the NHANES II survey, it is possible that the most sensitive segment (i.e., highly exposed) of the population is not being accurately characterized since for that group there is likely to be a different distribution of exposures from the homogenous NHANES II subgroups. This is indicated by the fact that the GSD for all black children living in central cities was 1.46 and for all children sampled in NHANES II, the GSD was 1.47, not adjusted for age, income, or degree of urbanization (DHHS, 1984). The range of GSDs presented above which are assumed to be constant for the entire distribution should therefore be interpreted as preliminary attempts to characterize the most appropriate sub-populations of children given the available data in the CD. The calculations of blood lead distributions under various air lead levels using the three models presented below should also be considered as preliminary until further comment and CASAC guidance is received on this issue.

Analytical variation which exists in any measurement has an impact on the bias and precision of statistical estimates such as the GSDs derived from NHANES II. For this reason, it is important to recognize the magnitude of analytical variation in blood lead measurements due to measurement variation (i.e., between measurements run at the same time) and variation created by analyzing blood samples at different times (CD, p. 11-26). Correcting these GSDs for the overall estimate of analytical variation for the NHANES II study (0.02083) yields estimated GSDs in the range of 1.29 to 1.34. Using GSDs corrected in such a way, although providing

a more accurate characterization of a given blood lead distribution, may not be appropriate for this assessment because the health effects studies used to define a maximum acceptable PbB did not correct their PbB measurements for analytical variance. These studies, like NHANES II, generally employed the best available measurement techniques and quality control. Using "corrected" GSDs on one hand to predict percentages of children with various PbB levels given a target mean population PbB, and then matching those predicted PbB levels with "uncorrected" PbB levels derived from health studies in order to assess the risks associated with that population mean PbB, would result in a somewhat biased assessment. Therefore, the range of GSDs presented in the CD from NHANES II that are not corrected for analytical variance will be used in further calculations. The staff encourages any comment or additional information on this issue.

In setting the current lead NAAQS in 1978, EPA estimated that in order to protect 99.5% of U.S. children from attaining a PbB of 30 µg/dl, a target population mean PbB would be approximately 15 µg/dl assuming a GSD of 1.3. Similar calculations can be made for other percentages of the population, e.g., 99.9 or 99.0%. There are approximately 25 million children under 7 years of age in the U.S., some 14 million in urban areas, and approximately 240,000 living near point sources where atmospheric lead exposures may be high (CD, p. 13-47; Battye, 1985c).

Table 7-6 presents the population mean PbB levels that would be required to protect 99.5% of U.S. children from reaching various PbB levels given the range of uncorrected GSDs derived from NHANES II for homogeneous subpopulations. (Mean PbB levels necessary to provide 99.9% protection would be somewhat lower; conversely, they would be higher for 99.0% protection).

These values were calculated using the formula given to describe a

lognormal distribution (Yankel et al., 1977): $Mg \cdot GSD^n = Dn$

where

Mg = geometric mean PbB

GSD = geometric standard deviation

n = the number of standard deviations

Dn = value of PbB at a standard deviation.

Table 7-6. POPULATION MEAN BLOOD LEAD LEVELS (µg/dl) REQUIRED TO PREVENT 99.5% OF U.S. CHILDREN FROM EXCEEDING SPECIFIED BLOOD LEAD LEVELS (Assuming GSDs of 1.34 - 1.39)

	Maximum Acceptable Blood Lead Level (µg/dl)			
GSD	25	20	15	10
1.39	10.7	8.6	6.4	4.3
1.34	11.8	9.4	7.1	4.7

It should be noted that if the GSD of 1.47 calculated for all children sampled by NHANES II (not adjusted for age, sex, income, or degree of urbanization) is used, the population mean PbB levels required to protect 99.5% of children from exceeding 25, 20, 15, and 10 µg/dl would be 9.3, 7.4, 5.5, and 3.7 µg/dl, respectively.

a) Integrated Lead Uptake/Biokinetic Model

Table 7-7 presents the upper and lower bound estimates of average daily lead uptake derived in the Integrated Lead Uptake Model in Section V.A.1 for point sources and general urban/rural areas under different average air lead concentrations, along with the corresponding PbB levels predicted for 2 year old children by the biokinetic model presented in Section V.A.2 (Harley and Kneip, 1985).

Several uncertainties associated with these estimates are discussed in Section V.A.1 and Appendix B. It is important to emphasize that because air lead (and associated dietary, soil, and dust lead) levels were assumed to be constant at whatever air level was analyzed, the upper ends of

Table 7-7. AVERAGE BLOOD LEAD LEVELS FOR CHILDREN UNDER DIFFERENT AIR LEAD LEVELS (ESTIMATED USING INTEGRATED LEAD UPTAKE/BIOKINETIC MODEL)

Average Air Lead ($\mu g/m^3$)[1]	Type of Area	Average Lead Uptake ($\mu g/day$)[2]	Average Blood Lead ($\mu g/dl$)[3]
0.25	General	4.8 - 11.1	1.9 - 4.4
	Pt. Source	7.0 - 21.3	2.8 - 8.6
0.50	General	9.2 - 17.8	3.7 - 7.2
	Pt. Source	16.3 - 29.0	6.6 - 9.3
0.75	General	14.1 - 29.4	5.7 - 11.9
	Pt. Source	22.0 - 35.8	8.9 - 14.5
1.0	General	18.9 - 33.9	7.7 - 13.7
	Pt. Source	27.4 - 45.0	11.1 - 18.2
1.25	General	24.4 - 42.8	9.9 - 17.3
	Pt. Source	37.1 - 50.3	15.0 - 20.3
1.5	General	28.2 - 48.4	11.4 - 19.6
	Pt. Source	41.8 - 62.3	16.9 - 25.2
1.75	General	29.8 - 50.9	12.0 - 20.6
	Pt. Source	46.3 - 69.1	18.7 - 27.9

[1]Air lead levels that were used to calculate daily uptake levels were assumed to be constant and therefore can represent either monthly or calendar quarterly averages.

[2]Uptake estimates derived in Table 5-1. Range under each air lead level and location reflects upper and lower bound sets of estimates used to calculate uptake levels.

[3]PbB levels for 2 year old children derived from lead biokinetic model (Harley and Kneip, 1985) discussed in Section V.A.2. Range under each air lead level and location reflects uncertainties in uptake estimates.

these ranges in particular may represent "worst case" population mean uptake and PbB estimates for each air lead concentration. Furthermore, estimated PbB levels at 2 years of age were selected in order to predict the maximum impacts on young children. At this age, PbB levels would be highest, assuming constant exposure, according to the biokinetic model (consistent with the NHANES II data). The staff believes, therefore, that given the available data and necessary assumptions used in this model, the lower ends of the ranges of PbB levels for the different air lead levels reflect the best estimates of lead exposure, uptake, and metabolism among individuals in different locations within the population. The lower bound estimates for 2 year old children will thus be used as the predicted mean PbB levels under each air level in later calculations. Finally, using standard statistical techniques and identified characteristics of the PbB distribution within the population (discussed previously), it is possible to calculate for any mean PbB, the individual PbB at a specified standard deviation. This calculation is illustrated below for the other two modeling approaches and the results are later summarized in Table 7-12.

b) Application of "Aggregate" Blood Lead/Air Lead Relationships from Epidemiological Studies

i) Blood/Air Lead Slope

The epidemiological studies discussed in Section V.B. provide quantitative estimates of the relationship between air lead exposures and PbB levels in various populations of children. In assessing the total impact that atmospheric lead makes on total exposure, the aggregate modeling approach discussed in Section V.B.2 attempts to recognize the simultaneous presence of lead in multiple environmental media. Thus, the median blood/air lead inhalation slope for children (β) is estimated in the CD to be 1.92 from three major studies (Yankel et al., 1977; Roels

et al., 1980; Angle and McIntire, 1979), and aggregate slopes that include both direct (inhalation) and indirect (via soil, dust, etc.) air lead contributions typically yield values in the range 3-5 (CD, p. 11-108).

To acount for possible re-entry of lead into the blood transferred from bone or other long-term storage, Chamberlain (1983) estimates that blood/air lead relationships for adults must be multiplied by a factor of 1.3, yielding a range of aggregate slopes between 4 and 6 for total air lead exposure. It is possible that the rapid growth and high rate of turnover in children's skeletal systems would require an even higher adjustment.

Assuming that these slopes are reasonably accurate, and that at lower levels of exposure (< 30 µg/dl) a linear relationship applies (Chamberlain, 1983; CD, p. 11-64), a 1 $\mu g/m^3$ change in the average air lead concentration would produce a corresponding increase of between 4 and 6 µg/dl in the average equilibrated blood lead level of young children.

ii) Contributions from Non-Air Sources of Lead

To predict PbB levels associated with alternative air lead levels using these aggregate slopes, it is necessary to estimate the contribution to total lead exposure from emission sources not subject to control by implementing an air quality standard. These sources may include lead-soldered food cans, lead plumbing, lead-based paint, and indirect occupational exposures (i.e., from clothing and shoes of parents who work in lead-related industries). It should be noted that by using observed lead concentrations in dust from a wide range of locations and conditions, the integrated uptake model discussed in the previous section attempted to implicitly account for average contributions to total exposure from lead-based paint. In addition, the estimates provided in the criteria document based on

recent FDA and industry data directly provide estimates for non-air sources of lead in the diet which were used in the model.

In attempting to explicitly estimate exposures from non-air sources of lead, which is necessary in applying the aggregate blood/air lead slopes to determine an appropriate lead NAAQS, several difficulties arise:

1) With the exception of non-air lead in diet, few studies provide detailed information on the relative contribution of various sources to children's PbB levels in the U.S. Estimates must be made by inference from earlier survey data and theoretical calculations; and

2) Because non-air contributions to PbB levels probably vary widely in space and time among children, a single estimate for the average case may result in a lead NAAQS that is not protective for all children. This can be expected, for example, for children who regularly ingest lead-based paint. Conversely, the air standard will be overprotective in areas where lead from non-air sources is below the average.

In setting the 1978 lead NAAQS, the Agency estimated that non-air sources of lead contributed on average, 12 µg/dl to children's PbB levels. Since then, significant reductions in PbB levels have occurred, attributable not only to declines in atmospheric lead emissions but to the gradual conversion by manufacturers to non-lead soldered cans, the reduction of old, lead-painted homes, cleaner working conditions, as well as efforts by parents and public health agencies to minimize children's lead exposure. It is not surprising, therefore, that the non-air lead contribution to average PbB levels appears to be lower today. In children sampled in NHANES II between 1976 and 1980 living in rural areas where air emissions can be expected to be minimal, the measured geometric mean PbB was approximately 12 µg/dl (Mahaffey et al., 1982). After three adjustments are made to the NHANES II data, a true "non-air" PbB in the range of 5.9 to 6.6 µg/dl

is estimated for children living in the U.S. today. The rationale for the adjusted value is described below.

1) Although automobile and industrial emissions may be low, rural populations in the U.S. are still exposed to atmospheric lead through long-range transport from urban and point source areas and indirectly from atmospheric deposition of lead on crops grown around the country that enters their diet. No data are available on U.S. children, although preliminary analyses of the Isotopic Lead Experiment, which manipulated the isotopic composition of gasoline sold in and around Turin, Italy, found that between 11 and 14% of the blood lead in adult men living in the countryside can be directly and indirectly traced to gasoline lead locally consumed over 7 years (Facchetti and Geiss, 1982; Colombo and Fantechi; 1983). It can be reasonably assumed that the contribution of total atmospheric (not only gasoline) lead to active children who are regularly exposed to dirt and dust is likely to be significantly higher compared to adults. In the absence of direct data, the range of 11-14% for rural Turin men is multiplied by two, yielding a range of 20-30% for PbB related to gasoline lead and industrial sources in rural U.S. children. Thus, the remaining 70-80% of children's blood lead is assumed to be attributable to non-atmospheric sources.

2) The NHANES II data are based on blood lead measurements made between 1976 and 1980. Since then, in addition to the phasedown of gasoline lead, efforts by the food industry to remove sources of lead consumed by young children have continued. The use of lead-soldered cans in the canning industry has decreased from 90% in 1979 to 63% in 1982 and as the switchover continues, lead in canned foods for children should decrease by as much as 70% (CD, p. 7-48). Since

lead from solder and other metals is estimated to account for approximately 21% of a typical child's background lead exposure (Table 7-25), it is estimated that the average child's total PbB levels will decline by (0.21 x 0.7) or 14%.

3) The staff estimates that ongoing efforts to reduce occupational exposures and to prevent childhood lead poisoning, and the gradual reduction of lead exposure to lead-based paint in old homes have resulted in a 20% reduction in the average PbB level in U.S. children since the 1976-1980 time period.

Based on these three considerations, the NHANES II mean value of 12 µg/dl for rural children sampled between 1976 and 1980 is adjusted in the following calculation:

12 µg/dl x (0.7 to 0.8) x (0.86) x (0.8) = 5.8 to 6.6 µg/dl

This range represents the mean PbB levels that would be expected today in U.S. children not exposed to atmospheric lead directly or indirectly, based on the data and assumptions presented above.

Another method to estimate children's mean "non-air" PbB is to use available data on typical background levels of lead in food, water, dust, and soil ingested by U.S. children and the relationship between lead taken up through these media and children's PbB levels. Table 13-6 of the criteria document uses such data in calculating a mean PbB of 4.42 µg/dl to be expected at an air lead level of zero. Because this estimate is based on observations limited to a few studies not necessarily representative of all U.S. children, it will be used with and added to the estimates derived from the NHANES II survey to construct a range of PbB levels (4.4 to 6.6 µg/dl) predicted for U.S. children not exposed to atmospheric lead emissions, either directly or indirectly.

It must be emphasized that these estimates for non-air contributions to average PbB levels represent average values. Many children may be at risk for significantly higher lead exposures that cannot be prevented by atmospheric emission controls. In particular, these include children who ingest paint chips and other non-food items containing leaded paint, children exposed to high drinking water lead levels from eroding lead pipes or solders in plumbing or distribution systems, those living in deteriorated or recently resurfaced lead-painted housing who inadvertantly take up paint dust through normal mouthing activities, children of parents with high occupational exposures to lead dust that is carried home on clothing, or children living near lead smelters and other point sources where historical soil and dust lead accumulations are excessive. The staff urges that other regulatory agencies and public health programs, including other EPA components, responsible for minimizing children's lead exposures from non-air sources, or from historical atmospheric lead deposition, maintain or increase, where necessary, their efforts.

iii) Calculation of Alternative Lead NAAQS

Based on the conclusions reached in the preceeding sections, alternative target air lead levels can be derived using the "aggregate" modeling approach by:

1) determining a maximum acceptable PbB level for individual children (no greater than 25 μg/dl) to protect against effects discussed in Sections V.B and VI.A.1 with an adequate margin of safety;

2) calculating a target geometric mean PbB level for U.S. children based on placing a specified percentage of them below the maximum acceptable PbB: for purposes of the present discussion the goal is assumed to be 99.5% (Table 7-6);

3) estimating the PbB level attributed to non-air sources such as leaded paint and canned food (4.4 -6.6 µg/dl).

4) subtracting the non-air contributions from the target geometric mean PbB level; and

5) dividing the remaining allowable contribution to blood lead from air sources by the aggregate blood lead/air lead slopes (4-6 µg/dl per µg/m^3) discussed in Section V.B.

Tables 7-8 and 7-9 present the alternative air lead levels derived from these calculations assuming a goal of protecting 99.5% of the population and GSDs of 1.39 and 1.34 respectively. For purposes of this analysis, no distinction is made between monthly or quarterly averaging times because each air lead level is assumed to be constant. For each possible PbB that could be accepted as the level of concern, different target air lead values arise depending on which blood/air lead slope, which non-air blood lead contribution, and which GSD is ultimately taken. For example, in order to protect 99.5% of the population of children from exceeding a PbB level of 20 µg/dl, and assuming a GSD of 1.34, a non-air blood contribution of 4.4, and a blood lead/air lead slope of 5, an air lead level of 1.0 µg/m^3 would be adequate. At this time, the staff does not attempt to distinguish the validity of the values presented for either of these parameters (i.e., GSD, blood/air lead slope, non-air PbB) and awaits comment on these issues before discussing the margins of safety associated with alternative lead NAAQS. It is clear, however, that unless 25 µg/dl is determined to be an acceptable PbB for an individual child, and the non-air contribution to blood lead is taken as 4.4 µg/dl and the aggregate blood/air lead slope is assumed to be less than 5, all of the air lead alternatives predicted by the aggregate epidemiological model are below the current standard level of

Table 7-8. Air Lead Levels ($\mu g/m^3$, monthly or quarterly average) Required to Protect 99.5% of Children from Exceeding Alternative Maximum Acceptable Blood Lead Levels, According to Aggregate Epidemiological Model, for Different Non-Air Lead Contributions and Blood/Air Lead Slopes; GSD for Population Assumed to be 1.39

	Maximum Individual PbB							
	10 µg/dl		15 µg/dl		20 µg/dl		25 µg/dl	
Blood/Air Lead Slope	Non-Air PbB 4.4	6.6	Non-Air PbB 4.4	6.6	Non-Air PbB 4.4	6.6	Non-Air PbB 4.4	6.6
4	-	-	0.5	-	1.1	0.5	1.6	1.0
5	-	-	0.4	-	0.8	0.4	1.3	0.8
6	-	-	0.3	-	0.7	0.3	1.1	0.7

Table 7-9. Air Lead Levels ($\mu g/m^3$, monthly or quarterly average) Required to Protect 99.5% of Children from Exceeding Alternative Maximum Acceptable Blood Lead Levels, According to Aggregate Epidemiological Model, for Different Non-Air Lead Contributions and Blood/Air Lead Slopes; GSD for Population Assumed to be 1.34

	Maximum Individual PbB							
	10 µg/dl		15 µg/dl		20 µg/dl		25 µg/dl	
Blood/Air Lead Slope	Non-Air PbB 4.4	6.6	Non-Air PbB 4.4	6.6	Non-Air PbB 4.4	6.6	Non-Air PbB 4.4	6.6
4	0.08	-	0.7	0.1	1.25	0.7	1.85	1.3
5	0.06	-	0.5	0.1	1.0	0.6	1.5	1.0
6	0.05	-	0.5	0.08	0.8	0.5	1.2	0.9

1.5 $\mu g/m^3$. It is also clear that according to this model, even an air lead level close to zero would not be fully protective for children from exceeding PbB levels of 10 µg/dl, and assuming a non-air contribution of 6.6 µg/dl, from exceeding 15 µg/dl. These results are compared in Table 7-12 with PbB levels predicted under various air lead levels by the other two models.

In addition, it once again should be noted that none of these air lead levels can fully protect children who are excessively exposed to non-air sources of lead, such as paint chips and heavily contaminated soils and dusts.

c) Predicting Blood Lead Levels Using "Disaggregated" Slopes for Individual Media

Just as mathematical relationships have been derived between blood lead and air lead levels among different populations, various studies have investigated the relationship between blood lead levels in children and concentrations of lead in food, water, soil, and dust to which they are exposed. The CD has applied the most reliable and relevant of these relationships to currently representative concentrations of lead in these individual media in order to estimate proportional inputs to total PbB levels in U.S. children (CD, Section 13.4.3).

Table 7-10 (CD, Table 13-6) presents estimates for the direct and indirect contributions of air lead to 2-year old children's blood lead at different air lead levels and typical background levels of lead in food, water and dust. Calculations and assumptions used in deriving the estimates are summarized in footnotes to the table and are referenced to specific sections of the criteria document.

This disaggregated analysis shares similarities to both approaches presented earlier in this paper that were used to estimate PbB levels under alternative air lead levels. For example, the integrated lead uptake/bio-

TABLE 7-10. CONTRIBUTIONS FROM VARIOUS MEDIA TO BLOOD LEAD LEVELS (μg/dl) OF U.S. CHILDREN (AGE = 2 YEARS): BACKGROUND LEVELS AND INCREMENTAL CONTRIBUTIONS FROM AIR

Source	Air Lead (μg/m³)						
	0	.25	.50	.75	1.0	1.25	1.5
Background-non air							
Food[1]	1.55	1.55	1.55	1.55	1.55	1.55	1.55
Water[2]	.94	.94	.94	.94	.94	.94	.94
Dust[3]	.30	.30	.30	.30	.30	.30	.30
Subtotal	2.79	2.79	2.79	2.79	2.79	2.79	2.79
Background-air							
Food[4]	1.47	1.47	1.47	1.47	1.47	1.47	1.47
Water[5]	.16	.16	.16	.16	.16	.16	.16
Subtotal	1.63	1.63	1.63	1.63	1.63	1.63	1.63
Ingested Dust (with Pb deposited from air)[6]	0.00	1.57	3.09	4.70	6.27	7.84	9.40
Inhaled air[7]	0.00	.50	1.00	1.50	2.00	2.50	3.00
Total	4.42	6.49	8.51	10.62	12.69	14.76	16.82

[1]From Table 7-25, (18.9 - 9.2) μg/day x (0.16 from Ryu et al., 1983) = 1.55 μg/dl.

[2]From Table 7-25, (6.9 - 1.0) μg/day x (0.16 from Ryu et al., 1983) = 0.94 μg/dl. Alternatively, Tables 7-20, 7-21 give a weighted mean concentration of liquids as 0.012 μg/g. 1/7 is atmospheric, leaving 0.01 μg/g (10 μg/l) non-atmospheric. 10 x (0.06 from Pocock et al., 1983) = 0.6 μg/dl.

[3]From Chapter 7, 1/10 dust not atmospheric. Using Angle et al. (1984) low area (Area S) for soil and house dust and their regression equation, we have: (1/10) x (97 μg/g x 0.00681 + 324 μg/g x 0.00718) = 0.30 μg/dl. Alternatively, the consumption from non air would be (1/10) x (97 μg/g soil dust + 324 μg/g house dust) x 0.05 grams ingested of each = 2.1 μg ingested. Using Ryu et al. (1983), 2.1 x 0.16 = 0.34 μg/dl added to blood.

[4]As in 1 above, but using 9.2 instead of (18.9 - 9.2) yields 1.47 μg/dl. Values are derived for component of background Pb in food from past deposition from air onto soil and into other media leading into human food chain (not expected to change much except over long-term).

[5]As in 2 above, but using 1.0 instead of (6.9 - 1.0) yields 0.16 μg/dl. Values are derived for component of background Pb in food from past deposition from air onto soil and into other media leading into human food chain (not expected to change much except over long-term).

[6]The regression equations of Angle et al. (1984) are used, as well as levels of soil dust and house dust in the low area (S) and high area (C) of that study. For example, the increase at 1.0 μg/m³ in air would result in increases in soil as follows:

$$\frac{1.00 - 0.29}{0.86 - 0.29} \times (519 - 97) = 526 \text{ μg/g}$$

Similarly the increase in house dust would be:

$$\frac{1.00 - 0.29}{0.86 - 0.29} \times (625 - 324) = 374 \text{ μg/g}$$

The effect on blood lead would be (526 x 0.00681) + (374 x 0.00718) = 6.27 μg/dl.

[7]Using the 2.0 slope from Angle et al. (1984), i.e., 1.93 rounded up.

Source: CD, Table 13-6.

kinetic model estimated the range of contributions that both atmospheric and non-atmospheric lead make to total exposure, directly and indirectly, via the individual media pathways. The second "aggregate" blood lead/air lead approach relied on mathematical relationships derived from some of the same population studies between blood lead and lead in the environment.

It is of interest to note that after adjusting the estimated PbB in Table 7-10 for children exposed to 1.25 $\mu g/m^3$ air lead to a level that would be expected given the dietary and background lead conditions during 1976-1980 when NHANES II was conducted, the result is roughly comparable to the mean PbB measured by the NHANES II survey for children living in U.S. urban areas which then had an average air level of approximately 1.20 $\mu g/m^3$ (15.6 vs. 16.8 µg/dl) (CD, p. 13-26 to 13-28).

The PbB levels listed under each air lead level in Table 7-10 represent the predicted population mean PbB levels for 2-year olds. Using the equation presented previously in this section, it is possible to estimate, given a geometric mean PbB level and known distribution characteristics of the population, the individual PbB at a specified standard deviation. Table 7-6 for example, indicates that given a geometric mean PbB level between 8.6 and 9.4 µg/dl, 99.5% of the population would have PbB levels below 20 µg/dl (depending on which geometric standard deviation is chosen). Similarly, a population mean PbB of 8.51 for example (predicted under an air lead level of 0.50 $\mu g/m^3$ in Table 7-10), would prevent 99.5% of the population from exceeding a PbB of either 18.1 or 19.8 µg/dl (for GSD's of 1.34 and 1.39, respectively). Table 7-11 lists the maximum individual PbB predicted in 99.5% of the population for each estimate of mean PbB predicted by the criteria document in Table 7-10. These results are presented in Table 7-12 for comparison with those of the other two modeling approaches.

Table 7-11. Maximum Individual Blood Lead Levels for 99.5% of Children Under Different Air Lead Levels, Based on Mean PbB Predictions from CD Disaggregate Model (see Table 7-10) and Assuming Different Geometric Standard Deviations

Air Lead ($\mu g/m^3$)	Predicted Geometric Mean PbB ($\mu g/dl$)	Maximum PbB ($\mu g/dl$)	
		GSD	
		1.34	1.39
0	4.42	9.4	10.3
0.25	6.49	13.8	15.1
0.50	8.51	18.1	19.9
0.75	10.62	22.5	24.8
1.0	12.69	26.9	29.6
1.25	14.76	31.3	34.4
1.50	16.82	35.7	39.2

d) Summary of Predicted PbB Levels under Alternative Air Lead Levels

Table 7-12 presents the various estimates of PbB levels for children (both mean and individual maximum for 99.5% of the population) under different average (monthly or quarterly) air lead levels based on the three modeling approaches discussed in this section and on the assumption that the population GSD is a constant between 1.34 and 1.39. It must be emphasized that for present purposes, each of the air lead levels are considered constant. In reality, if all areas are in attainment with a standard, air lead levels are generally below the standard so these results may be interpreted as conservative. Analyses are underway to better represent actual exposures in the future under alternative lead NAAQS.

The ranges of PbB estimates under each air lead level reflect the differences among the available modeling approaches. Even within the individual approaches, there are ranges of estimates for both estimated mean PbB levels and estimated individual maximum PbB levels among 99.5% of the population. This reflects the uncertainty surrounding many of the

Table 7-12. SUMMARY OF ESTIMATED BLOOD LEAD LEVELS UNDER DIFFERENT AIR LEAD LEVELS USING THREE MODELLING APPROACHES[a]

Model		Air Lead Level ($\mu g/m^3$; monthly or quarterly average) 0.25	0.5	0.75	1.0	1.25	1.5
Integrated Uptake/ Biokinetic[b]	Urban/ Rural:	4.0-4.4 (1.9)	7.9-8.6 (3.7)	12.1-13.3 (5.7)	16.3-18.0 (7.7)	21.0-23.1 (9.9)	24.2-26.6 (11.4)
	Point Source:	5.9-6.5 (2.8)	14.0-15.4 (6.6)	18.9-20.8 (8.9)	23.6-25.9 (11.1)	31.8-35.0 (15.0)	35.8-39.4 (16.9)
Aggregate Model[c]		11.5-18.9 (5.4-8.1)	13.6-22.4 (6.4-9.6)	15.7-25.9 (7.4-11.1)	17.8-29.4 (8.4-12.6)	20.0-32.9 (9.4-14.1)	22.1-36.4 (10.4-15.6)
Criteria Document Disaggregate Model[d]		13.8-15.1 (6.49)	18.1-19.9 (8.51)	22.5-24.8 (10.62)	26.9-29.6 (12.69)	31.3-34.4 (14.76)	35.7-39.2 (16.82)

[a]PbB levels are given in µg/dl and represent the estimated levels (using specified GSDs) that 99.5% of children will not exceed for a given air lead level. Estimated population mean PbB levels are given in parentheses.

[b]Range of PbB levels represent best estimates for individual children (2 years old) living in either general urban/rural areas or within 2-5 km of a lead point source and reflect range of GSDs used (1.34-1.39) to convert population mean PbB levels into 99.5% maximum individual levels.

[c]Range of PbB levels reflects range of possible values for different parameters: Blood/air lead slope (4-6 µg/dl per $\mu g/m^3$); non-air PbB contribution (4.4-6.6 µg/dl); GSD (1.34 - 1.39).

[d]Range of PbB levels (for 2 year old children) reflects range of GSDs used (1.34 - 1.39) to convert population mean PbB levels into 99.5% maximum individual levels.

parameters used in the separate models, as well as actual variability in these parameters. For example, ranges of average absorption rates, hours spent outdoors, and soil and dust concentrations were necessary in the integrated uptake/biokinetic model to capture the physiological and behavioral variability among children and significant variability and uncertainty surrounding the relationship between air lead and soil/dust lead levels. In addition, the future impacts of the recent revisions to EPA's lead-in-gasoline phasedown schedule on atmospheric lead contributions to dietary lead consumption were necessary to project under alternative air lead levels. As discussed, the PbB estimates that are presented for the integrated uptake/biokinetic model for children living in general urban/rural areas and near point sources are the lower bound estimates from this model that are considered by the staff to be best estimates given the available data and the necessary assumptions used in the model. (Individual PbB levels that would not be exceeded for 99.5% of the population given different population mean PbB levels were calculated for the integrated uptake/biokinetic model using the same procedure (and the same GSD values of 1.34 to 1.39) presented previously in this section). Both epidemiological approaches, the aggregate and disaggregate models, rely on estimates of blood lead/air lead slopes, non-air PbB contributions, and GSDs, all of which contain ranges of interpretations. As in the integrated uptake/biokinetic model, these epidemiological models attempt to account for the contribution of air lead via all exposure pathways and to adjust non-air PbB contributions according to recent and future trends in various sources (e.g., canned food, paint lead).

For each air lead level, the protection predicted by the three models is comparable. For example, the integrated lead uptake/biokinetic model estimates that, assuming a GSD between 1.34 and 1.39, an air lead level of 0.75 $\mu g/m^3$ would result in PbB levels no higher than 20.8 µg/dl among

2-year old children without excessive exposures to non-atmospheric lead (e.g., paint chips). Similarly, using the most conservative parameters in the "aggregated" blood/air lead slope model (i.e., blood/air lead slope of 6, non-air lead of 6.6 µg/dl, GSD of 1.34), a 0.75 µg/m^3 air lead level would protect 99.5% of children from exceeing 25.9 µg/dl, while using intermediately conservative parameters (i.e., blood/air lead slope of 5, non-air lead of 4.4, GSD of 1.34) results in a maximum PbB of 19.0 µg/dl. In comparison, the criteria document's estimates yield maximum individual PbB levels (for 99.5% of children) between 22.5 and 24.8 µg/dl for an air lead level of 0.75 µg/m^3.

It can be concluded that unless the least conservative parameter values are assumed in the aggregate epidemiological model (i.e., aggregate blood/air slope of 4, non-air PbB contribution of 4.4 µg/dl; see Table 7-8 and 7-9), the models predict that if the current lead NAAQS level was just met so that the average air lead concentration was a constant 1.5 µg/m^3, some fraction within the 99.5% of children would not be protected from exceeding 25 µg/dl, assuming a constant GSD between 1.34 and 1.39 for the entire distribution of blood lead levels. In fact, if 20 µg/dl is determined to be the maximum acceptable PbB for an individual child, regardless of which modeling approach is accepted, an air lead level no higher than 1.25 µg/m^3 would be required to protect 99.5% of the population, if that air lead level was constant and assuming the same "constant GSD" range.

Should only one modeling approach be accepted as providing reliable estimates, these predictions would be revised accordingly. For example, if only the criteria document's disaggregate model is considered, assuming a constant GSD of 1.34 - 1.39, an air lead level no higher than 0.75 µg/m^3 would be required to protect 99.5% of children from exceeding 25 µg/dl, and no higher than 0.5 µg/m^3 in order to protect against PbB levels above 20 µg/dl. Roughly similar predictions for air lead levels of 0.5 to 0.75

not used to derive inhalation slopes (i.e., Zielhuis et al., 1979; Brunekreef et al., 1981, 1983) and b) aggregate analyses that include both direct (inhalation) and indirect (via soil, dust, etc.) air lead contributions in the key "inhalation slope" studies cited in the criteria document. Although far from conclusive, these studies and analyses suggest a range of possible blood lead/air lead aggregate slopes in the range of 2 to 10 for young, moderately exposed children with the most reliable slopes falling between 3 and 5 (CD, p. 11-104).

Because the blood/air lead relationships were derived from studies which measured air lead concentrations averaged over periods ranging between one month and one year (See Table 5-3), and because long-term averages (e.g., annual) may not reflect short-term (e.g., monthly) peak averages, it is possible that applying these slopes to estimate the impacts of different air lead levels would yield overestimates of PbB levels if the air lead standard considered is a one-month average (See Section VII.A). Any overestimation, however, is likely to be small given the long-term pattern of lead accumulation in the environmental media to which children are predominantly exposed (i.e., soils, dust, food) and the resulting modulation by the environment of potential short-term peak exposure levels. Therefore, it can be assumed that these slopes are applicable in estimating PbB levels associated with different monthly, as well as calendar quarterly, average air lead levels.

It is important to add, as discussed in Appendix A, that some of the absorbed lead that accumulates in the skeleton deposits in the spongy trabecular bones (e.g., rib, vertebrae) where it may be resorbed into the blood stream. Because air-blood slopes are derived from epidemiological studies in which exposure to air lead was assessed over days, weeks, or

months, an additional factor must be allowed for possible re-entry of lead into the blood transferred from bone or other long-term storage (Chamberlain, 1983). Based on isotopic ratio and radiolabel tracer studies on adults, Chamberlain et al. (1978) estimated this factor to be 1.3, although it is likely to be higher in children because of the rapid growth and high rate of turnover in their skeletal systems. Applying this factor to the blood lead/air lead aggregate slope range discussed above (3-5 $\mu g/m^3$) yields a range of about 4 to 6. Use of these slopes to evaluate alternative air lead levels is discussed in Section VII.C.2 along with the two other modeling approaches introduced in this section.

VI. CRITICAL ELEMENTS IN THE REVIEW OF THE PRIMARY STANDARD

A. Mechanisms of Toxicity

The toxicological impact of environmental lead can either be the cumulative product of continuous low-level exposure, or of single or repeated acute exposures. Adverse effects are due essentially to the mobile fraction of absorbed lead within the body. Thus, a major determinant of toxicity is the distribution of lead among binding proteins and compartments that contain susceptible enzyme systems or other target sites (Raghavan et al., 1981; Silbergeld, 1983). The effects of lead on subcellular structures and processes result in biochemical derangements common to and affecting, many tissues and organ systems. These biochemical alterations can be linked to the diverse types of lead-based functional disruptions of organ systems that operate in a coordinated, interdependent way.

The major molecular basis underlying lead's toxicity in various human organ systems and tissues is believed to be its ability as a metallic cation to bind with specific biochemical ligands, such as sulfhydryl, amino, and carboxyl groups, present in biomolecular substances crucial to normal physiological functions (Moore et al., 1980). This binding interferes with physiological processes through the following mechanisms:

1. Inhibition of enzyme activity

Lead inhibits at least two enzymes in the heme biosynthetic pathway, delta-aminolevulinate dehydrase (ALA-D) and ferrochelatase (Chisolm, 1981), as well as enzymes and cofactors involved in maintaining the structural integrity of red blood cell and protecting them against oxidation -- Na^+, K^+-activated adenosine triphosphatase (Na^+, K^+ - ATPase), pyrimidine-5'-nucleotidase (Py-5-N), superoxide dismutase, and glutathione (Hasan et al., 1967; Secchi et al., 1973; Raghavan et al., 1981; Paglia et al., 1975;

Valentine et al., 1976; Levander et al., 1980; Gelman et al., 1978). The synthesis of tetrahydrobiopterin (a cofactor in brain neurochemistry; see below) and the activity of brain adenyl cyclase (associated with neurochemical receptors) are also inhibited by lead in vitro and in vivo at low concentrations (Purdy et al., 1981; Sauerhoff and Michaelson, 1973; Nathanson and Bloom, 1975). It is important to note that although catalytic activity of these susceptible enzymes may be diminished across a wide range of lead exposure down to very low levels, sometimes without an observable threshold, the physiological or functional consequences of such inhibitions depend on the reserve capacity of the enzymes, the health and nutritional status of the individual, and subsequent exposures to lead and other environmental stress factors. These issues as well as dose-response relationships are addressed in Section VII.C. and Appendix D.

2. Altered cellular energy metabolism and ion transport

Energy metabolism occupies a central position in all biologic processes and substantial interference with one or more steps in cellular energetics can have immediate and severe effects on the usual functional outputs of a cell, tissue, or organ. Mitochondrial structure and a variety of its functions in energy metabolism are very sensitive to lead, particularly in rapidly developing tissues in the young (Holtzman and Shen Hsu, 1976; Bull et al., 1979; Holtzman et al., 1978). Effects including uncoupled oxidative phosphorylation (Goyer and Moore, 1974), inhibited substrate oxidation (Bull et al., 1975), and changes in mitochondrial membrane permeability and transport of ions, especially calcium (Ca^{++}) (Holtzman et al. 1977; Bull, 1980), occur at levels as low as 10 micromoles (μ moles) in intact cellular systems. Because of the pervasive role calcium plays in regulating cellular

function, a wide range of linkages between lead's impacts on Ca^{++} and energy metabolism, and altered functional activity and developmental delays in the kidney, liver, brain and smooth muscle have been proposed (Bull et al., 1975, 1979; Bull, 1980; McCauley et al., 1979; Silbergeld, 1983; Pounds et al., 1982) and are discussed below.

3. Competition with ions for essential binding sites and altered neurochemistry

Lead absorption, distribution, and retention is known to vary depending on dietary intake of calcium, iron, copper, and zinc, as well as other nutrients (e.g., protein, fat, vitamin D) (Mahaffey and Michaelson, 1980). In addition, increased susceptibility to the toxic effects of lead on heme synthesis and on neurological function has been associated with deficiencies in calcium, iron, copper, and zinc (Mahaffey-Six and Goyer, 1970, 1972; Klauder and Petering, 1977; Cerklewski and Forbes, 1976). These metabolic interactions can be expected among elements that share common chemical properties and compete for common metabolic binding sites, such as the mucosal proteins responsible for absorption and transport across the intestinal wall, and on specific intracellular enzymes.

Lead-induced alteration of cellular calcium homeostasis, at levels as low as 10 μ moles, either by direct competition at receptor binding sites (Barton et al., 1978; Ong and Lee, 1980; Habermann et al., 1983) or indirectly by reducing energy production and impairing mitochondrial and cell membrane transport "pumps" (Pounds et al., 1982a) could disturb multiple cell functions of different tissues that depend upon calcium as a messenger of hormonal and electrical stimuli or as a modulator of cyclic nucleotide metabolism (Rasmussen and Waisman, 1983; Rosen, 1983). For example, low levels of lead inhibit the calcium-mediated regulation of pyruvate kinase activity essential to hepatic glycolysis (Pounds et al., 1982b), and some

calcium-dependent neurotransmission that regulates the propagation of nerve impulses in the brain (Silbergeld et al., 1977; Silbergeld and Adler, 1978).

Besides competition with calcium at synaptic binding sites, other mechanisms by which lead at low doses may alter the functioning of neurotransmitter pathways (see CD, Table 12-7) include: 1) inhibition in the brain of the enzymes (Na,K)-ATPase which helps maintain the ion distribution about the cellular membrane required for neuronal activity (Vallee and Ulmer, 1972), and adenyl cyclase, which regulates cyclic AMP metabolism and synaptic transmission (Nathanson and Bloom, 1975); 2) inhibition of sodium-dependent neurotransmitter uptake (Silbergeld and Goldberg, 1975); 3) impairment of cerebellar and cerebral energy metabolism (Holtzman et al., 1978; Bull et al., 1979); 4) inhibition of tetrahydrobiopterin, which helps control the synthesis of the neurotransmitters dopamine and norepinephrine (Purdy et al., 1981); and 5) inhibition of heme synthesis resulting in a) an accumulation of ALA in the brain that disrupts the synthesis and function of the neurotransmitter GABA (Sassa et al., 1979; Silbergeld and Lamon, 1980), and b) reduced heme levels in the liver that appear to alter the activity in the brain of the amino acid, tryptophan, and the transmitter to which it contributes, serotonin (Litman and Correia, 1983).

In addition to the above mechanisms, lead may exert its toxicity by its ability to rapidly cleave messenger RNA (at concentrations in solution as low as 0.001 millimoles) and disrupt protein synthesis (Farkas, 1975; Brown et al., 1983).

It is uncertain whether a common underlying mechanism is involved in the diverse functional impairments produced by lead. It does appear however, that lead affects biological systems directly rather than through metabolic transformation, and that there may be no biological threshold for its

effects at subcellular or cellular sites of action. External exposure levels or internal circulating levels (blood lead concentrations) of lead sufficient to achieve subcellular or cellular concentrations associated with the biochemical changes described above remain to be defined.

B. Effects of Concern

Lead may produce physiological, and ultimately, pathological effects in a variety of tissue and organ systems across a broad range of exposure levels. Evidence for such effects is drawn from in vitro, animal toxicological, and human clinical and epidemiological studies. Based on these data, summarized in the CD (Chapter 12), effects in the following areas are of primary interest:

1) heme biosynthesis and related functions
2) neurobehavioral function
3) cardiovascular function
4) kidney function
5) reproduction and development
6) possible carcinogenesis/mutagenesis
7) immunological function
8) liver, gastrointestinal, and endocrine function

The major implications of the available literature related to each of these effect areas are discussed in Appendix D and summarized in Section VII.C. as they relate to assessing the risks associated with alternative lead NAAQS.

C. Sensitive Population Groups

Two populations, pre-school age children ($\leq$ 6 years old) and pregnant women, are defined in the CD as particularly sensitive to lead. Several factors predispose young children to lead-related risks: 1) greater lead

content of their diets which include large portions of processed foods, canned milk, and drinking water; 2) normal mouthing behavior (e.g., finger licking and immature dietary habits) which can transfer lead-contaminated soil and dust from their hands into the gastrointestinal (GI) tract; 3) greater lead intake into the respiratory and GI tracts on a body weight basis; 4) greater lead absorption and retention rates; 5) greater prevalence of nutrient deficiencies which enhance lead GI absorption rates and toxicological effects; 6) relatively greater proportion of their lead body burden in soft tissues and other labile pools rather than in slow exchange pools (e.g., dense bone matrix) as compared to adults; 7) a less developed blood-brain barrier that can allow greater entry of lead into the brain; and 8) an inherently greater physiological sensitivity of developing tissues and organs, as indicated by lower thresholds, and greater severity for lead-induced effects in the hematological and neurological systems.

In addition, dietary and metabolic imbalances, and periods of physiological stress, not unusual in young children, can cause variations in the level of toxicologically active lead through bone-lead mobilization and changes in lead absorption rates (Chisolm and Harrison, 1956; Rosen and Markowitz, 1980; Araki and Ushio, 1982).

Physiological sensitivity to lead may be at a maximum during fetal development when the central nervous system is undergoing its most pronounced growth. Persistent effects on neurological function have been observed following *in utero* lead exposure in experimental animals and have been suggested by some preliminary results from human longitudinal studies. The pregnant woman is considered sensitive insofar as she is the exposure vehicle for her unborn child, since lead is transferred across the placenta. However, there is some evidence that indicates a greater risk of maternal

delivery complications at relatively low PbB levels as well (Appendix D.5).

There were about 23.3 million pre-schoolage children in the U.S. in 1982 (U.S. Bureau of the Census, 1982); some 14.2 million lived in urban areas and approximately 240,000 live near point sources where lead exposure is generally higher (CD, Table 13-10; Battye, 1985c). The CD estimates that about 4.4 million children between ages 3 and 5 years are particularly sensitive to lead because of iron deficiency (CD, p. 13-47). The total number of women of child-bearing age (between 15 and 44 years) is estimated to be about 54 million, with about 33 million living in urban areas (CD, Table 13-10); of these, approximately 7 percent are pregnant at any given time (CD, p. 13-47). Levels of risk are not uniform throughout these populations but are likely to be distributed according to individual exposure conditions, behavioral patterns, and physiological sensitivity to lead.

VII. FACTORS TO BE CONSIDERED IN SELECTING A PRIMARY STANDARD FOR LEAD

This section, drawing upon the previous evaluation of scientific information from the criteria document, outlines the key factors that should be considered by the Administrator in designating an appropriate averaging time and sampling frequency criteria and in establishing the level of the lead primary standard. Preliminary staff conclusions and recommendations regarding the most appropriate policy options in each of these areas are presented.

A. Averaging Time

To be protective of human health, the averaging period for the lead standard should be chosen such that variations of exposure that could result in adverse effects do not occur unless the standard is exceeded. The current averaging time for the lead primary NAAQS is a calendar quarter (3 months). When the lead standard was proposed in 1977, the averaging time for the primary lead NAAQS was specified as a calendar month which is somewhat shorter than the approximately 60 days before steady state PbB levels in adults adjust to changes in air lead concentration (Rabinowitz et al., 1973; Griffin et al., 1975). A month averaging time was considered appropriate because of the greater risk of exposure of young children (42 FR 63076). Subsequently, EPA promulgated the current NAAQS with a calendar quarter averaging time based on the conclusion that an air level of 1.5 $\mu g/m^3$ as a ceiling would be safe for indefinite exposure of young children and that the slightly greater possibility of elevated air lead levels within the quarterly period was not significant for health (43 FR 46246). The following assessment of additional health and exposure information available since 1978 and other evidence suggests, however, that a shorter averaging time than a calendar quarter may be more appropriate.

1. Equilibration Period for Blood Lead in Children

No direct measurements have been made on this parameter, although the higher metabolic rates in children would be expected to produce a more rapid turnover rate of red blood cells, along with lead, in their blood compared to adults (Chamberlain et al., 1978). Duggan (1983), based on limited lead balance data in infants, has preliminarily estimated a considerably shorter half-life of blood lead in children (< 1 week) than in adults (18-28 days; Griffin et al., 1975; Rabinowitz et al., 1976; Chamberlain et al., 1978). It is of interest to note that regression analyses of NHANES II and national gasoline consumption data found that average blood lead levels in children were most closely correlated with gasoline lead use when a month lag was introduced (EPA, 1985c).

Perhaps a more important consideration is the time it takes for the very small fraction of "active" lead to be transported in plasma and extracellular fluid to the various target body organs and tissues. It appears that lead levels in plasma rise with levels in whole blood (PbB) in adults (Everson and Patterson, 1980; DeSilva, 1981; Cavalleri et al., 1978) and that lead is removed from plasma with a half-life of less than one hour; indeed, ingested lead appears within urine in less than an hour (Chamberlain et al., 1978). These findings suggest that the rate by which lead is transferred to soft tissues via the plasma is fast enough that excess lead entering the blood stream would be rapidly transported via plasma to tissues. In addition, as illustrated in Figure 10-2 of the CD (p. 10-18; Manton and Cook, 1984), the relationship between plasma lead and blood lead is curvilinear upwards suggesting that transient shifts in blood lead would result in plasma values greater than that predicted on the basis of equilibrated percentages at lower PbB values. This curvilinearity becomes manifest in adult subjects

at 50-60 µg/dl (DeSilva, 1981; Manton and Cook, 1984), but may well apply at relatively lower PbB levels in children.

Further support comes from data on experimental animals whose levels of lead in brain, kidney, and femur followed more of a direct proportionality with the level of dosing than with blood lead, which may relate to the fact that plasma lead rises proportionally faster than whole blood lead (Azar et al., 1973; Grant et al., 1980).

Based on these data, it appears reasonable to assume that increased lead exposure may produce increases in steady state PbB levels in children sooner than the 60 days observed in adults, and that such changes may not reflect those occurring in the levels of toxicologically active, or mobile, lead throughout the body, particularly if exposure is in the form of intermittent pulses.

2. Health Impacts Associated with Short-term Peaks in Lead Concentrations

Most animal and human studies of lead toxicity use measures of lead exposure which reflect accumulations over time (such as blood and tooth lead) and thus do not readily allow effects of different exposure patterns to be distinguished. It is generally accepted, however, that acute exposures to very high lead levels can result in immediate changes in blood lead and overt toxicity.

Little information is available on the effects of acute exposures to lower levels of lead that are relevant to ambient air conditions although there may be some cause for concern. For example, consistent with the fact that lead is rapidly transported via blood plasma into target tissues such as bone marrow, single experimental lead exposures were followed by a rapid (<2 weeks) alteration in the heme production cycle, as indicated by

significantly elevated EP in adult men and women (Stuik, 1974; Cools et al., 1976).

Despite limited quantitative health effects data on humans, it appears appropriate in deciding whether to retain the calendar quarter averaging time to consider the extent of short-term peaks in air lead levels that can be anticipated as a result of the implementation of such a standard. The risks of shorter term exposures to lead elevated above a quarterly-averaged standard that might go undetected were considered in the 1978 standard decision to be minimized because 1) based on the ambient data available at that time, the possibilities for significant, sustained excursions were considered small, and 2) it was determined that direct inhalation of air lead is a relatively small component of total airborne lead exposure (43 FR 46246). More recent data on short-term air lead levels are considered below.

Air quality analyses were performed on all available SAROAD data (10,712 monitor-quarters) collected from stationary source, microscale (for mobile source emissions), and neighborhood scale monitors between 1980 and 1984 (Battye, 1984). Maximum monthly average lead concentrations were higher than quarterly averages by an average factor of 1.35. Monthly-to-quarterly average concentration ratios for point source monitors were higher than roadside and neighborhood monitors with peak ratios for point source sites as high as 2.86 (See Table 7-1). These ratios were largely independent of average lead concentration. These results suggest that in order to protect against maximum monthly average concentrations of 1.5 $\mu g/m^3$, for example, a quarterly average of approximately 1.1 $\mu g/m^3$ would be required, while a quarterly average of 1.5 $\mu g/m^3$ would allow monthly maximum averages as high as 2.1 $\mu g/m^3$. Daily maximum levels were greater than quarterly and monthly averages by an average factor of 2.08 and 1.47, respectively. Daily to quarterly and daily to monthly ratios near point sources were 2.59 and 1.72, respectively; at

TABLE 7-1. MONTHLY-TO-QUARTERLY AVERAGE CONCENTRATION RATIOS FOR DIFFERENT SITES

Distribution property	All monitors	Point source monitors	Microscale roadside monitors	Neighborhood scale roadside monitors
Mean ratio	1.35	1.40	1.27	1.27
Median	1.28	1.31	1.23	1.25
Distribution peak	1.20	1.25	1.20	1.20
Upper limits (one tailed)				
80 percent	1.50	1.60	1.30	1.39
90 percent	1.68	1.82	1.56	1.50
95 percent	1.89	2.09	1.79	1.67
98 percent	2.24	2.43	1.80	1.89
99 percent	2.62	2.86	2.00	2.09

Source: Battye (1984)

microscale and neighborhood scale sites these ratios were 2.08 to 2.15, and 1.57 to 1.61, respectively.

The magnitude of such excursions in air lead levels over a given quarterly average standard are clearly of concern, especially if they are repeated. The health significance of these variations, however, is difficult to determine at present.

In summary, although the frequency and health risks associated with repeated, short-term increases in children's lead exposure above that allowed under any given standard is difficult to quantify at this time, there does appear to be some cause for concern given that: 1) lead accumulates in the body and is only slowly removed, therefore repeated exposures to small amounts over many months may produce elevated PbB levels (CDC, 1985); 2) the mean-life of lead in blood is approximately 30 days and the toxicologically active fraction of blood lead appears to respond quickly to changes in exposure; and 3) based on limited studies, short-term increases to moderate levels of lead exposure may result in significant interference in heme biosynthesis. Effects on other physiological processes associated with similar short-term exposures remain to be studied.

Based on the above discussion, the staff recommends that consideration be given to a monthly average since it would be more protective of children's health than the current quarterly standard, especially around point sources where emissions may be more sporadic. Guidance is requested from CASAC on whether the added protection provided by a change to a monthly standard would warrant a revision of the current quarterly averaging period. The staff also requests comment on whether the available information suggests the need for an averaging time less than a month.

Given the normal operation of the one in six day lead sampling schedule, the number of samples that are collected in the course of a month would

not provide a statistically valid estimate of the actual air quality for the period (Thrall et al., 1984). Consequently, should a monthly average lead NAAQS be chosen, it would be necessary to increase the air lead sampling from one in six days, especially during periods and in areas of maximum concentration. Analyses are underway to determine the most appropriate sampling schedules under a monthly standard.

B. Form of the Standard

The staff recommends that the primary lead NAAQS be stated in a statistical form rather than the current deterministic form. Under the current standard, the maximum arithmetic mean average over a calendar quarter is not to exceed 1.5 $\mu g/m^3$.

The statistical form can offer a more stable target for control programs and, with reasonably complete data, is less sensitive to truly unusual meteorological conditions than is the deterministic form. In general, monthly or quarterly mean concentrations of lead will vary from one month or quarter to the next, even if emissions remain constant, due to the random nature of meteorological conditions that affect the dispersion of lead particles in the atmosphere. Thus, under a deterministic form, compliance with the standard, and consequently emission control requirements, may be determined on the basis of a month or quarter with unusually adverse weather conditions. The general limitations of the deterministic form are discussed more fully elsewhere (Biller and Feagans, 1981). Recognition of these limitations has most recently led EPA to propose statistical forms for the particulate matter standards.

Conceptually, assuming either a monthly or quarterly averaging time, a simple approach would be to express the statistical form as an expected maximum monthly or quarterly arithmetic mean determined by averaging the annual maximum monthly or quarterly arithmetic averages over a 3-year

period. Specific adjustments to the computations necessary for analyzing lead data may be required to account for possible changes in the frequency of sampling.

An alternative approach would be to directly recognize the statistical variability associated with the estimated maximum monthly or quarterly average and develop a tolerance interval so that a site would not be classified as in attainment unless the estimated exceedance rate is below the standard level by more than this tolerance interval. Similarly, the tolerance interval approach might also be applied in the other direction, so that a site would not be considered as non-attainment unless the maximum monthly or quarterly average plus the tolerance limit is greater than the standard level. The magnitude of this tolerance interval could be determined by developing a statistical model to account for the underlying variability of the data and could incorporate factors such as autocorrelation.

The Agency has solicited comments on this general type of statistical standard in the proposal for the particulate matter NAAQS issued on March 20, 1984 (49 FR 10408). These comments will be examined by staff as it assesses these alternative statistical forms.

Because the level of protection afforded by a standard varies significantly with the averaging period, form, and sampling frequency, these interactions must be explicitly considered in setting the standard level. Rather than attempting to address these variables simultaneously, it may be easier to first select an acceptable standard level under one set of conditions, and then adjust the level so as to provide roughly equivalent protection under alternative averaging periods, forms, and sampling schedules.

For purposes of this paper, alternative air lead levels presented later will assume a constant average (regardless of averaging period), deterministic form, with 1 in 6 day sampling. Analyses are underway to better characterize the distribution of quarterly or monthly ambient lead concentrations and to examine whether adjustments would be necessary under the alternative statistical form approaches, with possibly more frequent sampling, to provide equivalent protection.

C. Level of the Standard

To assess the degree of health protection that would be afforded by alternative lead NAAQS, it is necessary to predict the blood lead (PbB) levels associated with various concentrations of air lead for the sensitive populations and to determine the toxicological consequences associated with different PbB levels among young children.

1. Summary of Health Risks Associated with Different PbB Levels

Table 7-2 summarizes the lowest observed effect levels (in terms of PbB levels) that the CD concludes to be thus far credibly associated with "unacceptable risk" for particular health effects of concern occurring among at least some children (CD, p. 13-32). Many other individuals may not experience the stated effect until distinctly higher PbB levels are reached (CD, p. 13-32), or conversely respond to even lower PbB levels due to wide ranges of individual biological susceptibility, variations in nutritional status, and other factors.

It is clear, as discussed in Section VI and in Appendix D, that lead affects many different organ systems and biochemical/physiological processes across a wide range of exposure levels. These effects range from biochemical changes in energy metabolism and synaptic neurotransmission, with no apparent threshold on a subcellular molecular level, as well as alterations in blood

Table 7-2. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN CHILDREN

Lowest Observed Effect Level (PbB)	Heme Synthesis and Hematological Effects	Neurological Effects	Renal System Effects	Gastrointestinal Effects
80-100 µg/dl		Encephalopathic signs and symptoms	Chronic nephropathy (aminoaciduria, etc.)	Colic, other overt gastrointestinal symptoms
70 µg/dl	Frank anemia			
60 µg/dl		Peripheral neuropathies		
50 µg/dl		?		
40 µg/dl	Reduced hemoglobin synthesis	CNS cognitive effects (IQ deficits, etc.)		
	Elevated coproporphyrin	Peripheral nerve dysfunction (slowed NCV's)		
	Increased urinary ALA			
30 µg/dl			Vitamin D metabolism interference	
15 µg/dl	Erythrocyte protoporphyin elevation	Altered CNS electrophysiological responses		
10 µg/dl	ALA-D inhibition		?	
	Py-5-N activity inhibition	?		
	?			

Abbreviations: PbB = blood lead concentrations; Py-5-N = pyrimidine-5'-nucleotidase.

Source: CD, Table 13-8.

enzyme activity detectable at PbB levels at or below 10-15 µg/dl (e.g., ALA-D, pyrimidine-5-nucleotidase) (CD, Table 12-9; Angle et al., 1982) to severe, irreversible central nervous system damage manifested by mental retardation, encephalopathy (degenerative brain disease), and possibly, death at PbB levels starting between 80 and 100 µg/dl (CD, p. 12-62). Other overt neurological damage such as peripheral neuropathies have been observed at PbB levels as low as 40-60 µg/dl (CD, p. 12-95). Clearly adverse effects occur in other organ systems at these elevated levels (60-100 µg/dl) including chronic nephropathy, gastrointestinal symptoms, and frank anemia, representing an extreme manisfestation of reduced hemoglobin synthesis which has been observed at PbB levels as low as 40 µg/dl (CD, p. 12-47).

Less severe but important signs of impairment in normal physiological function are evident at similar and lower exposure levels than those associated with overt intoxication. The nervous system is a critical target for low-level lead effects, which are summarized in Table 7-3. Indications of sensory and peripheral motor nerve dysfunction, such-as slowed nerve conduction velocities (NCV), have been observed in adults with PbB levels as low as 30-50 µg/dl (CD, p. 12-61). Significant delays in neurological development and persistent alterations in neurobehavior have been found in young animals exposed to relatively low levels of lead (See Appendix D.2). Determining the subtle interactive effects of low level lead exposure on children's neuropsychological development in relation to social (especially caregiving), genetic, nutritional, and other influential variables over time and controlling for experimental and analytical biases has proved to be difficult, however, and has generated contrasting interpretations. Problems encountered in the conduct and interpretation of childhood lead studies are discussed in the criteria document and in Appendix D.2.

Table 7-3. SUMMARY OF LEAD'S EFFECTS ON THE NERVOUS SYSTEM

Effect	Exposure	Reference
Biochemical		
In vitro impairment of: synthesis of tetrahydrobiopterin (neurotransmitter cofactor) in rat brain; adenyl cyclase and Na,K-ATPase activity in rat brain homogenates; energy metabolism in rat brain mitochondria	0.1 - 5 μM lead solution	Purdy et al., 1981; Godard and Robinson, 1976; Taylor et al., 1978; Gmerek et al., 1981; Holtzman et al., 1978
Delayed development of rat brain energy metabolism and respiration (*in vivo*)	0.02% lead salt in drinking water	McCauley et al., 1979; Bull et al., 1979, Bull, 1983
Altered synthesis, release, and/or uptake of several neurotransmitters *in vivo* (dopamine, norepinephrine, serotonin, GABA)	0.004 - 2.0% lead salt in drinking water	Govoni et al., 1978, 1984; Memo et al., 1980a,b, 1981; Lucchi et al., 1981; Silbergeld et al., 1979; 1980a; Dubas et al., 1978; Goldman et al., 1980; Litman and Correia, 1983
Morphological and Functional Development		
Impaired myelin, glial cell development in rat brain	0.1 - 4.0% lead in diet	Reyners et al., 1979; Windebank et al., 1980; Stephens and Gerber, 1981
Delayed synaptogenesis and neuronal development in young, rat brain	0.2 - 4.0% lead in diet	McCauley et al., 1979, 1982; Petit and LeBoutillier, 1979; Averill and Needleman, 1980; Campbell et al., 1982; Alfano and Petit, 1982; Petit et al., 1983; Costa and Fox, 1983
Delayed development of exploratory and locomotor activity; persistent learning and behavior deficits in animals exposed *in utero* or since birth	>0.005% lead in diet	Brown, 1975; Overmann, 1977; Overmann et al., 1981; Winneke et al., 1977; Hastings et al., 1979; Bull et al., 1979, 1983; McCauley et al., 1979, 1982; Bushnell and Bowman, 1979; Rice and Willes, 1979; Crofton et al., 1980; Jason and Kellogg, 1981; Gross-Selbeck and Gross-Selbeck, 1981; Petit et al., 1983; Levin and Bowman, 1983
Conflicting preliminary findings; possible small deficits in early sensorimotor and mental development in infants	<15 μg/dl PbB	Dietrich et al., 1984; Bellinger et al., 1984
Electrophysiological		
Altered electrical activity of isolated neurons (*in vitro*)	>1 μm lead solution >1% lead in drinking water	Fox and Sillman, 1979; Sillman et al. 1982; Taylor et al., 1978; Palmer et al., 1981; Olson et al., 1981
Altered visual and electrical evoked responses, visual acuity, and spatial resolution in young rats, monkeys	0.2% lead in diet	Bushnell et al., 1977; Fox et al., 1977, 1979, 1982; Winneke, 1980; Cooper et al., 1980; Impelman et al., 1982
Subtle, persistent alterations of brain electrical activity (EEG patterns, brainstem and auditory evoked potentials) in young children	No apparent threshold down to 15-30 μg/dl PbB and possibly below	Otto et al., 1981, 1982, 1984; Beningnus et al., 1981; Burchfiel et al., 1980
Depressed conduction velocities in sensory and motor nerves of adults and children	>30-50 μg/dl PbB	Seppalainen et al., 1975; Araki and Honma, 1976; Melgaard et al., 1976; Ashby, 1980; Bordo et al., 1982; Johnson et al., 1980; Seppalainen and Hernberg, 1980, 1982; Singer et al., 1983; Triebig and Nottbohm, 1983; Feldman et al., 1977

Table 7-3. SUMMARY OF LEAD'S EFFECTS ON THE NERVOUS SYSTEM (CONTINUED)

Effect	Exposure	Reference
Motor Nerve Function		
Small deficits in perceptual-motor integration and fine motor coordination in young children	50-60 µg/dl PbB, possibly as low as 30-40 µg/dl or lower	de la Burde and Choate, 1972, 1975; Landrigan et al., 1975; McBride et al., 1982; Needleman et al., 1979; 1984; Winneke et al., 1982a, 1983
Conflicting results at similar exposure levels		Rummo, 1974; Rummo et al.,1979; Perino and Ernhart, 1974; Kotok et al., 1977; Winneke et al., 1984
Behavioral Disorders		
Symptoms associated with hyperactivity in children	Effect level not adequately defined	Baloh et al., 1975; Gittleman and Eskenazi, 1983; David et al., 1976, 1983
Attention (reaction time) deficits and distractability in young children	>30-50 µg/dl PbB and possibly as low as 15-20 µg/dl	Winneke et al., 1983, 1984; Needleman et al., 1979, 1984; Yule and Landsdown, 1983; Hunter et al., 1983
Auditory and Language Processing		
Deficits in motor speech behavior, language comprehension, formulation behaviors, auditory processing	>30-50 µg/dl PbB	de la Burde and Choate, 1975; Needleman et al., 1979, 1984
Cognitive Function		
Small deficits in IQ scores on verbal performance, visual-motor perception, short-term memory, general intelligence among young children	>30-50 µg/dl PbB; [possibly as low as 15-30 µg/dl in socially disadvantaged children]	de la Burde and Choate, 1972, 1975; Rummo, 1974; Rummo et al., 1979; Perino and Ernhart, 1974; Ernhart et al., 1981; Ernhart, 1983, 1984; Needleman et al., 1979, 1984; [Smith et al., 1983; Harvey et al., 1983, 1984; Yule et al., 1984; Winneke et al., 1983, 1984]
Conflicting results at similar exposure levels		Yule et al., 1983; Yule and Landsdown, 1983, Winneke et al., 1983, 1984
Overt Toxicity		
Peripheral nerve damage among chronically exposed adults and children	>40 µg/dl	Lillis et al., 1977; Spivey et al., 1979, Haenninen et al., 1979; Zimmerman-Tansella et al., 1983; Erenberg et al., 1974
Encephalopathy, mental retardation, possibly death among children	>80-100 µg/dl	Gant et al., 1938; Smith et al., 1938; Bradley et al., 1956; Chisolm and Harrison, 1956; Chisolm, 1965; Bradley and Baumgartner, 1958; Cumings, 1959; Rummo et al., 1979

The criteria document concludes that:

> "none of the available studies on the subject, individually, can be said to prove conclusively that significant cognitive (IQ) or behavioral effects occur in children at PbB levels < 30 µg/dl. Rather, the collective neurobehavioral studies can probably now be most reasonably interpreted as being clearly indicative of likely associations between neuropsychologic deficits and low level lead exposures in young children resulting in PbB levels ranging to as low as 30-50 µg/dl. The magnitude of average observed IQ deficits appears to be approximately 5 points at mean PbB levels of 50-70 µg/dl and about 4 points at mean PbB levels of 30-50 µg/dl (CD, p. 13-35). Although such IQ deficits are relatively small on average, such shifts in the mean can make a substantial difference in the percentage of children with IQ's in the extremes of the population distribution (i.e., below 80 and above 125) and may impact the intellectual development, school achievement, and social development of the affected children sufficiently so as to be regarded as adverse" (CD, p. 13-36).

In children estimated to have PbB levels between 15 and 30 µg/dl, small deficits in IQ and attentiveness have been observed, although no consistent statistically significant associations have been found (Smith et al., 1983; Harvey et al., 1983, 1984; Yule et al., 1984; Hunter et al., 1984; Winneke et al., 1983, 1984). Because the most reliable of these studies found 1-2 point IQ deficits remaining after correction for confounding factors, the criteria document concludes that "lead cannot be totally ruled out as a possible etiological factor contributing to the induction of such effects in the 15-30 µg/dl range, based on existing published studies" (CD, p. 13-36).

In addition to IQ decrements, PbB levels in the 30-50 µg/dl range may be associated with deficits in auditory and language processing, motor coordination, appropriate social behavior, and the ability to focus attention (de la Burde and Choate, 1972, 1975; Needleman et al., 1979; Winneke et al., 1983). The degree to which lead's effects on neuropsychological performance at these levels persist into later life remains to be established.

Altered electrical activity in the brain has also been associated with PbB levels in children (along with IQ decrements; Burchfiel et al., 1980)

in the range of 30-50 µg/dl, with no evident threshold down to 15 µg/dl or somewhat lower (Benignus et al., 1981; Otto et al., 1981, 1982, 1984). The functional significance of many of the electrophysiological changes observed below 30 µg/dl (i.e., slow wave potentials, synchronized EEG amplitudes, visual evoked potentials) has not been established, although some changes persisted for at least two years (Otto et al., 1982). However, slowed nerve conduction in the auditory pathway has been related to pathological lesions and to non-specific demyelinating diseases such as multiple sclerosis; thus the effects on auditory brainstem evoked potentials observed across the range of PbB levels between 6 and 59 µg/dl may be indicative of subtle neurological impairment (Otto et al., 1984).

Alterations in neurochemistry (e.g., neurotransmission, brain mitochondrial function) are evident within minutes of exposure to submicromolar concentrations of lead in vitro and in vivo. Although the functional significance is difficult to assess and no estimates can be made of PbB levels at which such effects occur in humans, these neurochemical changes (e.g., inhibition of acetylcholine release and Na,K-ATPase activity) exhibit continuous dose-response relationships which may form the bases of delayed brain development and disrupted neurobehavioral function (Silbergeld, 1983). For example, effects have been found on certain behavioral (e.g., reaction time deficits), and electrophysiological (e.g., altered EEG patterns, nerve conduction velocities) measures indicative of CNS and peripheral nerve function perturbations, supporting a continuous dose-effect gradient between lead and neurotoxicity down to exposure levels as low as 15-30 µg/dl PbB, or perhaps, somewhat lower (CD, p. 12-137).

In summary, although there have been inconclusive findings and contrasting interpretations regarding lead's effects on specific neurobehavioral indicators

and functions (e.g., verbal performance, emotional reactivity, perceptual-motor integration, short-term memory, attention electrical activity in the brain) and the mechanisms involved, the overall evidence indicates that lead is associated with neurological impairment in some children with PbB levels between 30 and 50 µg/dl and that possibly lower levels of exposure (i.e., down to 15 µg/dl) may have some small, but potentially important and persistent effects on neurological function.

The impacts of lead on heme synthesis and related systems are summarized in Table 7-4. Because heme synthesis is a continuous process, most of these effects are reversible upon removal or reduction of lead from the organism or cellular systems involved. However, given: a) that there may be long-term effects of even transitory changes in developing tissues in children; b) heme's pervasive role in many organ systems and physiological processes; and c) the sensitivity of heme production to lead, lead's interference in the heme synthetic pathway must be carefully considered.

As discussed in Appendix D, lead interferes with heme synthesis at several points in its metabolic pathway:

1) Activity of the enzyme ALA-D, which catalyzes the conversion of ALA to porphobilinogen, is inhibited in red blood cells at PbB levels below 10-15 µg/dl with no clear threshold. ALA-D activity in soft tissues such as liver, brain, and kidney, appears to be inhibited to the same degree at similar PbB levels;

2) Accumulations of ALA, which result from inhibited ALA-D activity, have been noted in plasma and urine at PbB levels of 40 µg/dl, and possibly as low as 18 µg/dl. Increases in non-utilized ALA likely occur in brain, kidney, and other tissues at roughly the same PbB levels associated with ALA accumulations in plasma;

Table 7-4. SUMMARY OF LEAD'S EFFECTS ON HEME BIOSYNTHESIS AND RELATED SYSTEMS IN CHILDREN

PbB (μg/dl)[1]	Effect	References
≤10	Inhibition of ALA-D, Py-5-N, red cell ATPase activity	Hernberg and Nikkanen, 1970; Secchi et al., 1973; Wada et al., 1976; Angle and McIntire, 1978; Valentine and Paglia, 1980
>12	Reduction in vitamin D hormone synthesis	Rosen et al., 1980
≈15	Accumulation of EP indicating impaired heme synthesis	Roels et al., 1976; Piomelli et al., 1977; 1982; Hammond et al., 1984; Rabinowitz et al., 1985
>20	Impaired globin synthesis	White and Harvey, 1972; Dresner et al., 1982
25 - 30	Significant EP elevation above normal	Roels et al., 1976; Piomelli et al., 1982
>33	Significant interference with vitamin D hormone synthesis comparable to that seen in renal diseases	Rosen and Chesney, 1983; Chesney et al., 1983
18 - 40	Accumulation of underutilized ALA; possible interference with neuro-transmission	Meredith et al., 1978; O'Flaherty et al., 1980; Nicoll, 1976; Brennan and Cantrill, 1979; Silbergeld et al., 1980, 1982
≈40	Significant reduction in hemoglobin levels (anemia)	Betts et al., 1973; Rosen et al., 1974; Adenbojo, 1974; Pueschel et al., 1972
?	Impairment of cytochrome synthesis and function (e.g., drug metabolism, cellular energy metabolism)	Alvares et al., 1975; 1976, Meredith et al., 1977; Saenger et al., 1984; Holtzman and Shen Hsu, 1976; Bull et al., 1979
?	Alterations in heme-based neurochemical synthesis and neurological tissue development	Litman and Correia, 1983; Whetsell and Kappas, 1981; Whetsell et al., 1984

[1] These levels represent lowest observed effect levels in a significant fraction of children studied. In some cases, no threshold has been detected, as noted by < or > signs.

relationship between lead concentrations in tissue and cumulative lead intake is only approximately linear at low levels of intake, and that successive increments in intake or exposure result in progressively smaller contributions to blood lead concentrations (Azar et al., 1975; Moore, 1977; Gross, 1981; DeSilva 1981; Sherlock et al., 1982). This curvilinear relationship may be due to increased renal clearance with higher blood lead (Gross, 1981), distributional non-linearities due to differences in lead binding sites in different tissues (Hammond et al., 1981), and/or to a sizeable pool of mobile lead in bone maintained more or less independently of uptake (Rabinowitz et al., 1977; Chamberlain, 1983). It appears however, that none of the mechanisms introduce significant non-linearities at blood lead levels below 30 µg/dl (Marcus, 1984, 1985; Chamberlain, 1983) and that a linear mathematical model is valid for relatively low to moderate lead exposures (CD, p. 10-31, Appdx. 11A-2). As discussed in Appendix A, above 30-40 µg/dl, blood lead may be an inadequate index for tissue lead burdens in many children (Piomelli et al., 1984) and linear models are likely to lose their predictive power. For this reason, the relationships depicted in Figure 5-1 are truncated at 30 µg/dl. To estimate PbB levels above 30 µg/dl, which is now above the maximum PbB level of health-related concern for children (see Section VII.C), would require use of non-linear models which are discussed in the criteria document (Appendix II.B).

The compartmental biokinetic model of lead metabolism developed by Mallon (1983) and Kneip et al. (1983) and revised for children by Harley and Kneip (1985) relied on a broad array of experimental and observational measurements of mammalian metabolism and growth patterns, and has been successfully validated using available human experimental and autopsy data. As is the case for any mathematical model, there are inherent limitations and un-

certainties associated with it. Because this model however is based on the most comprehensive data available and has been developed specifically to predict organ lead concentrations over time in young children with continuous lead uptake, it appears that the outputs of the Harley and Kneip (1985) biokinetic model may be the most appropriate to predict PbB levels in children using the integrated lead uptake estimates presented in Table 5-1 and Appendix B. PbB levels calculated from the conjunction of the integrated lead uptake and biokinetic models are presented in Section VII.C.2 (along with estimates using other modeling approaches that are discussed later) in order to estimate potential health impacts among children under alternative air lead levels.

B. Statistical Relationships between Blood Lead and Airborne Lead

This section addresses two other methods of determining the contribution of air lead to total exposure and the potential health impacts associated with alternative air lead levels. The previous section examined the relationships between blood lead in children and estimated levels of lead uptake from the air, housedust, outdoor soil and dust, and diet. The approaches presented here will be to develop a direct relationship between air lead and blood lead in children and to 1) consider how air lead alone can serve as an index for lead exposure through other media affected by atmospheric lead deposition as well (i.e., "aggregate" modeling approach), and 2) how these other environmental media can be taken into account separately (i.e., "disaggregate" modeling approach).

Various experimental and community studies provide quantitative relationships between air lead and blood lead. Experimental studies, summarized in Table 5-2, include those in which adult volunteers have been exposed to controlled levels of laboratory generated lead aerosols, in some cases with

Table 5-2. SUMMARY OF EXPERIMENTAL LEAD INHALATION STUDIES

Study/Subjects	Exposure	Other Controlled Lead Exposures	Source of Analysis	Estimated Mean Inhalation Slope (μg/dl per μg/m^3)
Griffin et al., 1975				
14 adult males	3.2 μg/m^3 -	Diet	CD	3.00
			Snee, 1981	2.3
17 adult males	10.9 μg/m^3 -	Diet		
	submicron lead oxide aerosol for 4-14 weeks, 23 hrs/day		Hammond et al., 1981	1.9
			CD	0.65-2.17 mean ≈ 1.57 ± 0.26
6 adult males (controls)	Ambient air (0.1-0.2 μg/m^3)	Diet		
			CD	0.20 ± 1.48
Rabinowitz et al., 1977				
5 adult males	Ambient air (≈ 4 μg/m^3)[1], room with unfiltered air, (0.4-2.1 μg/m^3), and room with filtered air	Diet supplemented with isotopic lead tracer	CD	1.59-3.56 mean ≈ 2.14
			Snee, 1981	1.7-3.9
	Ambient air (2.1 μg/m^3)[2] Other exposures identical		CD	2.63-5.88 mean = 3.51
Chamberlain et al., 1978				
10 adult males	Pb labeled submicron car exhaust, lead oxide, and lead nitrate aerosols for several minutes		CD	2.2-2.7[3]
				3.0-3.5[4]
Kehoe, 1961				
6 adult males	0.6-0.9 μg/m^3 submicron lead sesquioxide aerosol for various daily intervals over three-five years	Diet	CD	-0.34 to 2.60 mean ≈ 1.25
			Gross, 1981	0.57
9 adult males	0.6-3.6 μg/m^3 over similar period	Diet	Hammond et al., 1981	0.59

[1]Based on stationary monitor readings not representative of personal exposures while outside (10 hrs/day) (CD, p. 11-47).

[2]CD (p. 11-48) estimates outdoor exposure most likely to be 2.1 μg/m^3 resulting in estimated lead intake and β to be significantly different.

[3]Depends on assumptions regarding residence time of lead and volume of blood (CD, p. 11-49 to 11-50).

[4]After adjustment for long-term bone resorption of lead with chronic exposure (Chamberlain et al., 1978).

isotopic lead tracer. Data from the most relevant studies have been re-analyzed in the CD to yield blood lead-air lead "slopes" (β), where β measures the change in blood lead that is expected for a unit change in air lead. Because intake of air lead through the diet and dust was probably minimal for the adult subjects in these experiments, these studies may underestimate the dose response that would be seen among children to environmental changes in air lead (Angle et al., 1985).

Epidemiological (i.e., community) studies provide correlations between air lead and blood lead in different populations of children and adults under varying conditions of lead, from current or previous atmospheric fall out and other sources, and may yield estimates of dose response that are biologically more relevant. Two modeling approaches using the best available epidemiological data can be applied to estimate quantitatively the relationship between air lead and blood lead in children: 1) a disaggregate model in which total exposure to air lead is assessed by separately analyzing the relationship between blood lead and inhaled air lead versus the associated changes in blood lead as a result of surface deposition of lead onto soil, dust, food, and water; and 2) an aggregate model in which blood lead/air lead relationships are analyzed such that integrated environmental lead exposure is represented by a single variable. Before discussing these approaches, several important limitations in interpreting the epidemiological studies should be noted.

a) Measurements of lead in the environment were generally limited and taken from samples separated in time and space from actual population exposures (as indexed by blood lead). Consequently, reported air lead concentrations in outdoor air (measured at centralized, stationary monitors), for example, have different relationships to the true personal airborne lead exposure of the target population in different studies;

b) In order for the relationships between blood lead and environmental lead to have general predictive value for other populations, steady state or near steady state conditions must have prevailed wherein the amount of lead inhaled and ingested per unit time was reasonably constant long enough for virtual equilibration to occur between lead in air, food, dust, etc., and blood lead (Hammond et al., 1981). As discussed below, in situations where lead concentrations in different media are only moderately correlated, environmental exposure cannot simply be characterized by the lead concentration in one medium, like air or dust. (Brunekreef, 1984);

c) The blood/air lead relationships generally are limited in that at most two or three, but frequently, only one environmental source of lead is measured in each study. Because of the simultaneous presence of lead in multiple media, such relationships underestimate or otherwise confound air lead's effect on total exposure unless lead intake from the other sources remains approximately constant and lead concentrations in different media are well correlated. In situations where the latter condition does not hold, environmental exposure cannot be simply characterized by the lead levels in air (for example, near point sources where the accumulation of lead in soil is related more to historical, rather than present, emissions, especially when control measures are being or have been taken). These difficulties can be partly overcome but unfortunately, longitudinal assessments of simultaneous exposure to all media have not been made and only limited information exists from studies measuring lead isotope ratios in blood and in the environment, a method which has emerged as a valuable tool to apportion lead exposure among different sources (Facchetti and Geiss, 1982; Yaffe et al., 1983);

d) As with the uptake/biokinetic approach, the importance of specific

sources of exposure varies widely from one individual to the next, and reliance on a blood/air relationship from an "average" case may be inappropriate to predict different individual risks but can provide reasonable estimates of possible population-wide impacts.

e) Again, similar to the uptake/biokinetic approach, environmental and blood lead sampling, analytical techniques, and quality control (if any) differ among studies and may explain part of the variability of the results; and

f) Possible confounding variables that influence PbB levels but which are not related to air lead measurements (e.g., lead in paint, canned food and plumbing, socioeconomic status, parental care, housing and play conditions, calcium intake) cannot always be disentangled. Control for confounders can be achieved by comparing populations that differ only in their exposure to airborne-derived lead. However, identifying such groups has been difficult. Another possibility is to perform a multivariate statistical analysis in which adjustments are made for some or all of the confounders before calculating the blood lead/air lead relationship. This requires information on the value of each confounder for each individual, which is also very difficult to estimate. In the case of lead, several confounders tend to work in the same direction as air lead. For example, elevated exposure and unfavorable social conditions often are both concentrated in central cities. Consequently, when statistical adjustment is incomplete, the relationship between air lead and blood lead will likely be inflated. The situation is complicated when more than one exposure variable besides air lead is entered into the analysis. Adjustment for a confounding variable usually implies that all of the shared variance between confounder and exposure

variable is attributed to the confounder; this can inevitably lead to underestimation of the "true" impact of the exposure variable (Rutter, 1983). Thus, adjusting for environmental exposures such as soil or dust lead, which are determined to a large extent by air lead levels, can result in an underestimation of the total impact of airborne-derived lead on blood lead (Brunekreef, 1984).

1. Blood/Air Lead Relationship Using Disaggregate Model

The CD concludes that experimental inhalation studies (see Table 5-2) and epidemiological studies on adults (Azar et al., 1975) exposed to relatively low air lead levels (<3.0 $\mu g/m^3$) produce linear inhalation blood lead/air lead slopes of 1.64 and in the range of 1.08-2.57 respectively (CD, Tables 11-38, 11-40). Inhalation slopes for children were estimated in the CD from the population studies of Angle and McIntire (1.92 $\pm$ .60), Roels et al. (2.46 $\pm$ 0.58), and Yankel et al. (1.53 $\pm$ 0.064), yielding an unweighted mean slope of 1.97 $\pm$ 0.39 (CD, p. 11-76). These studies were chosen for analysis and emphasis in the CD because they were judged to address several key factors sufficiently well to establish meaningful relationships. These factors include a well-defined study population, a good measure of individual exposure, measurement of blood lead with adequate quality control, a statistical analysis model that is biologically plausible and consistent with the data, and control or measurement of important covariates (CD, p. 11-63). In addition, they were selected so that, with the exception of some children in the Yankel et al. study, attention can be restricted "to those individuals without known excessive occupational or personal exposures" (CD, p. 11-65).

The relationship between blood lead and direct inhalation of airborne lead provides information useful for changes in air lead on a time scale of only several months (CD, p. 11-186). Over time, suspended lead deposits and is incorporated into soil, dust, and water, and enters the food chain. Since prior and current atmospheric fallout directly modify the daily burden of ingested lead, larger changes in blood lead would be predicted by the associated changes in the surface deposition of lead (Angle et al., 1985). To account for the simultaneous presence of lead in multiple environmental media, the CD has analyzed the separate relationships between children's blood lead and dietary, soil, and dust lead. These analyses are summarized in the tables included in Appendix C and are described in detail in Chapter 11.4 of the CD. A set of the most reliable relationships derived from these analyses are applied in a further analysis presented in the CD (CD, Table 13-6) and reproduced in this paper (Table 7-10) as a way to characterize average total lead exposure among U.S. children under alternative air lead levels. A similar disaggregate model was developed by Angle and McIntire (1979) and Angle et al. (1985) in forming an integrated lead exposure function from measurements of lead in air, soil, and house dust and relating that to PbB levels of children living in various areas of Omaha.

2. Blood/Air Lead Relationship Using Aggregate Model

In the disaggregate modeling approach, "inhalation" lead slopes are derived by statistically adjusting blood lead/air lead slopes by whatever non-air exposure variables (e.g., house dust lead) that were measured in the individual epidemiological studies, and then combining separate slopes available for other exposure media (e.g., dust, food, water) to arrive at an integrated lead exposure function. With the exception of Angle and McIntire (1979), the community studies from which inhalation slopes have

been derived have not simultaneously measured lead in more than two or three media and consequently, the integrated lead exposure function is necessarily based on data from multiple studies involving different populations, exposure conditions, measurement techniques, etc. An alternative method of calculating the effect of changes in air lead on children's blood lead is to analyze individual community studies in which reliable "unadjusted" blood lead/air lead relationships can be derived such that the impact of both direct (inhaled) and indirect (via dust, soil, etc.) contributions of air lead are combined, or aggregated, in one variable (i.e., air lead) at a time. To simply use an "adjusted" blood lead/air lead slope (i.e., inhalation slope) would be to underestimate the impact of atmospheric lead on children's total exposure since air lead levels, in general, are significantly correlated with other important exposure variables such as hand and household dust lead (Brunekreef, 1984).

The population studies with identifiable air monitoring methods and reliable blood lead data are summarized in Table 5-3. As is the case for the data in each of the experimental studies, different statistical analyses of the studies have resulted in a range of possible values for the blood lead/air lead relationship (β). Unadjusted (i.e., aggregate) relationships are presented in addition to adjusted relationships derived from regression analyses, the latter which refer to the blood lead/air lead relationships due to direct inhalation exposure. Note that in the majority of these studies adjustment for confounding factors has been absent or incomplete.

In Table 5-4, the calculated β values listed in Table 5-3 for each study are presented according to the blood lead levels, ages, and type of location of the investigated children. Relatively wide ranges of β values are observed for industrial and urban areas at low and high PbB levels and for

Table 5-3. SUMMARY OF EPIDEMIOLOGICAL STUDIES ON LEAD-EXPOSED CHILDREN

Study	Population[a]	Air Lead[b] ($\mu g/m^3$)	Blood Lead ($\mu g/dl$)	Statistical Model (Analyst)	Covariates Measured	Blood Lead/ Air Lead Slope
Roels et al., 1976,1978,1980	<1km: 10-15 yrs n=214 2.5km: 10-13 yrs n=168 Urban: 10-14 yrs n=55 Rural: 10-13 yrs n=223 Living near lead smelter (Antwerp, Belgium)	2.68-4.06 0.54-1.00 0.45-0.56 0.29-0.37 (9 month avgs; low volume sampler)[c]	24.6-30.1 13.3-21.1 10.4-12.7 9.0-10.7	Multiple regressions: Roels et al., 1980 (8 group means) CD (148 subjects)	Age, drinking water, income plus hand dust Pb adjustment -plus hand dust Pb adjustment	5.3 0.007 2.46
Yankel et al., 1977; Walter et al., 1980	1-9 yrs n=1149 (1974) 1-10 yrs n=781 (1975) living at varying distances from lead smelter (Kellogg)	0-1.6km: 18.0 1.6-4km: 14.0 4-10km : 6.7 10-24km: 3.1 24-32km: 1.5 ~ 75km: 1.2 (monthly avgs.)	65.9 47.7 33.8 32.2 27.5 21.2 21.2	Multiple regressions: Yankel et al. (1977) Snee (1982b) Snee (1982a) CD (linear) CD (non-linear) Walter et al. (1980) Group comparisons (Brunekreef, 1984)	Age, drinking water, paint, SES, house dust -plus soil & dust Pb occupation adjustment -plus soil Pb, occupation, cleanliness, pica adjustment -same as above -same as above -same as above No adjustment for soil or dust Pb	At 1.0 $\mu g/m^3$; 1974 data 1.16 1.13 1.07 1.52 1.16 1.26 2.4-3.3 depending on age
Angle and McIntire, 1979	1-18 yrs n=831 living in industrial urban, suburban areas of Omaha	industrial: 0.37-1.66 urban: 0.32-1.44 suburban: 0.22-0.73 (annual avgs. 1970-1977)	24.8 22.0 18.0	Regression Analyses: Angle and McIntire (1979) (6-18yr. olds) CD (Table 11-33) (1-18 yr. olds) CD-(Table 11-33) Brunkreef, 1984; (all children) (1-5 yr. olds) (6-18 yr. olds)	Age, drinking water, food -plus soil & house dust Pb adjustment -same as above -same as above No adjustment for soil or dust lead	1.4 0.6 1.92 4.40 0.66 -2.63 2.10
Brunekreef et al., 1981; Zielhuis et al., 1979	1976:2-3 yrs n=108 1977:1-7 yrs n=690 1978:1-3 yrs n=95 living <2km and 2-5km from secondary smelter (Arnheim)	0.5-2.5(0.4km) 0.4-1.6(0.4km) 0.28-0.51(<1km) (2 month avg.)	11.8(2-5km)-19.7(.4-1km) 14.6(1-2km)-18.2(.4-1km) 16.1(.4-1km)	Group comparison (Brunekreef, 1984) Multiple regression (Brunekreef, 1984)	Age, parental education and exposure, drinking water, food, age of home, mouthing behavior/hand dirt, house dust - plus adjustment for parental education	4.0 (1976) 3.6 (1977) 3.6 (1976)
Landrigan et al., 1975; Morse et al. 1977	1972:1-18 yrs n=259 (exposed) 1977:1-18 yrs n=499 (control) 1-18 yrs n=140 (exposed) living near primary smelter (El Paso)	<.8km / .8-1.6km 10.0 / 6.0[d] 5.5 / 3.0[d] (4 month avg.)	<.8km / .8-1.6km 41.4 / 31.2 17.7[e] / 20.2	Group comparison (Brunekreef, 1984)	Age, drinking water, milk consumption, parental income, home paint status	2.6 (1972) 3.7 (1977)

Table 5-3. SUMMARY OF EPIDEMIOLOGICAL STUDIES ON LEAD-EXPOSED CHILDREN (CONTINUED)

Study	Population[a]	Air Lead[b] ($\mu g/m^3$)	Blood Lead ($\mu g/dl$)	Statistical Model (Analyst)	Covariates Measured	Blood Lead/ Air Lead Slope
Billick et al., 1979, 1980; Nathanson & Nudleman, 1980	0-6 yrs n=178,533 living in NYC	0.8-2.5 (quarterly averages, 1970-1974)	20-33	Regression analysis (Brunekreef, 1984)	Season, location, plus adjustment for age & race	2.9
Brunekreef et al., 1983	4-6 yrs n=195 living in city center or in suburban area (Rotterdam)	.25 city .13 suburban (6-month avg., low volume sampler[c])	13.1 8.2	Group mean comparisons Regression analysis (Brunekreef, 1984) Regression analysis (Brunekreef et al., 1983, 1984)	Age, drinking water, house paint, SES, parental exposure, location -plus adjustment for Pb deposition outdoors, age of home, milk consumption, number of rooms, hand dirt, mouthing behavior, pets	24.5 18.5 3.0-8.5

[a]Refers to age of children sampled and sample sizes (n).

[b]Represents average levels measured either at various locations specified in "population" column or at various distances from specified point sources.

[c]Air lead levels sampled by low volume methods likely underestimated levels that would have been measured by hi-volume samplers used in other studies, especially near smelter where larger lead particles predominate. This could result in inflated blood/air lead ratios.

[d]Estimated by interpolation of air quality data presented.

[e]Based on only 3 samples - blood/air lead slope for 1977 based on reduction of air and blood lead at 0.8-1.6km from source.

Table 5-4. BLOOD LEAD/AIR LEAD SLOPES[1] IN CHILDREN FOR DIFFERENT AGES AND EXPOSURES

Blood Lead (μg/dl)/ Age (years)	Type of Location (Study)		
	Urban		Near Point Source(s)
<25/0-9	8.5[a,b] (Brunekreef et al., 1983)		3.6-4.0[a] (Zielhuis et al., 1979; Brunekreef et al., 1981)
<25/0-9, 10+	0.6 (Angle and McIntire; 1979, CD) 1.4[a] 1.92 4.40	0.66[a] (Brunekreef, 1984 from Angle and McIntire, 1979) -2.63[a] 2.10[a]	-
<25/10+		-	2.46 (CD from Roels et al. 1976) 5.3[a] (Roels et al. 1980) ≈ 5.9-9.8[a,b] Brunekreef, 1984 from Roels et al., 1976, 1978, 1980)
>25/0-9	2.9 (Billick et al., 1979, 1980; Nathanson and Nudleman, 1980)		1.07-1.52 (Yankel et al., 1977; Walter et al., 1980; Snee, 1982b; CD) 2.4-3.3[a] (Brunekreef, 1984 from Yankel et al., 1977)
>25/0-9, 10+		-	2.6-3.7[a] (Landrigan et al. 1975; Morse et al., 1977) 4.6[a] (Brunekreef, 1984 from Roels et al., 1976, 1978, 1980)

[1]Slopes are in units of μg lead/dl blood per μg lead/m^3 air.

[a]"Aggregate" slopes derived from group comparisons or multiple regression analyses that were unadjusted for soil or dust lead, thereby attempting to account for influence of deposited atmospheric lead through these exposure routes. Remaining slopes represent relationships between blood lead and air lead due solely to direct inhalation which have been calculated by adjusting for the influence of soil and/or dust lead.

[b]Use of low-volume particulate samplers likely underestimated air lead exposures, and overestimated the β value, especially near point source where large particles predominate.

all ages of children. The apparent trend towards lower slopes with increasing PbB levels is consistent with findings within some studies (Angle and McIntire, 1979; Roels et al., 1980) and other observations of curvilinear blood lead/exposure relationships (Azar et al., 1975; Moore et al., 1977; Gross, 1981; DeSilva, 1981; Sherlock et al., 1982; Hammond et al., 1981).

As discussed, the CD determined that the inhalation slopes derived from the studies by Angle and McIntire, Roels et al., and Yankel et al. are the most reliable given their overall quality. It is important to note several additional studies and analyses that may provide equally relevant and useful information for purposes of estimating an aggregate blood lead/air lead slope. Tables 5-3 and 5-4 identify surveys besides those of Angle and McIntire and Roels et al. which studied children (0-10 yrs) whose blood lead levels were below 25 µg/dl. These studies (Brunekreef et al., 1983; Zielhuis et al. 1979; Brunekreef et al., 1981) reported well-defined study populations, employed available quality control procedures for blood lead analysis, and measured or controlled for important covariates (see Table 5-3). Several specific comments should be made regarding these studies:

1. The series of studies reported by Zielhuis et al. (1979) and Brunekreef et al. (1981) included many environmental measurements (lead in ambient and indoor air, lead in dustfall indoors and outdoors, soil, streetdust, floordust, tapwater, and dustiness of homes) and regression analyses to determine the impact on PbB levels of different variables (i.e., the above environmental indices as well as distance from the smelter, parental education, age of the child, mouthing activity, cleanliness of the child). Venous blood lead samples were analyzed by standard techniques and although information on interlaboratory comparisons is not given in the original study, quality control participation is reported by one of the

investigators in a subsequent review (Brunekreef, 1984). Air lead was measured at two sites in 1976, and presumably in 1977, 0.2 and 0.4 km from the smelter. The levels in Table 5-3 were taken from Brunekreef (1984) and represent those measured at 0.4 km from the smelter. Six monitors measured air lead at 6 sites continuously for 2 months in 1978. Brunekreef (1984) estimates β for 1976 by assuming a difference of 2.0 $\mu g/m^3$ in average air lead exposure levels between the 2-3 year old children with the highest and lowest PbB levels. The blood lead difference of about 8 µg/dl decreased to 7.2 µg/dl after adjustment for parental education, resulting in a slightly lower β estimate (3.6). For 1977, a difference of 1.0 $\mu g/m^3$ was assumed for air lead exposure levels between exposed and control children of 2-3 years who had PbB levels of 18.2 and 14.6 µg/dl, respectively, again resulting in a β of 3.6. In 1978, only children living between 0.4 and 1.0 km of the smelter were sampled and air levels did not correlate with blood lead within this population. Thus, no direct estimate of β can be derived, although soil lead and indoor and outdoor dust lead, and therefore, accumulated lead deposition, accounted for a significant fraction of the variance in PbB levels (Brunekreef et al., 1981). Based on the aforementioned criteria used to determine key studies in the CD (p. 11-63), it appears that this series of studies near Arnheim and the subsequent analyses in Brunekreef (1984) is of sufficient quality to provide reliable aggregate relationships between blood lead and air lead.

2. The more recent study by Brunekreef et al. (1983) on Dutch city and suburban children also measured venous blood (which was analyzed as part of the European Community laboratory quality control program) and many environmental and social variables and potential confounders (lead in drinking water, soil, street and playground dust, hand dust, indoor dust,

mouthing behavior, dietary intakes, parental education and occupation, age of home, etc). The very high β value (8.5) derived by Brunekreef (1984) even after adjustment in a multiple regression analysis for six of the confounders, may be related to an underestimation of ambient air lead levels due to the fact that low volume British Smoke air monitors were employed, in contrast to the hi-vol samplers used in most other studies. The extent of inflation in the estimated slope as a result of any underestimated air lead level is uncertain. Brunekreef (1984) notes however that even if this bias is accounted for, the difference in urban and suburban air lead levels was probably not larger than 0.2 $\mu g/m^3$. The contrast in lead deposition between the areas was significant (i.e., 643 vs. 220 $\mu g/m^2$/day), indicating that ongoing lead pollution accounted for a good deal of the differences in PbB levels, although variations in historical emissions can not be entirely ruled out. The relatively low PbB levels in this study (≈ 8-13 µg/dl) could be another partial explanation of the high β estimates, given that other studies used to derive β included children with PbB levels on average closer to, and above, 30 µg/dl, at which point the blood lead/lead intake relationship is estimated to be non-linear and levels off; below 30 µg/dl, this relationship appears to be approximately linear (CD, p. 11-104).

Despite the uncertainties in the air monitoring data, this study appears to have been carefully designed and conducted and though the precise value of the blood lead/air lead relationship is not certain, the estimated β value appears to be significantly higher than the mean inhalation slope derived from other studies of comparable quality and relevance.

In addition to these studies, the available statistical aggregate analyses on the criteria document's three "key inhalation slope" studies

on children require brief discussion.

3. The three inhalation β values (0.6, 1.92, and 4.40) attributed to regression analyses performed by Angle and McIntire (1979) (CD, Table 11-39) all included adjustments for soil and house dust lead. An unadjusted regression analysis found a β of 1.4 for 6-18 year olds (Angle and McIntire, 1979). Unadjusted coefficients of 0.66 (all children), -2.63 (1-5 yr olds) and 2.10 (6-18 year olds) were obtained by Brunekreef (1984). The surprising β for the 1-5 year olds could be due to the fact that this age group was only sampled during one year, whereas sampling of older children was performed over 6 years. Brunekreef's reanalysis illustrates two points: 1) any slope derived for all children in the study (1-18 yrs) likely is deflated by including the discrepant results of the 1-5 year olds; and 2) by adjusting for soil and house dust lead in the analysis, the slope for air lead decreased three-fold from 2.10 to 0.69 in the 6-18 year olds.

4. The inhalation β value of 2.46 from Roels et al. (1976) was estimated in the CD by adjusting for dust lead levels measured on the children's hands. An unadjusted regression analysis by the authors of the combined data (1976 through 1980) yielded a β value of 5.3 (Roels et al., 1980). Brunekreef (1984) segregated the data and compared groups with large differences in exposure (i.e., <1 km from smelter vs. urban/rural; $\beta \approx 5.9$) groups with small differences in exposure at high exposure levels (i.e., <1 km vs. 2.5 km from smelter; $\beta \approx 4.6$) and groups with small differences in exposures at low levels (i.e., 2.5 km from smelter/urban vs. urban/rural; $\beta \approx 13.7$). The high estimate at the lower exposure level is influenced by two extreme values; removing them leaves a slope of approximately 9.8. As in the Brunekreef et al. (1983) study, the use of low-volume samplers likely underestimated air lead exposures, and overestimated the β value, especially

for those children near the smelter where large particles predominate. The slope may be underestimated for young children, however, since this study only sampled children older than 10. Given these different factors and analyses, it is difficult to estimate a "true" aggregate slope from Roels et al. (1976, 1980). It is clear that a range of possible slopes for this study has been calculated that are dependent on exposure levels and adjustments for dust lead, and which are all greater than the slope for inhaled air lead alone (2.46) cited in the criteria document.

5. Similarly, analyses of the Yankel et al. (1977) data adjusted for soil lead, cleanliness, dust, education, and/or pica have yielded inhalation βestimates ranging between 1.01 and 1.53 at an air lead level of 1.0 $\mu g/m^3$ (Yankel et al., 1977; Snee, 1982; Walter et al., 1980; CD, Table 11-39). Brunekreef (1984) estimated β values between 2.4 and 3.3 depending on age after comparing the highest and lowest exposed children's unadjusted PbB levels from 1974.

The remaining slopes listed in Table 5-4 are based on data from children whose PbB levels, as some in Yankel et al. (1977), exceeded 25 µg/dl. As discussed in the CD, the relationship between lead uptake and PbB levels above about 30 µg/dl appears to be non-linear (CD, p. 10-31; Marcus, 1985). Because PbB levels above 25-30 µg/dl are above the maximum PbB level of health-related concern (see Section VII.C), however, these slopes are less relevant to the present review.

In summary, the above analyses using the aggregate approach assume the same source for most lead in air, soil, and housedust, and that adjustment of PbB levels for soil or dust lead that yields an inhalation slope underestimates the "true" impact of atmospheric lead on PbB levels. A range of values can be estimated from a) additional, and apparently relevant, studies

TABLE 3. FETAL DEATH RATIOS BY AGE GROUP OF MOTHER AND RACE OF CHILD, 1978

Age group	Race	Number of live births	Number of fetal deaths[a]	Fetal death ratio[b]
15-19	White	227,158	2,158	9.5
	All others	105,417	1,518	14.4
20-34	White	1,290,604	9,951	7.7
	All others	269,933	3,802	14.1
35 up	White	67,567	1,057	15.6
	All others	17,123	533	31.1
	Totals:	1,977,802	19,019	9.6

[a]Number of reported fetal deaths, gestation 20 weeks plus.

[b]Fetal death ratio is number of fetal deaths per 1000 live births in specific group.

Data on fetal deaths are fairly accurate for those fetal deaths attended by a physician where reporting is required by law; however, laws on registering fetal deaths vary from State to State. Only six States require the reporting of fetal deaths occurring in the first 16 weeks of pregnancy; most States do not require reporting in the first 20 weeks. This practice of nonreporting eliminates most abortions from fetal death statistics and may substantially alter the accuracy of the data.

An estimate of the number of identifiable fetal deaths in early pregnancy may be gleaned from those States that require reporting of all fetal deaths. Table 4 shows, by mother's age, the number of fetal deaths occurring under 20 weeks' gestation and the number occurring after a gestation period of 20 weeks or more. Data represent five States that require fetal death reporting for all gestation periods. An underreporting adjustment factor was calculated for each age group by using the ratio of total deaths to deaths after 20 weeks, or more gestation. If all areas of the United States experience the same ratio of deaths above and below 20 weeks, these underreporting factors may be used to adjust upward the actual number of fetal deaths where a fetal death ratio is based on deaths reported after 20 weeks' or more gestation periods, such as the ratios in Table 3.

TABLE 4. NUMBER OF FETAL DEATHS BY SPECIFIED PERIODS OF GESTATION FOR STATES REQUIRING REPORTING OF ALL FETAL DEATHS, 1978[a]

Age of mother, yr	Gestation period			Totals	Under reporting adjustment factor[b]
	20 weeks and over	Under 20 weeks	Not stated		
Under 15	28	77	9	114	4.071
15 to 19	797	2,254	225	3,276	4.110
20 to 24	1,560	4,965	532	7,057	4.524
25 to 29	1,510	5,237	474	7,221	4.782
30 to 34	860	3,217	275	4,352	5.060
35 to 39	376	1,332	118	1,826	4.856
40 to 44	109	416	36	561	5.147
45 to 49	8	55	7	70	8.750
Totals:	5,248	17,553	1,676	24,477	4.664

[a]Reporting States include Arkansas, Colorado, Georgia, New York, Rhode Island, and Virginia. Arkansas not included in data for technical reasons (Reference 10).

[b]Underreporting adjustment factor is the ratio of total deaths to deaths reported for gestation periods over 20 weeks.

Fertility of women varies greatly with age. The 1980 data shows the greatest fertility among women occurs at age 20 to 29, but teenage (age 15 to 19) fertility was also significantly high, comparable to that of the 30 to 34 age group. Fertility of women age 35 to 39 was lower, and fertility of women age 40 to 44 was very low. Thus, age-specific birth rates are used in estimating numbers of pregnant women.

The following procedure was used to estimate the population of pregnant women in each census tract:

1. The SASD library of 1980 demographic data was used to find the number of women in each of three age groups. Age groups were further subdivided by race (black and nonblack).

2. The expected number of live births was calculated for each group of women by using age and race-specific live birth rates from Table 2.

$$E_{art} = (W_{art})(F_{ar})(1000) \qquad (4)$$

where E_{art} = Expected live births for a specific age (a), race (r), and in census tract (t)

W_{art} = Number of women in age group (a) and race (r) in census tract (t)

F_{ar} = Birth rate per 1000 women in age group (a) and race (r) from Table 2.

3. The total number of births (B_t) in the census tract in 1980 was determined by the number of children age 0 to 1.

4. The expected live births by mother's age and child's race were adjusted up or down so that total births from census data (B_t) was equal to total of births for all races and ages.

$$B_{art} = [E_{art}] \frac{(B_t - \Sigma E_{art})}{\Sigma E_{art}} \quad (5)$$

5. The number of fetal deaths was estimated by using an age- and race-specific fetal death ratio from Table 3 and the underreporting adjustment factor from Table 4 as follows:

$$D_{art} = \frac{(B_{art})(R_{ar})(U_a)}{1000} \quad (6)$$

where D_{art} = Fetal deaths for age group (a) and race (r) in census tract (t)

B_{art} = Live births from Equation 5

R_{ar} = Fetal death ratio per 1000 live births for age group (a) and race (r)

U_a = Underreporting adjustment factor for age group (a).

6. The number of pregnancies in 1 year (= number of fetuses) for each race, age, and poverty level was estimated by adding the estimated number of fetal deaths to estimated live births.

$$P_{art} = B_{art} + D_{art} \quad (7)$$

where P_{ar} = Pregnancies for mother's age group (a) and child's race (r) in census tract (t).

3.6 POPULATION PROJECTIONS

Estimated demographic group populations around a point source were based on 1980 census data. Control strategies for lead, however, may not become effective until future years (e.g., 1990 or 1995). Over this time period the population may change, especially in rapidly growing urban areas.

Estimates of population of children in future years were based on 1980 projections by the U.S. Bureau of Economic Analysis (BEA) previously called "OBERS" projections. The BEA projections are based on 1) projections of future employment for persons in the labor pool and 2) projections of population factors estimated by the BOC. The BEA studied historical trends of a State's share of basic industries whose products are exported or exportable. For service industries, trends of service industry location quotients were studied. For population projections at the national level, BEA relied on the BOC projections of three factors:

1) Amount of future net immigration by age, sex, and race

2) Age-, sex-, and race-specific mortality rates

3) Age- and race-specific fertility rates.

PEI used overall results of SMSA-specific population projections by BEA as shown in Table 5. The selected projections assume no change in each industry's share of the State's employment. Growth or decline depends on an SMSA having a greater or lesser portion of the State's fast-growing industries. A projection fraction was developed for each projection year, defined as the ratio of the projected-year population to the base-year population. Note that the base year 1978 is different from base year 1979 used by the BOC. Future-year population of a particular demographic subgroup around a point source was estimated by multiplying the base-year population of the subgroup by the corresponding SMSA-projection fraction.

The procedure developed for this program was simple to implement. A somewhat more resource-intensive approach, however, could take into account the characteristics of net migration, age, and race in the census tracts around the point source. These data could be used to adjust the city-wide BEA projections to produce projections that are more specific to the area around the point source.

TABLE 5. BEA POPULATION PROJECTIONS AND CORRESPONDING PROJECTION FRACTIONS

SMSA	Projection year		
	Base 1978	1990	2000
Dallas-Ft. Worth	2,719,853	3,457,730 (1.271)	3,986,199 (1.466)
Chicago	7,029,602	7,428,395 (1.057)	7,736,542 (1.101)
Tampa-St. Petersburg	1,396,261	1,820,692 (1.304)	2,084,093 (1.493)

SECTION 4

OUTPUTS FROM THE DEMOGRAPHIC PROGRAM

PEI has developed a computer program (MATCH-AQ) which performs the population calculations described in Section 3. Execution of MATCH-AQ requires the following inputs:

1) An air quality file containing monthly lead concentrations by census tract

2) A data file on pregnancy rates by age and sex

3) A tape file of STF3A census data for all States in the chosen SMSA

4) User-specified data to be introduced in the runstream.

Air quality data must be in the format shown in Figure 1. Each line (record) contains a 2-digit State code, a 3-digit county code, and a 7-digit census tract code. Federal Information Processing Standards (FIPS) codes are used, consistent with BOC data files. Locations of centers of census tracts are given in latitude and longitude. [Program converts to Universal Transverse Mercator (UTM) coordinates.] Each of the last 12 columns represents average lead concentrations in nanograms/cubic meter for one of 12 months.

Pregnancy data (file SASD*PREG-DATA) used in the program are printed in an output table for purposes of documentation, as shown in Figure 2.

User-specified data are also documented in the output, as shown in Figure 3. These data include name of study area city, point source name, SMSA FIPS code, and the number of census tracts (which should correspond to the number of lines in the air quality data file). The location of the plant stack(s) is expressed in UTM X and Y coordinates and UTM zone. The estimated number of persons employed in lead production is provided, as well as the projection year and projection fraction. If the desired year is 1980 (base), the projection fraction is 1.00. The BOC Region code is given along with four fractions indicating the fraction of houses in each of the four BOC regions that are unsound.

AIR QUALITY ESTIMATES FOR CENSUS TRACTS:

47 037 0119.00	4003.6060	521.6184	41	12	44	17	59	33	48	92	42	63	17	2
47 037 0120.00	4003.2192	522.1680	19	49	68	51	98	54	108	62	60	27	42	66
47 037 0121.00	4003.7555	523.6594	8	9	22	9	7	5	8	9	14	5	22	23
47 037 0122.00	4002.7909	523.8240	7	8	19	7	6	4	7	8	12	5	20	20
47 037 0123.00	4002.2987	522.2153	22	49	76	51	85	51	100	60	61	26	51	74
47 037 0124.00	4002.4968	521.5673	45	13	45	15	49	31	39	86	40	66	19	3
47 037 0125.00	4002.6616	520.9463	24	5	16	3	7	9	5	27	17	37	13	2
47 037 0141.00	4002.5241	519.0400	5	1	3	0	1	1	1	5	3	6	3	[illegible]
47 037 0145.00	4000.7047	518.8550	4	1	2	0	1	1	0	4	3	7	3	0
47 037 0146.00	4001.6717	519.7614	7	1	4	1	2	2	1	7	5	12	4	1
47 037 0147.00	4001.1863	520.9139	23	5	15	3	7	9	5	25	16	36	13	2
47 037 0148.00	4000.5671	521.7070	29	9	32	16	72	32	61	88	40	55	13	2
47 037 0149.00	4000.6165	523.6409	8	9	22	9	7	5	8	9	14	5	22	23
47 037 0158.00	3998.1945	526.1130	2	2	6	2	2	1	2	2	4	1	6	6
47 037 0159.00	3998.9078	523.4387	9	11	26	11	9	6	10	11	17	7	26	27
47 037 0160.00	3999.8562	521.2499	37	8	27	6	16	16	11	45	26	55	20	3
47 037 0161.00	3998.7903	520.8206	21	4	13	3	6	7	4	22	14	32	12	2
47 037 0162.00	3999.0205	519.6234	7	1	4	1	1	2	1	7	5	11	4	1
47 037 0163.00	3999.4403	518.8757	3	2	5	1	1	1	0	2	1	6	3	1
47 037 0164.00	3999.0511	518.4086	3	1	2	0	1	1	0	3	3	6	2	[illegible]
47 037 0165.00	4000.3239	517.0655	2	0	1	0	0	1	0	2	2	4	1	0
47 037 0168.00	3998.7157	517.0687	2	0	1	0	0	1	0	2	2	4	1	0
47 037 0169.00	3997.6189	517.7278	2	0	1	0	0	1	0	2	2	5	2	0
47 037 0170.00	3998.0550	519.3646	4	1	3	0	1	2	1	6	4	10	3	1
47 037 0171.00	3997.2907	519.8343	8	1	4	1	2	2	1	8	6	13	5	1
47 037 0172.00	3997.0513	521.7878	17	6	19	10	49	18	40	47	23	31	10	1
47 037 0173.00	3996.6437	522.8777	16	21	47	21	18	13	23	21	30	12	46	49
47 037 0174.00	3995.6173	524.7526	4	4	11	4	1	2	4	4	7	2	11	11

Figure 1. Sample of air quality data used by program MATCH-AQ.

PREGNANCY DATA FROM NATIONAL FILE

WOMEN AGE GROUP	UNDER-REPORTING FACTOR(A)	RACE	BIRTH RATE(B)	FETAL DEATH RATIO(C)
15 - 19	4.110	BLACK	100.00	14.40
		NON-BLACK	45.10	9.50
20 - 24	4.524	BLACK	146.30	13.20
		NON-BLACK	109.50	7.50
25 - 29	4.782	BLACK	109.10	13.90
		NON-BLACK	112.40	7.40
30 - 34	5.060	BLACK	62.90	17.50
		NON-BLACK	60.40	8.90
35 - 44	4.922	BLACK	15.90	31.10
		NON-BLACK	12.20	15.60

NOTES:
(A) APPLIES TO FETAL DEATH RATIO.
(B) RATE PER 1,000 FEMALES IN GROUP.
(C) RATE PER 1,000 LIVE BIRTHS.

Figure 2. Pregnancy data used in program MATCH-AQ.

```
INPUT DATA FOR PROGRAM MATCH-AQ4:

STUDY_AREA='DALLAS, TX      ';
SOURCE_NAME='GOULD INC.     ';
SMSA_CODE='=192';
N_TRACTS=                6;
SOURCE_X= 7.0246799E+002;
SOURCE_Y= 3.6687129E+003;
ZONE=                   14;
EMPL_PB_PROD= 1.2700000E+002;
PROJ_YR(0)=            1980                PROJ_YR(1)=            1985;
PROJ_FRACT= 1.0000000E+000;
BOC_REGION=                3;
FRACT_UNSOUND(1)= 6.0000000E-002  FRACT_UNSOUND(2)= 3.8999999E-002;
FRACT_UNSOUND(3)= 3.8000000E-002  FRACT_UNSOUND(4)= 3.8000000E-002;
```

Figure 3. User-specified inputs for program MATCH-AQ.

Outputs from the program include one table of geographic data for census tracts, one table of air quality data, and a series of eight tables of demographic data (one for pregnant women and one for each children's age group). Figure 4 is an example showing the table of geographic data for the census tracts around a particular point source. State, county, and census tract codes follow the census tract sequence number. The sequence number may be used as a cross reference between the geographic table, the air quality table, and each of the demographic tables. The distance from the census tract center to the point source (in meters) is listed next. The last three columns show the UTM X and Y coordinates and zone for the census tract center.

Figure 5 shows air quality data by census tract sequence number, census tract code, and 12 monthly averages in nanograms/cubic meter. Also shown are quarterly averages in the same units, where each quarter consists of three calendar months.

Figure 6 shows a sample output table for one children's age-group for census tracts around a point source. Census tract sequence number, State code, county code, and census tract code are listed, followed by populations of six demographic subgroups within the age category. For example, the first column shows numbers of children <1 year living in unsound LPH's who are estimated to have a high probability of secondary occupational exposure. The last column shows the total of all children <1 year in the census tracts (the sum all six subgroups). The same table is produced for pregnant women and children 1 to 1.99, 2 to 2.99, 3 to 3.99, 4 to 4.99, 5 to 5.99, and 6 to 6.99 years of age.

Data from the demographic and air quality tables are also placed in an output file. This file may be used as input to other programs, e.g., the lead-uptake model described in a separate report.[3] Figure 7 shows samples of output file records for two census tracts. On the first line, the census tract code is followed by the population of pregnant women in each of the six demographic subgroups shown in Figure 6. The second line (or record) contains the six demographic subgroup populations for children <1 year of age. Data for each succeeding age group follows on each succeeding line up to age group 6 to 6.99 years. The ninth line lists monthly average lead concentrations in nanograms/cubic meter. The same pattern is repeated for the second census tract. More information concerning program MATCH-AQ may be found in the source code listing (Appendix A).

CENSUS TRACTS AROUND POINT SOURCE GOULD INC.

Tract Seq.	FIPS State	FIPS County	Census Tract	Meters to Source	UTM Coordinates X	UTM Coordinates Y	Zone
1	48	085	0304.00	1993	704.4259	3669.0866	14
2	48	085	0305.00	8044	710.0215	3671.4797	14
3	48	085	0316.04	12140	709.9499	3659.1523	14
4	48	085	0316.06	10025	710.2266	3662.3644	14
5	48	085	0316.07	10470	706.6524	3659.1154	14
6	48	121	0215.03	8824	694.1804	3665.6828	14

Figure 4. Sample of geographic data table for census tracts around a point source.

CENSUS TRACT LEAD CONCENTRATIONS

Tract Seq.	Census Tract	Monthly Averages (Nanograms/cu.m.) 1	2	3	4	5	6	7	8	9	10	11	12	Quarterly Averages 1	2	3	4
1	0304.00	35	18	16	8	3	8	10	21	8	29	55	46	23	6	13	44
2	0305.00	7	10	5	3	2	3	1	4	2	18	9	10	7	3	2	12
3	0316.04	8	10	4	6	0	1	1	0	1	8	6	9	7	2	1	8
4	0316.06	6	10	3	2	5	5	1	1	1	9	7	5	6	4	1	7
5	0316.07	8	19	8	6	1	4	1	2	2	13	12	8	12	4	2	11
6	0215.03	3	12	6	3	4	8	3	8	9	11	4	2	7	5	7	6

Figure 5. Sample of air quality data table for census tracts around a point source.

ESTIMATED 1980 CENSUS TRACT POPULATIONS OF CHILDREN < 1 YEAR

Tract Seq.	FIPS State	FIPS County	Census Tract	LPH/Unsound SOE High	LPH/Unsound SOE Low	LPH/Sound SOE High	LPH/Sound SOE Low	Non-LPH SOE High	Non-LPH SOE Low	Total
1	48	085	0304.00	0	1	0	35	0	67	103
2	48	085	0305.00	0	0	0	11	1	21	33
3	48	085	0316.04	0	0	0	2	5	178	185
4	48	085	0316.06	0	0	0	0	0	6	6
5	48	085	0316.07	0	0	0	3	0	47	50
6	48	121	0215.03	0	1	0	15	1	379	396

LPH = living in lead-based painted home.
Unsound LPHs estimated by regional factors provided by PEI Associates, Inc.
SOE-Hi/low indicates probability of secondary occupational exposure.

Figure 6. Sample of demographic data table for one age group.

```
)ED,R       GOULD-8C.
READ-ONLY MODE
ED 16R1C THU-09/26/85-16:53:28-(C,)
EDIT
0304.00,      0,      1,      0,     20,      0,    37
0304.00,      0,      1,      0,     35,      0,    67
0304.00,      0,      1,      0,     19,      0,    36
0304.00,      0,      1,      0,     19,      0,    36
0304.00,      0,      1,      0,     29,      0,    55
0304.00,      0,      1,      0,     29,      0,    55
0304.00,      0,      1,      0,     19,      0,    36
0304.00,      0,      1,      0,     30,      0,    58
    35,    18,    16,     8,     3,     8,    10,    21,     8,    29,    55,    48
0305.00,      0,      0,      0,      6,      0,    10
0305.00,      0,      0,      0,     11,      1,    21
0305.00,      0,      0,      0,     10,      0,    17
0305.00,      0,      0,      0,     10,      0,    17
0305.00,      0,      0,      0,      2,      0,     4
0305.00,      0,      0,      0,      2,      0,     4
0305.00,      0,      0,      0,      6,      0,    12
0305.00,      0,      0,      0,      4,      0,     7
     7,    10,     5,     3,     2,     3,     1,     4,     2,    18,     9,    10
```

Figure 7. Sample of output file records.

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9. National Center for Health Statistics. Vital Statistics of the U.S., Vol. I, Natality. DHHS Pub. No. (PHS) 82-1100. Public Health Service, Washington, D.C. 1982.

10. National Center for Health Statistics. Vital Statistics of the U.S., Vol. II, Mortality. DHHS Pub. No. (PHS) 83-1101. Public Health Service, Washington, D.C. 1982.

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APPENDIX A

SOURCE CODE FOR DEMOGRAPHIC PROGRAM

```
@ED,R    SASD=PR.MATCH-AQ4/PB
READ-ONLY MODE
ED 16R1C WED-09/25/85-16:49:46-(46,)
EDIT
      1:MATCH_AQ4:    PROCEDURE OPTIONS(MAIN);
      2:
      3:/*  This program matches population data with a set of Pb air quality
      4:    data inputs from ISC-LT.  Population data is for selected groups
      5:    of children and estimated numbers of pregnant women.  Populations
      6:    are subdivided into 3 groups of housing and by whether or not there
      7:    is a high probability of secondary occupational exposure.
      8:        Nine output tables provide geographic data on census tracts
      9:    around a given point source, monthly AQ data on the same tracts,
     10:    and a series of population tables, one for each age group.  */
     11:
     12:    DCL ( STUDY_AREA, SOURCE_NAME )  CHAR(15) STATIC,
     13:        SOURCE_STATE(3)      FIXED STATIC,
     14:        SMSA_CODE            CHAR(4) STATIC,
     15:        SOURCE_X             FLOAT STATIC,   /*  UTM horiz. coordinate  */
     16:        SOURCE_Y             FLOAT STATIC,   /*  UTM vert. coordinate  */
     17:        EMPL_PB_PROD         FLOAT STATIC,
     18:/*      Fraction durable goods mfg. workers in pb-related production.  */
     19:        PROJ_FRACT           FLOAT STATIC,
     20:        PROJ_YR(0:1)         FIXED STATIC,   /* 0=1980, 1=projection yr */
     21:        FRACT_UNSOUND(4)     FLOAT STATIC INIT(.06, .039, .038, .038),
     22:        /*  1=Northeast, 2=Midwest, 3=South, 4=West  */
     23:        BOC_REGION           FIXED STATIC,  /* See B.O.C. Guide */
     24:        N_TRACTS             FIXED STATIC;
     25:
     26:/*  Input data for pregnant women:  */
     27:    DCL ( BIRTH_RATE(5,2),  FETAL_D_RATIO(5,2),   /*  By age, race  */
     28:          UNDER_RPT_FACTOR(5), EXP_BIRTHS(5,2) ) FLOAT STATIC,
     29:          PREGDATA                    INPUT FILE,
     30:          RACE_NAME(2)                CHAR(10) INIT
     31:        ( 'BLACK', 'NON-BLACK' ),
     32:          AGE_GRP_NAME(5)             CHAR(10) INIT
     33:        ( '15 - 19', '20 - 24', '25 - 29', '30 - 34', '35 - 44' ),
     34:          SNGL52(52)                  CHAR(1) INIT ((52)('-'));
     35:
     36:/*  Inputs from monthly AQ file:  */
     37:    DCL (XO, YO, LAT, LONG )      FLOAT,
     38:        MO_AQ(12)                 FLOAT,
     39:        TRACTDATA                 OUTPUT FILE,
     40:        MONTHLYAQ                 INPUT FILE,
     41:       ( EOF, NCD_DONE )          BIT(1) STATIC INIT('0'B);
     42:
     43:/*  Inputs from B.O.C. tapes:  */
     44:    DCL STF3A                       FILE VARIABLE,
     45:        ( TAPE1, TAPE2, TAPE3 )     FILE INPUT ENV
     46:        ( ANSI, FB, RECSIZE(12096), BLKSIZE(12096) ),
     47:        BOC_RACE(3)                 FLOAT STATIC,
     48:/*      Subscript 1 = total, 2 = white, 3 = black  */
     49:        LABR_FRCE(8)                FLOAT STATIC,
     50:        BOC_WOMEN(11)               FLOAT STATIC,
     51:/*      Subscript 1 = 15 yrs, 2 = 16, 3 = 17, 4 = 18, 5 = 19, 6 = 20,
     52:        7 = 21 yrs, 8 = 22-24, 9 =  25-29, 10 = 30-34, 11 = 35-44   */
     53:        BOC_CHILD(5)                FLOAT STATIC,
```

```
54:/*     Subscript 1 = under 1 year,   2 = 1 & 2 years,  3 = 3 & 4,
55:       4 = 5 years, 5 = 6 years                    */
56:     ( HS_UNITS(7),              /* Table 109 - Total       */
57:       WOMEN(5,2) )                FLOAT STATIC,
58:       C_TRACT                     CHAR(7),
59:     ( RCD_LEVEL, STATE, SUFFIX)   CHAR(2),
60:       COUNTY                      CHAR(3),
61:       BTRACT                      CHAR(4),
62:       S_FLAG1                     CHAR(1),  /* Data suppression flag  */
63:       TR                           FIXED STATIC;
64:
65:     DCL  1   TRACT(130)     STATIC,
66:              2   T_STATE       CHAR(2),
67:              2   T_CNTY        CHAR(3),
68:              2   T_CODE        CHAR(7),
69:              2   M_TO_SRC     FLOAT,
70:              2   T_UTMX        FLOAT,
71:              2   T_UTMY        FLOAT;
72:
73:     DCL 1    AQ_DATA(130)     STATIC,
74:              2   MONTHLY(12),
75:                  3   AQ        FLOAT,
76:              2   QTRLY(4),
77:                  3   AQ        FLOAT;
78:
79:     DCL 1    POP_DATA(130)    STATIC,
80:              2   PROJECTION(0:1),     /* 1980 + 1 Projection yr */
81:                  3   AGE_GRP(0:7),    /* Preg. + 7 child groups */
82:                      4   BY_HOUSE(3),
83:                 /*   subscript 1 = living in LPH, unsound
84:                      subscript 2 = living in LPH, sound
85:                      subscript 3 = not in LPH                */
86:                          5   BY_SOE(2),
87:                              6   POP       FLOAT,
88:                      4   SUBTOT            FLOAT;
89:
90:     DCL  1   TR_DATA(130)    STATIC,       /*  Census tract data:  */
91:              2   EMPL_DUR_GOODS    FLOAT,  /* Employed in durable goods mfg.
92:              2   TOT_HSNG          FLOAT,  /* Total housing units in tract.
93:              2   PB_HSNG           FLOAT,  /* Housing with leaded paint.
94:              2   TOT_CHILD        FLOAT,  /* Total children age 0-6.99 yrs
95:              2   TOT_EMPL         FLOAT,  /* Total employees in tract.
96:              2   SOE_CHILD        FLOAT;  /* Children exposed to SOE.    */
97:
98:/*  Variables used in SAI subroutines -- REL.SAI-ROUTINES  */
99:     DCL ( UTMX, UTMY, ALON, ALAT )       FLOAT BIN STATIC,
100:          IZONE                           FIXED BIN STATIC,
101:          MAPGTU ENTRY( FLOAT, FLOAT, FIXED, FLOAT, FLOAT )
102:          EXTERNAL OPTIONS(FTN),
103:          MAPUTG ENTRY( FLOAT, FLOAT, FIXED, FLOAT, FLOAT )
104:          EXTERNAL OPTIONS(FTN),
105:          VVGTUT ENTRY EXTERNAL OPTIONS(FTN);
106:
107:/*  Used in MATCH-AQ2 subroutine calculations:    */
108:     DCL ( AGE1, AGE2, F_DEATHS, PR_WOMEN, BL_FRACT,
109:           RACE_FRACT, TOT_EMPL )    FLOAT STATIC,
110:         ( PB_HSNG, TOT_HSNG )       FLOAT STATIC,
```

```
111:          LAST_BL_FRACT              FLOAT STATIC INIT(1.0),
112:          LAST_RATIO                 FLOAT STATIC INIT(1.0),
113:          SQRT                       BUILTIN;
114:
115:
116:      %INCLUDE(SASD+PR.MATCH-AQ4/SUBR);
117:
118:
119:INITIALIZE:
120:    SUBTOT = 0.0;
121:
122:RLN_INPUTS:
123:    GET EDIT (STUDY_AREA, SMSA_CODE, SOURCE_NAME, N_TRACTS )
124:    ( COL(1),A(15), COL(23),A(4), COL(30),A(15), COL(60),F(3)
125:    GET SKIP EDIT (SOURCE_X, SOURCE_Y, ZONE )
126:    (COL(6),F(8,4), COL(21),F(9,4), COL(38),F(2) );
127:    GET SKIP EDIT(SOURCE_STATE) (COL(1), 3( X(8),F(2)) );
128:    GET SKIP EDIT(N_TAPES, EMPL_PB_PROD) (COL(12),F(1), COL(30),
129:    PROJ_YR(1) = 1980;
130:    GET SKIP LIST (PROJ_YR(1),PROJ_FRACT);
131:    GET SKIP EDIT (BOC_REGION) (COL(12),F(1));
132:    PUT PAGE EDIT ("INPUT DATA FOR PROGRAM MATCH-AQ4:") (A);
133:    PUT SKIP(3) DATA (STUDY_AREA);
134:    PUT SKIP DATA (SOURCE_NAME);
135:    PUT SKIP DATA (SMSA_CODE);
136:    PUT SKIP DATA (N_TRACTS);
137:    PUT SKIP DATA (SOURCE_X);
138:    PUT SKIP DATA (SOURCE_Y);
139:    PUT SKIP DATA (ZONE);
140:    PUT SKIP DATA (EMPL_PB_PROD);
141:    PUT SKIP DATA (PROJ_YR);
142:    PUT SKIP DATA (PROJ_FRACT);
143:    PUT SKIP DATA (BOC_REGION);
144:    PUT SKIP DATA (FRACT_UNSOUND(1), FRACT_UNSOUND(2) );
145:    PUT SKIP DATA (FRACT_UNSOUND(3), FRACT_UNSOUND(4) );
146:
147:PREG_INPUTS:
148:    GET FILE(PREGDATA) EDIT (((UNDER_RPT_FACTOR(A))DO A=1 TO 5))
149:    (COL(1),5F(8) );
150:    GET FILE(PREGDATA) EDIT ((((BIRTH_RATE(A,R))DO R=1 TO 2)
151:    DO A=1 TO 5))  (COL(1),10F(8) );
152:    GET FILE(PREGDATA) EDIT ((((FETAL_D_RATIO(A,R))DO R=1 TO 2)
153:    DO A=1 TO 5))  (COL(1),10F(8) );
154:
155:    PUT SKIP(4) EDIT ("PREGNANCY DATA FROM NATIONAL FILE")
156:    ( LINE(3), COL(21),A );
157:    PUT SKIP(2) EDIT (SN6L52)  (COL(10),52A );
158:    PUT SKIP EDIT ("WOMEN", "UNDER-", "FETAL" )
159:    ( COL(10),A, COL(21),A, COL(56),A );
160:    PUT SKIP EDIT ("AGE", "REPORTING", "BIRTH", "DEATH" )
161:    (COL(11),A, COL(20),A, COL(44),A, COL(56),A );
162:    PUT SKIP EDIT ("GROUP", "FACTOR(A)", "RACE", "RATE(B)", "RATIO(C)")
163:    (COL(10),A, COL(20),A, COL(32),A, COL(44),A, COL(55),A );
164:    PUT SKIP(2) EDIT (SN6L52)  (COL(10),52A );
165:    PUT SKIP(2);
166:    DO A = 1 TO 5;
167:        PUT EDIT (AGE_GRP_NAME(A), UNDER_RPT_FACTOR(A) )
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168:          (COL(10),A, COL(20),F(7,3) );
169:          DO R = 1 TO 2;
170:              PUT EDIT (RACE_NAME(R), BIRTH_RATE(A,R),
171:              FETAL_D_RATIO(A,R) )
172:              (COL(30),A, COL(40),F(10,2), COL(51),F(10,2));
173:          END;END;
174:      PUT SKIP(2) EDIT (SNGLSZ)  (COL(10),S2A );
175:      PUT SKIP EDIT ("NOTES:") ( COL(10),A);
176:      PUT SKIP EDIT ("  (A) APPLIES TO FETAL DEATH RATIO.") (COL(10),A);
177:      PUT SKIP EDIT ("  (B) RATE PER 1,000 FEMALES IN GROUP.") (COL(10),A);
178:      PUT SKIP EDIT ("  (C) RATE PER 1,000 LIVE BIRTHS.") (COL(10),A);
179:
180:A6_INPUTS:      /* From ISC-LT outputs  */
181:      PUT SKIP(4) EDIT ("AIR QUALITY ESTIMATES FOR CENSUS TRACTS:") (A);
182:      PUT SKIP;
183:      DO T = 1 TO N_TRACTS;
184:          GET FILE(MONTHLYAQ) EDIT (T_STATE(T), T_CNTY(T), T_CODE(T),
185:          LAT, LONG, (MONTHLY_AQ(T,M) DO M=1 TO 12))  (COL(3),A(2),
186:          X(1),A(3), COL(10),A(7), COL(26),2F(9,4), COL(44),12F(7,0));
187:          /*  Convert lat-long to UTM coordinates.  */
188:          ALAT = LAT;
189:          ALON = LONG;
190:          IZONE = ZONE;    /* From runstream */
191:          IF ALON > 0.0 THEN ALON = -ALON;  /* Subr needs -  */
192:          CALL MAPGTU(ALON,ALAT,IZONE,UTMX,UTMY);
193:          T_UTMX(T) = UTMX;   /*  From subroutine  */
194:          T_UTMY(T) = UTMY;   /*  From subroutine  */
195:          PUT EDIT (T_STATE(T), T_CNTY(T), T_CODE(T),
196:          UTMY, UTMX, (MONTHLY_AQ(T,M)DO M=1 TO 12))  (COL(3),A(2),
197:          X(1),A(3), COL(10),A(7), COL(24),2F(10,4), COL(44),12F(7,0));
198:          /*  Calculate distance to source.  */
199:          XD = SOURCE_X - UTMX;
200:          YD = SOURCE_Y - UTMY;
201:          M_TO_SRC(T) = ( SQRT(XD**2 + YD**2)) * 1000.0;
202:          END;
203:
204:GTAPES:    /*  Read demographic data from census tapes:  */
205:DO BOCTAPE = 1 TO N_TAPES;
206:      IF BOCTAPE = 1 THEN STF3A = TAPE1;
207:      ELSE IF BOCTAPE = 2 THEN STF3A = TAPE2;
208:      ELSE IF BOCTAPE = 3 THEN STF3A = TAPE3;
209:      PUT PAGE EDIT ( "BEGIN READING STF3A TAPE ", BOCTAPE )
210:      ( A, F(1) );
211:      EOF = '0'B;
212:      ON ENDFILE(STF3A) EOF = '1'B;
213:      TP: DO WHILE (^EOF);
214:          GET FILE(STF3A) EDIT ( RCD_LEVEL, STATE, SMSA, COUNTY,
215:          BTRACT, SUFFIX, S_FLAG1 )   ( COL(10), A(2), COL(34),
216:          A(2), A(4), A(3), COL(50), A(4), A(2), COL(209), A(1) );
217:          IF RCD_LEVEL ^= '14' /* tract */  THEN GO TO NEXT_BOC_RECORD;
218:          IF SUFFIX = ' ' THEN SUFFIX = '00';
219:          C_TRACT = BTRACT !! '.' !! SUFFIX;
220:          DO TR = 1 TO N_TRACTS;
221:              IF (C_TRACT=T_CODE(TR) & STATE = T_STATE(TR)
222:              & COUNTY = T_CNTY(TR) ) THEN GO TO SUP_FLAG;
223:              END;
224:          GO TO NEXT_BOC_RECORD;      /* no AQ data to match.  */
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282:                MM = (Q-1) * 3 + M;
283:                QTRLY(TR,Q).AQ = QTRLY(TR,Q).AQ + MONTHLY(TR,MM).AQ;
284:                END;
285:            QTRLY(TR,Q).AQ = QTRLY(TR,Q).AQ / 3.0;
286:        END;END;
287:    PUT PAGE EDIT ("CENSUS TRACT LEAD CONCENTRATIONS ") (COL(45),A);
288:    PUT SKIP(2) EDIT (LINE2) (117A);
289:    PUT SKIP EDIT ("Tract    Census",
290:    "Monthly Averages(Nanograms/cu.m.)", "Quarterly Averages")
291:    (COL(1),A, COL(39),A, COL(98),A );
292:    PUT SKIP EDIT ("Seq.     Tract  ", "1     2     3     4",
293:    "     5     6     7     8     9     10    11    12",
294:    "1     2     3     4")  (COL(1),A, COL(24),2A, COL(98),A );
295:    PUT SKIP EDIT (LINE2) (117A);
296:    DO TR = 1 TO N_TRACTS;
297:        PUT EDIT (TR, T_CODE(TR),
298:        ((MONTHLY(TR,M).AQ)DO M=1 TO 12), ((QTRLY(TR,Q).AQ)DO Q=1 TO 4))
299:        ( COL(1),F(3), X(6),A(7), COL(20),12F(6),
300:        X(2), SF(6)  );
301:        END;
302:
303:    GROUP_NAME(0) = "PREGNANT WOMEN";
304:    GROUP_NAME(1) = "CHILDREN < 1 YEAR";
305:    GROUP_NAME(2) = "CHILDREN 1 TO 1.99 YEARS";
306:    GROUP_NAME(3) = "CHILDREN 2 TO 2.99 YEARS";
307:    GROUP_NAME(4) = "CHILDREN 3 TO 3.99 YEARS";
308:    GROUP_NAME(5) = "CHILDREN 4 TO 4.99 YEARS";
309:    GROUP_NAME(6) = "CHILDREN 5 TO 5.99 YEARS";
310:    GROUP_NAME(7) = "CHILDREN 6 TO 6.99 YEARS";
311:    POP_TBLS:
312:    DO GP = 0 TO 7;
313:        IF GP = 0 THEN PUT PAGE EDIT (" ") (COL(8),A);
314:        ELSE IF GP = 1 THEN PUT PAGE EDIT (" ") (COL(74),A);
315:        ELSE IF GP >= 2 THEN PUT PAGE EDIT (" ") (COL(111),A);
316:        PUT EDIT ("ESTIMATED ", PROJ_YR(1), " CENSUS TRACT",
317:        " POPULATIONS OF ", GROUP_NAME(GP))  ( A, F(4), 3A);
318:        PUT SKIP(2) EDIT (LINE1) (89A);
319:        PUT SKIP EDIT ("LPH/Unsound       LPH/Sound         Non-LPH")
320:        (COL(38), A );
321:        PUT SKIP EDIT ("----------      ----------     ----------" )
322:        (COL(38), A );
323:        PUT SKIP EDIT ("Tract   FIPS     FIPS    Census      SOE",
324:        "      SOE      SOE      SOE      SOE      SOE" )  (COL(1),2A );
325:        PUT SKIP     EDIT (" Seq.   State   County   Tract      High    ",
326:        "  Low      High     Low      High     Low     Total") (COL(1),2A );
327:        PUT SKIP EDIT (LINE1A) (89A);
328:        DO TR = 1 TO N_TRACTS;
329:            PUT EDIT  (TR, T_STATE(TR), T_CNTY(TR), T_CODE(TR) )
330:            ( COL(1),F(3), X(6),A(2), X(6),A(3), X(5),A(7) );
331:            PUT EDIT ( AGE_GRP(TR,1,GP)) ( 3(X(2),2(P'ZZ2,ZZ9')) );
332:            END;
333:        PUT SKIP(2) EDIT (LINE1) (89A);
334:        PUT SKIP EDIT (" LPH = Living in lead-based painted home.") (A);
335:        PUT SKIP EDIT (" Unsound LPHs estimated by",
336:        " regional factors provided by PEI Associates, Inc.") (2A);
337:        PUT SKIP EDIT (" SOE-Hi/low indicates probability of",
338:        " secondary occupational exposure.")  (2A);
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225:
226:        SUP_FLAG:   /*  Data suppression flag  */
227:        IF S_FLAG1 = '1' THEN DO;   /*  i.e. if < 30 persons in tract  */
228:            PUT EDIT ( 'Less than 30 persons in census tract record ',
229:            STATE, COUNTY, C_TRACT, ' -- data suppressed.' )
230:            (COL(1), A,A(3),A(4),2A );
231:            PUT SKIP;
232:            GO TO NEXT_BOC_RECORD;
233:            END;
234:        GET FILE(STF3A) EDIT (BOC_RACE) (COL(631), 3F(9) );
235:        GET FILE(STF3A) EDIT (BOC_CHILD) (COL(676), 5F(9) );
236:        GET FILE(STF3A) EDIT (BOC_WOMEN) (COL(982), 11F(9) );
237:        GET FILE(STF3A) EDIT (LABR_FRCE) (COL(5080), 8F(9) );
238:        GET FILE(STF3A) EDIT (EMPL_DUR_GOODS(TR)) (COL(5518), F(9) );
239:        GET FILE(STF3A) EDIT (HS_UNITS) (COL(8680), 7F(9) );
240:        CALL PREG_WOMEN;
241:        PUT SKIP EDIT ('RECORD USED: ', STATE, COUNTY, BTRACT,
242:        '.', SUFFIX, '  ' )    ( COL(5),2A,X(1), A,X(1), 4A, );
243:        PUT EDIT ('  ', BOC_CHILD, '  ') (A, 5F(9), A);
244:        CALL TRACT_CALC;
245:        UR = UR + 1;
246:        NEXT_BOC_RECORD:
247:        GET SKIP(1) FILE(STF3A);
248:        N = N + 1;
249:/*      IF UR >= 5 THEN GO TO TAPES_DONE;      TEST */
250:        END TP;       /*  End of reading records on one tape  */
251:    END CTAPES;       /*  End of reading all census tapes  */
252:TAPES_DONE:
253:    CALL SUBDIVIDE_POP;
254:    CALL NORMAL_SCE;
255:    CALL PROJECTION;
256:
257:QLTPUTS:
258:    DCL  LINE1(89)       CHAR(1) INIT((89)('='));
259:         LINE1A(89)      CHAR(1) INIT((89)('-')),
260:         LINE2(117)      CHAR(1) INIT((117)('-')),
261:         LINE3(69)       CHAR(1) INIT((69)('-')),
262:         GROUP_NAME(0:7)  CHAR(25) VARIABLE;
263:
264:    PUT PAGE EDIT ('CENSUS TRACTS AROUND POINT SOURCE ',
265:    SOURCE_NAME )  (COL(12),2A);
266:    PUT SKIP(2) EDIT (LINE3)  (69A);
267:    PUT SKIP EDIT('Meters', 'UTM Coordinates')  (COL(35),A, COL(50),A);
268:    PUT SKIP EDIT ('Tract  FIPS     FIPS    Census      to  ',
269:    '-------------------------')  (A, COL(44),A );
270:    PUT SKIP EDIT ('Seq.   State    County   Tract     Source',
271:    'X', 'Y', 'Zone' )  (A, COL(48),A, COL(58),A, COL(65),A );
272:    PUT SKIP EDIT (LINE3)  (69A);
273:    DO TR = 1 TO N_TRACTS;
274:        PUT EDIT (TR, TRACT(TR), ZONE)  (COL(1),F(3), COL(9),A,
275:        COL(17),A, COL(25),A, COL(32),F(8,0), X(2),2F(11,4), F(4) );
276:        END;
277:
278:    QTRLY.AQ = 0.0;
279:    DO TR = 1 TO N_TRACTS;
280:        DO Q = 1 TO 4;
281:            DO M = 1 TO 3;
```

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    139:     END POP_TBLS;
    140:
    141:/*  Output files for UPTAKE program:   */
    142:     DCL   OUTFL                OUTPUT FILE;
    143:     DO T = 1 TO N_TRACTS;
    144:          DO GP = 0 TO 7;
    145:               PUT FILE(OUTFL) EDIT (T_CODE(T), ((*,*, POP(T,1,GP,HS,S)
    146:               DO S=1 TO 2)DO HS=1 TO 3) )  (COL(1),A, 6(A,F(7)) );
    147:               END;
    148:          PUT SKIP FILE(OUTFL) EDIT
    149:          ( (( MONTHLY.AQ(T,M), *,*)DO M=1 TO 11)) ( 11(F(6),A) );
    150:          PUT FILE(OUTFL) EDIT (MONTHLY.AQ(T,12))  (F(6));
    151:          END;
    152:
    153:PROG_END:
    154:END MATCH_AQ4;
ECF:154
END ED. NO CORRECTIONS APPLIED

$FIN
```