Memo, M.; Lucchi, L.; Spano, P.F.; Trabucchi, M. (1980a) Lack of correlation between the neurochemical and behavioral effects induced by d-amphetamine in chronically lead-treated rats. Neuropharmacology 19: 795-799.

Memo, M.; Lucchi, L.; Spano, P.F.; Trabucchi, M. (1980b) Effect of chronic lead treatment on gaba-ergic receptor function in rat brain. Toxicol. Lett. 6: 427-432.

Memo, M.; Lucchi, L.; Spano, P.F.; Trabucchi, M. (1981) Dose-dependent and reversible effects of lead on rat dopaminergic system. Life Sci. 28: 795-799.

Meredith, P.A.; Campbell, B.C.; Moore, M.R.; Goldberg, A. (1977) The effects of industrial lead poisoning on cytochrome P450 mediated phenazone (antipyrine) hydroxylation. Eur. J. Clin. Pharmacol. 12: 235-239.

Meredith, P.A.; Moore, M.R.; Campbell, B.C.; Thompson, G.G.; Goldberg, A. (1978) Delta-aminolaevulinic acid metabolism in normal and lead-exposed humans. Toxicology 9: 1-9.

Michaelson, I.A.; Sauerhoff, M.W. (1974) Animal models of human disease: severe and mild lead encephalopathy in the neonatal rat. Environ. Health Perspect. 7: 201-225.

Mielke, H.W.; Anderson, J.C.; Berry, K.J.; Mielke, P.W.; Chaney, R.L.; Leech, M. (1983) Lead concentrations in inner-city soils as a factor in the child lead problem. Am. J. Pub. Health 73: 1366-1369.

Milar, C.R.; Schroeder, S.R.; Mushak, P.; Boone, L. (1981) Failure to find hyperactivity in preschool children with moderately elevated lead burden. J. Pediatr. Psychol. 6: 85-95.

Miles, C.D.; Brandle, J.R.; Daniel, D.J.; Chuder, O.; Schnare, P.D.; Uhlik, D.J. (1972) Inhibition of photosystem II in isolated chloroplasts by lead. Plant Physiol. 49: 820-825.

Milford, J.B.; Davidson, C.I. (1985) The sizes of particulate trace elements in the atmosphere - a review. JAPCA 35(12): 1249-1260.

Millar, J.A.; Cummings, R.L.C.; Battistini, V.; Carswell, F.; Goldberg, A. (1970) Lead and delta-aminolaevulinic acid dehydratase levels in mentally retarded children and in lead-poisoned suckling rats. Lancet 2(7675): 695-698.

Miller, F.J.; Gardner, D.E.; Graham, J.A.; Lee, R.E., Jr.; Wilson, W.E.; Bachmann, J.D. (1979) Size considerations for establishing a standard for inhalable particles. J. Air Pollut. Control Assoc. 29: 610-615.

Miller, W.P.; McFee, W.W. (1983) Distribution of cadmium, zinc, copper, and lead in soils of industrial northwestern Indiana. J. Environ. Qual. 12: 29-33.

Millican, F.K.; Layman, E.M.; Lourie, R.S. et al. (1962) The prevalence of ingestion and mouthing of nonedible substances by children. Clin. Proc. Child. Hosp. 18: 207-214.

Momcilovic, B.; Kostial, R. (1974) Kinetics of lead retention and distribution in suckling and adult rats. Environ. Res. 8: 214-220.

Moore, M.R. (1977) Lead in drinking water in soft water areas--health hazards. Sci. Total Environ. 7: 109-115.

Moore, M.R.; Meredith, P.A.; Goldberg, A. (1980) Lead and heme biosynthesis. In: Singhal, P.L.; Thomas, J.A., eds. Lead toxicity. Baltimore, MD: Urban and Schwarzenberg, Inc.; pp. 79-118.

Moreau, T.; Orssaud, G.; Juguet, B.; Busquet, G. (1982) Plombemie et pression arterielle: premiers resultats d'une enquete transversale de 431 sujets de sexe masculin. [Blood lead levels and arterial pressure: initial results of a cross sectional study of 431 male subjects.] [Letter]. Rev. Epidemol. Sante Publique. 30: 395-397.

Morrow, P.E.; Beiter, H.; Amato, F.; Gibb, F.R. (1980) Pulmonary retention of lead: an experimental study in man. Environ. Res. 21: 373-384.

Morse, D.L.; Landrigan, P.J.; Rosenblum, B.F.; Hubert, J.S.; Houseworth, J. (1979) El Paso revisited: epidemiologic follow-up of an environmental lead problem. J. Am. Med. Assoc. 242: 739-741.

Moscheandras, D.J.; Zabransky, J.; Pelton, D.J. (1981) Comparison of indoor and outdoor air quality. Electric Power Research Institute. Report EA-1733, Research Project 1309; Palo Alto, CA.

Motto, H.L.; Daines, R.H.; Chilko, D.M.; Motto, C.K. (1970) Lead in soils and plants: its relationship to traffic volume and proximity to highways. Environ. Sci. Technol. 4: 231-238.

Murozumi, M.; Chow, T.J.; Patterson, C. (1969) Chemical concentrations of pollutant lead aerosols, terrestrial dusts and sea salts in Greenland and Antarctic snow strata. Geochim. Cosmochim. Acta 33: 1247-1294.

Mykkanen, H.M.; Dickerson, J.W.T.; Lancaster, M.C. (1979) Effect of age on the tissue distribution of lead in the rat. Toxicol. Appl. Pharmacol. 51: 447-454.

NAS [National Academy of Sciences] Committee on Biologic Effects of Atmospheric Pollutants (1972) Lead: airborne lead in perspective. Washington, D.C.; National Academy of Sciences.

NAS [National Academy of Sciences] Committee on Lead in the Human Environment (1980) Lead in the human environment. Washington, D.C.: National Academy of Sciences.

Nathanson, B.; Nudelman, H. (1980) Ambient lead concentrations in New York City and their health implications. Bull. N.Y. Acad. Med. 56: 866-875.

Nathanson, J.A.; Bloom, F.E. (1975) Lead-induced inhibition of brain adenyl cyclase. Nature (London) 255: 419-420.

National Food Processors Association; Can Manufacturers Institute, Inc. (1982) Comprehensive supplementary report covering further research, February 1980 through May 1983, on food borne lead in the diet of children. Available from: U.S. Department of Health and Human Services, Washington, D.C.; FDA docket no. 79N-0200.

Needleman, H.L. (1984) Comments on chapter 12 and appendix 12C, Air Quality Criteria for Lead (external review draft #1). Available for inspection at: U.S. Environmental Protection Agency, Central Docket Section, Washington, DC; docket no. ECAO-CD-81-2 IIA.E.C.1.20.

Needleman, H.L.; Gunnoe, C.; Leviton, A.; Reed, R.; Peresie, H.; Maher, C.; Barrett, P. (1979) Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N. Engl. J. Med. 300: 689-695.

Needleman, H.L.; Leviton, A.; Bellinger, D. (1982) Lead-associated intellectual deficit. N. Engl. J. Med. 306: 367.

Needleman, H.L.; Rabinowitz, M.; Leviton, A.; Linn, S.; Schoenbaum, S. (1984) The relationship between prenatal exposure to lead and congenital anomalies. J. Am. Med. Assoc. 251: 2956-2959.

Needleman, H.L.; Shapiro, S.M. (1974) Dentine lead levels in asymptomatic Philadelphia school children: subclinical exposure in high and low risk groups. Environ. Health Perspect. 7: 27-32.

Neri, L.C.; Johansen, H.L.; Schmitt, N.; Pagan, R.T.; Hewitt, D. (1978) Blood lead levels in children in two British Columbia communities. In: Hemphill, D.D., ed. Trace substances in environmental health-XII: [proceedings of University of Missouri's 12th annual conference on trace substances in environmental health]; June; Columbia, MO. Columbia, MO: University of Missouri-Columbia; pp. 403-410.

Newman, M.C.; McIntosh, A.W. (1982) The influence of lead in components of a freshwater ecosystem on molluscan tissue lead concentrations. Aquat. Toxicol. 2: 1-19.

Nicoll, R.A. (1976) The interaction of porphyrin precursors with GABA receptors in the isolated frog spinal cord. Life Sci. 19: 521-525.

Nieburg, P.I.; Weiner, L.S.; Oski, B.F.; Oski, F.A. (1974) Red blood cell delta-aminolevulinic acid dehydrase activity. Am. J. Dis. Child. 127: 348-350.

Nordman, C.H. (1975) Environmental lead exposure in Finland: a study on selected population groups. Helsinki, Finland: University of Helsinki.

Nordstrom, S.; Beckman, L.; Nordenson, I. (1978) Occupational and environmental risks in and around a smelter in northern Sweden. I. Variations in birth weight. Hereditas 88: 43-46.

Nordstrom, S.; Beckman, L.; Nordenson, I. (1979a) Occupational and environmental risks in and around a smelter in northern Sweden. V: Spontaneous abortion among female employees and decreased birth weight in their offspring. Hereditas 90: 291-296.

Nordstrom, S.; Beckman, L.; Nordenson, I. (1979b) Occupational and environmental risks in and around a smelter in northern Sweden. VI: Congenital malformations. Hereditas 90: 297-302.

Nozaki, K. (1966) Method for studies on inhaled particles in human respiratory system and retention of lead fume. Ind. Health 4: 118-128.

Nriagu, J.O. (1978) Lead in soils, sediments and major rock types. In: The biogeochemistry of lead in the environment. Part A: Ecological cycles (J.O. Nriagu, ed.); Amsterdam, The Netherlands: Elsevier/ North-Holland Biomedical Press; pp. 15-72.

Nutrition Foundation, Inc. (1982) Assessment of the safety of lead and lead salts in food: a report of the Nutrition Foundation's Expert Advisory Committee. Washington, D.C. The Nutrition Foundation.

Odone, P.; Castoldi, M.R.; Guercilena, S.; Alessio, L. (1979) Erythrocyte zinc protoporphyrin as an indicator of the biological effect of lead in adults and children. In: International conference: management and control of heavy metals in the environment; September; London, United Kingdom. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 66-69.

O'Flaherty, E.J.; Hammond, P.B.; Lerner, S.I. (1982) Dependence of apparent blood lead half-life on the length of previous lead exposure in humans. Fundam. Appl. Toxicol. 2: 49-54.

O'Flaherty, E.J.; Hammond, P.B.; Lerner, S.I.; Hanenson, I.B.; Roda, S.M.B. (1980) The renal handling of δ-aminolevulinic acid in the rat and in the human. Toxicol. Appl. Pharmacol. 55: 423-432.

Ogilvie, D.M.; Martin, A.H. (1982) Aggression and open-field activity of lead-exposed mice. Arch. Environ. Contam. Toxicol. 11: 249-252.

O'Hara, D. (1982) Social factors in the prevention of increased lead absorption in children. In: Lead Absorption in Children (J.J. Chisolm, Jr. and D.M. O'Hara, eds.), Urban and Schwarzenberg, Baltimore, Maryland, 1982.

Oliver, T. (1911) Lead poisoning and the race. Br. Med. J. 1(2628): 1096-1098.

Olson, K.W.; Skogerboe, R.K. (1975) Identification of soil lead compounds from automotive sources. Environ. Sci. Technol. 9: 227-230.

Ong, C.N.; Lee, W.R. (1980) Interaction of calcium and lead in human erythrocytes. Br. J. Ind. Med. 37: 70-77.

OSHA [U.S. Occupational Safety & Health Administration] (1978) Occupational safety and health standard for inorganic lead. 29 CFR 1910, 1025.

Otto, D.A. (1985) The relationhip of event-related brain potential and lead absorption: a review of current evidence to appear in: Lead environmental health: the current issues (L. Wysock; and L. Goldwater, eds.) (in press).

Otto, D.A.; Benignus, V.A.; Muller, K.E.; Barton, C.N. (1981) Effects of age and body lead burden on CNS function in young children. I: Slow cortical potentials. Electroencephalogr. Clin. Neurophysiol. 52: 229-239.

Otto, D.; Benignus, V.; Muller, K.; Barton, C.; Seiple, K.; Prah, J.; Schroeder, S. (1982) Effects of low to moderate lead exposure on slow cortical potentials in young children: two year follow-up study. Neurobehav. Toxicol. Teratol. 4: 733-737.

Otto, D.; Reiter, L. (1984) Developmental changes in slow cortical potentials of young children with elevated body lead burden. Ann. N.Y. Acad. Sci. 425: 377-383.

Otto, D.; Robinson, G.; Baumann, S.; Schroeder, S.; Mushak, P.; Kleinbaum, D.; Boone, L. (1985) Five-year follow-up study of children with low-to-moderate lead absorption: electrophysiological evaluation. Env. Res. 38: 168-186.

Overmann, S.R. (1977) Behavioral effects of asymptomatic lead exposure during neonatal development in rats. Toxicol. Appl. Pharmacol. 41: 459-471.

Overmann, S.R.; Fox, D.A.; Wooley, D.E. (1979) Neurobehavioral ontogeny of neonatally lead-exposed rats. I: Reflex development and somatic indices. Neurotoxicology 1: 125-147.

Overmann, S.R.; Zimmer, L.; Woolley, D.E. (1981) Motor development, tissue weights and seizure susceptibility in perinatally lead-exposed rats. Neurotoxicology 2: 725-742.

Owen, G.; Lippman, G. (1977) Nutritional status of infants and young children; U.S.A. Pediatr. Clin. North Am. 24: 211-227.

Page, A.L.; Ganje, T.J. (1970) Accumulation of lead in soils for regions of high and low motor vehicle traffic density. Environ. Sci. Technol. 4: 140-142.

Paglia, D.E.; Valentine, W.N.; Dahlgren, J.G. (1975) Effects of low-level lead exposure on pyrimidine 5'-nucleotidase and other erythrocyte enzymes: possible role of pyrimidine 5'-nucleotidase in the pathogenesis of lead-induced anemia. J. Clin. Invest. 56: 1164-1169.

Paivoke, A. (1979) The effects of lead and arsenate on the growth and acid phosphatase activity of pea seedlings. Ann. Bot. Fenn. 16: 18-27.

Palmer, K.T.; Kucera, C.L. (1980) Lead contamination of sycamore and soil from lead mining and smelting operations in eastern Missouri. J. Environ. Qual. 9: 106-111.

Palmer, M.R.; Bjorklund, H.; Freedman, R.; Taylor, D.A.; Marwaha, J.; Olson, L.; Seiger, A.; Hoffer, B.J. (1981) Permanent impairment of spontaneous Purkinje cell discharge in cerebellar grafts caused by chronic lead exposure. Toxicol. Appl. Pharmacol. 60: 431-440.

Pearson, D.T.; Dietrich, K.N. (1985) The behavioral toxicology and teratology of childhood models, methods, and implications for intervention. Neurotoxicology: in press.

PEDCo Environmental, Inc. (1977) Lead analysis for Kansas City and Cincinnati. Draft report no. PN3264E; EPA contract no. 68-02-2515.

PEDCo Environmental, Inc. (1981) Field study to determine spatial variability of lead from roadways, final report; EPA contract no. 68-02-3013.

Pennington, J.A.T. (1983) Revision of the total diet study food list and diets. J. Am. Diet. Assoc. 82: 166-173.

Perino, J.; Ernhart, C.B. (1974) The relation of subclinical lead level to cognitive and sensorimotor impairment in black preschoolers. J. Learn. Dis. 7: 616-620.

Perlstein, M.A.; Attala, R. (1966) Neurologic sequelae of plumbism in children. Clin. Pediatr. (Philadelphia) 5: 292-298.

Perry, H.M., Jr.; Erlanger, M.W. (1978) Pressor effects of chronically feeding cadmium and lead together. In: Hemphill, D.D., ed. Trace substances in environmental health-XII: [proceedings of University of Missouri's 12th annual conference on trace substances in environmental health]; June; Columbia, MO. University of Missouri - Columbia; pp. 268-275.

Petit, T.L.; Alfano, D.P. (1979) Differential experience following developmental lead exposure: effects on brain and behavior. Pharmacol. Biochem. Behav. 11: 165-171.

Petit, T.L.; Alfano, D.P.; LeBoutillier, J.C. (1983) Early lead exposure and the hippocampus: a review and recent advances. Neurotoxicol. 4: 79-94.

Petit, T.L.; LeBoutillier, J.C. (1979) Effects of lead exposure during development on neocortical dendritic and synaptic structure. Exp. Neurol. 64: 482-492.

Phalen, R.F.; Oldham, M.J.; Beavcage, C.B.; Crocker, T.T.; Mortenson, J.D. (1985) Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat. Rec. 212: 368-380.

Pierson, W.R.; Brachaczek, W.W. (1976) Particulate matter associated with vehicles on the road. Warrendale, PA: Society of Automotive Engineers; SAE technical paper no. 760039. SAE transactions 85: 209-227.

Pilegaard, K. (1978) Airborne metals and SO_2 monitored by epiphytic lichens in an industrial area. Environ. Pollut. 17: 81-92.

Piomelli, S.; Rosen, J.F.; Chisolm, J.J.; Graef, J.W. (1984) Management of childhood lead poisoning. J. Pediatrics. 105: 523-531.

Piomelli, S.; Seaman, C.; Zullow, D.; Curran, A.; Davidow, B. (1977) Metabolic evidence of lead toxicity in "normal" urban children. Clin. Res. 25: 459A.

Piomelli, S.; Seaman, C.; Zullow, D.; Curran, A.; Davidow, B. (1982) Threshold for lead damage to heme synthesis in urban children. Proc. Natl. Acad. Sci. U.S.A. 79: 3335-3339.

Pirkle, J.L.; Schwartz, J.; Landis, J.R.; Harlan, W.R. (1985) The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am. J. Epid. 121: 246-258.

Pocock, S.J.; Shaper, A.G.; Ashby, D.; Delves, T.; Whitehead, T.P. (1984) Blood lead concentration, blood pressure, and renal function. Br. Med. J. 289: 872-874.

Pocock, S.J.; Shaper, A.G.; Walker, M.; Wale, C.J.; Clayton, B.; Delves, T.; Lacey, R.F.; Packham, R.F.; Powell, P. (1983) Effects of tap water lead, water hardness, alcohol, and cigarettes on blood lead concentrations. J. Epidemiol. Comm. Health 37: 1-7.

Pope (1986a) Exposure to children to lead-based paints, PEI Associates, Inc. Durham, N.C. Prepared for Strategies and Air Standards Division, Office of Air Quality Planning and Standards, January, 1986.

Pope (1986b) Blood lead levels in children living in lead-based painted housing units. PEI Associates, Inc., Durham, N.C. Prepared for Strategies and Air Standards Division, Office of Air Quality Planning and Standards, January 1986.

Pope (1986c) Seasonal variations in the amount of time children spend indoors, outdoors, and in motor vehicles. PEI Associates, Inc., Durham, N.C. for Strategies and Air Standards Division, Office of Air Quality Planning and Standards, January 1986.

Pounds, J.G.; Morrison, D.; Wright, R.; Casciano, D.A.; Shaddock, J.G. (1982a) Effect of lead on calcium-mediated cell function in the isolated rat hepatocyte. Toxicol. Appl. Pharmacol. 63: 402-408.

Pounds, J.G.; Wright, R.; Kodell, R.L. (1982b) Cellular metabolism of lead: a kinetic analysis in the isolated rat hepatocyte. Toxicol. Appl. Pharmacol. 66: 88-101.

Provvedini, D.M.; Tsoukas, C.D.; Deftos, L.J.; Manolagas, S.C. (1983) 1,25-dihydroxyvitamin D_3 receptors in human leukocytes. Science (Washington D.C.) 221: 1181-1182.

Pueschel, S.M.; Kopito, L.; Scwachman, H. (1972) Children with an increased lead burden: a screening and follow-up study. J. Am. Med. Assoc. 222: 462-466.

Purdue, L.J. (1984). Letter to Leonard Bruckman, Director, Air Compliance, Connecticut Department of Environmental Protection concerning Connecticut's requests for approval of a modification of Federal Reference Method for ambient lead, February 29, 1984.

Purdy, S.E.; Blair, J.A.; Leeming, R.J.; Hilburn, M.E. (1981) Effect of lead on tetrahydrobiopterin synthesis and salvage: a cause of neurological dysfunction. Int. J. Environ. Stud. 17: 141-145.

Purser, D.A.; Berrill, K.R.; Majeed, S.K. (1983) Effects of lead exposure on peripheral nerve in the cynomolgous monkey. Br. J. Ind. Med. 40: 402-412.

Quah, R.F.; Stark, A.D.; Meigs, J.W.; DeLouise, E.R. (1982) Children's blood lead levels in New Haven: A population-based demographic profile. Env. Health perspect. 44: 159-164.

Quarles, H.D., III; Hanawalt, R.B.; Odum, W.E. (1974) Lead in small mammals, plants and soil at varying distances from a highway. J. Appl. Ecol. 11: 937-949.

Rabinowitz, M.B.; Kopple, J.D.; Wetherill, G.W. (1980) Effect of food intake and fasting on gastrointestinal lead absorption in humans. Am. J. Clin. Nutr. 33: 1784-1788.

Rabinowitz, M.; Leviton, A.; Needleman, H. (1984a) Variability of blood concentrations during infancy. Arch. Environ. Health 39: 74-77.

Rabinowitz, M.; Leviton, A.; Needleman, H. (1985) Occurrence of elevated protoporphyrin levels in relation to lead burden in infants. Environ. Res. under review.

Rabinowitz, M.B.; Needleman, H.L. (1982) Temporal trends in the lead concentrations of umbilical cord blood. Science (Washington, D.C.) 216: 1429-1432.

Rabinowitz, M.; Needleman, H.; Burly, M.; Finch, H.; Rees, J. (1984b) Lead in umbilical blood, indoor air, tap water, and gasoline in Boston. Arch. Environ. Health 39: 299-301.

Rabinowitz, M.B.; Wetherill, G.W.; Kopple, J.D. (1973) Lead metabolism in the normal human: stable isotope studies. Science (Washington, D.C.) 182: 725-727.

Rabinowitz, M.; Wetherill, G.W.; Kopple, J.D. (1974) Studies of human lead metabolism by use of stable isotope tracers. Environ. Health Perspect. 7: 145-153.

Rabinowitz, M.B.; Wetherill, G.W.; Kopple, J.D. (1976) Kinetic analysis of lead metabolism in healthy humans. J. Clin. Invest. 58: 260-270.

Rabinowitz, M.B.; Wetherill, G.W.; Kopple, J.D. (1977) Magnitude of lead intake from respiration by normal man. J. Lab. Clin. Med. 90: 238-248.

Raghavan, S.R.V.; Culver, B.D.; Gonick, H.C. (1981) Erythrocyte lead-binding protein after occupational exposure. II: Influence on lead inhibition of membrane Na^+, K^+ - adenosinetriphosphatase. J. Toxicol. Environ. Health 7: 561-568.

Rasmussen, H.; Waisman, D.M. (1983) Modulation of cell function in the calcium messenger system. Rev. Physiol. Biochem. Pharmacol. 95: 111-148.

Reiter, L.W.; Anderson, G.E.; Laskey, J.W.; Cahill, D.F. (1975) Developmental and behavioral changes in the rat during chronic exposure to lead. Environ. Health Perspect. 12: 119-123.

Remmer, H.; Schenkman, J.; Estabrook, R.W.; Sasame, H.; Gillette, J.; Narasimhulu, S.; Cooper, D.Y.; Rosenthal, O. (1966) Drug interaction with hepatic microsomal cytochrome. Mol. Pharmacol. 2: 187.

Repko, J.D.; Corum, C.R. (1979) Critical review and evaluation of the neurobiological and behavioral sequelae of inorganic lead absorption. CRC Crit. Rev. Toxicol. 6: 135-187.

Reyners, H.; Gianefelici de Reyners, E.; Maisin, J.R. (1979) An ultrastructural study of the effects of lead in the central nervous system of the rat. In: International conference: management and control of heavy metals in the environment; September; London, United Kingdom. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 58-61.

Rice, D.C. (1984) Behavioral deficit (delayed matching to sample) in monkeys exposed from birth to low levels of lead. Toxicol. Appl. Pharmacol. 75: 337-345.

Rice, D.C. (1985) Chronic low-lead exposure from birth produces deficits in discimination reversal in monkeys. Toxicol. Appl. Pharmacol. 77: 201-210.

Rice, D.C.; Gilbert, S.G.; Willes, R.F. (1979) Neonatal low-level lead exposure in monkeys: locomotor activity, schedule-controlled behavior, and the effects of amphetamine. Toxicol. Appl. Pharmacol. 51: 503-513.

Rice, D.C.; Willes, R.F. (1979) Neonatal low-level lead exposure in monkeys (Macaca fascicularis): effect on two-choice non-spatial form discrimination. J. Environ. Pathol. Toxicol. 2: 1195-1203.

Richet, G.; Albahary, C.; Morel-Maroger, L.; Guillaume, P.; Galle, P. (1966) Renal changes in 23 cases of occupational lead poisoning. Bull. Mem. Soc. Med. Hop. Paris 117: 441-466.

Rickard, D.T.; Nriagu, J.O. (1978) Aqueous environmental chemistry of lead. In: Nriagu, J. O., ed. The biochemistry of lead in the environment. Part A: Ecological cycles. Amsterdam, The Netherlands: Elsevier/ North Holland Biomedical Press; pp. 219-284.

Roberts, T.M.; Hutchinson, T.C.; Paciga, J.; Chattopadhyay, A.; Jervis, R.E.; Van Loon, J.; Parkinson, D.K. (1974) Lead contamination around secondary smelters: estimation of dispersal and accumulation by humans. Science (Washington, D.C.) 186: 1120-1123.

Robinson, G.; Baumann, S.; Kleinbaum, D.; Barton, C.; Schroeder, S.; Mushak, P.; Otto, D. (1985) Effects of low to moderate lead exposure on brainstem auditory evoked potentials in children. Environmental Health 38: 177-182.

Robinson, S.H.; Cantoni, O.; Costa, M. (1984) Analysis of metal-induced DNA lesions and DNA-repair replication in mammalian cells. Mutat. Res. 131: 173-181.

Roels, H.A.; Buchet, J-P.; Lauwerys, R.; Bruaux, P.; Claeys-Thoreau, F.; Lafontaine, A.; Van Overschelde, J.; Verduyn, G. (1978) Lead and cadmium absorption among children near a nonferrous metal plant: a follow-up study of a test case. Environ. Res. 15: 290-308.

Roels, H.A.; Buchet, J-P.; Lauwerys, R.; Bruaux, P.; Claeys-Thoreau, F.; Lafontaine, A.; Verduyn, G. (1980) Exposure to lead by the oral and the pulmonary routes of children living in the vicinity of a primary lead smelter. Environ. Res. 22: 81-94.

Roels, H.A.; Buchet, J-P.; Lauwerys, R.; Hubermont, G.; Bruaux, P.; Claeys-Thoreau, F.; Lafontaine, A.; Van Overschelde, J.; (1976) Impact of air pollution by lead on the heme biosynthetic pathway in school-age children. Arch. Environ. Health 31: 310-316.

Roels, H.A.; Buchet, J-P.; Lauwerys, R.R.; Sonnet, J. (1975b) Comparison of in vivo effect of inorganic lead and cadmium on glutathione reductase system and δ-aminolevulinate dehydratase in human erythrocytes. Br. J. Ind. Med. 32: 181-192.

Rolfe, G.L., A. Haney, and K.A. Reinbold (1977) Environmental contamination by lead and other heavy metals, Vol. 2: Ecosystem analysis; final report. University of Illinois at Urbana-Champaign, Institute for Environmental Studies, Urbana Ill. NTIS, Springfield, VA: PC-AD/MF-A01.

Rosén, I.; Wildt, K.; Gullberg, B.; Berlin, M. (1983) Neurophysiological effects of lead exposure. Scand. J. Work Environ. Health 9: 431-441.

Rosen, J.F. (1983) The metabolism of lead in isolated bone cell populations: interactions between lead and calcium. Toxicol. Appl. Pharmacol. 71: 101-112.

Rosen, J.F.; Chesney, R.W. (1983) Circulating calcitriol concentrations in health and disease. J. Pediatr. (St. Louis) 103: 1-7.

Rosen, J.F.; Chesney, R.W.; Hamstra, A.; DuLuca, H.F.; Mahaffey, K.R. (1980) Reduction in 1,25-dihydroxyvitamin D in children with increased lead absorption. N. Engl. J. Med. 302: 1128-1131.

Rosen, J.F.; Chesney, R.W.; Hamstra, A.; DuLuca, H.F.; Mahaffey, K.R. (1981) Reduction in 1-25-dihydroxyvitamin D in children with increased lead absorption. In: Brown, S.S.; Davis, D.S., eds. Organ-directed toxicity: chemical indices and mechanisms. New York, NY: Pergamon Press; pp.91-95

Rosen, J.F.; Markowitz, M.E. (1980) D-penicillamine: its actions on lead transport in bone organ culture. Pediatr. Res. 14: 330-335.

Rosen, J.F.; Wexler, E.E. (1977) Studies of lead transport in bone organ culture. Biochem. Pharmacol. 26: 650-652.

Rosen, J.F.; Zarate-Salvador, C.; Trinidad, E.E. (1974) Plasma lead levels in normal and lead-intoxicated children. J. Pediatr. (St. Louis) 84: 45-48.

Rostron, C. (1982) Are we at risk from lead-part 1. Fd. Chem. Toxic. 20: 617-621.

Rummo, J.H. (1974) Intellectual and behavioral effects of lead poisoning in children. Chapel Hill, NC: Unversity of North Carolina. Available from: University Microfilms, Ann Arbor, MI; publication no. 74-26,930. Ph.D. Thesis.

Rummo, J.H.; Routh, D.K.; Rummo, N.J.; Brown, J.F. (1979) Behavioral and neurological effects of symptomatic and asymptomatic lead exposure in children. Arch. Environ. Health 34: 120-124.

Rutter, M. (1980) Raised lead levels and impaired cognitive/behavioral functioning. Dev. Med. Child Neurol. (Suppl.) 42: 1-36.

Rutter, M. (1983) Low level lead exposure: sources, effects and implications. In: Rutter, M.; Jones, R. Russell, eds. Lead versus health: sources and effects of low level lead exposure. New York, NY: John Wiley & Sons; pp. 333-370.

Ryu, J.E.; Ziegler, E.E.; Fomon, S.J. (1978) Maternal lead exposure and blood lead concentration in infancy. J. Pediatr. (St. Louis) 93: 476-478.

Ryu, J.E.; Ziegler, E.E.; Nelson, S.E.; Fomon, S.J. (1983) Dietary intake of lead and blood lead concentration in early infancy. Am. J. Dis. Child. 137: 886-891.

Sachs, H.K. (1978) Intercurrent infection in lead poisoning. Am. J. Dis. Child. 132: 315-316.

Saenger, P.; Markowitz, M.E.; Rosen, J.F. (1984) Depressed excretion of 6ß-hydroxycortisol in lead-toxic children. J. Clin. Endocrinol. Metab. 58: 363-367.

Saenger, P.; Rosen, J.F.; Markowitz, M.E. (1982) Diagnostic significance of edetate disodium calcium testing in children with increased lead absorption. Am. J. Dis. Child. 136: 312-315.

Sandstead, H.H.; Galloway, R. (1967) Effect of chronic lead intoxication on *in vivo* ^{131}I uptake by the rat thyroid. Proc. Fed. Soc. Exp. Biol. Med. 124: 18-20.

Sandstead, H.H.; Orth, D.N.; Abe, K.; Stiel, J. (1970) Lead intoxication: effect on pituitary and adrenal function in man. Clin. Res.. 18: 76.

Sandstead, H.H.; Stant, E.G.; Brill, A.B.; Arias, L. I.; Terry, R.T. (1969) Lead intoxication and the thyroid. Arch. Int. Med. 123: 632-635.

Sassa, S.; Granick, J.L.; Granick, S.; Kappas, A.; Levere, R.D. (1973) Studies in lead poisoning. I: Microanalysis of erythrocyte protoporphyrin levels by spectrofluorometry in the detection of chronic lead intoxication in the subclinical range. Biochem. Med. 8: 135-148.

Sassa, S.; Whetsell, W.J., Jr.; Kappas, A. (1979) Studies on porphyrin-heme biosynthesis in organotypic cultures of chick dorsal root ganglia. II: The effect of lead. Environ. Res. 19: 415-426.

Sauerhoff, M.W.; Michaelson, I.A. (1973) Hyperactivity and brain catecholamines in lead-exposed developing rats. Science (Washington, D.C.) 182: 1022-1024.

Sayre, J.W.; Charney, E.; Vostal, J.; Pless, I.B. (1974) House and hand dust as a potential source of childhood lead exposure. Am. J. Dis. Child. 127: 167-170.

Schlesinger, R.B.; Lippmann, M. (1978) Particle deposition in the trachea: in vivo and in hollow casts. Thorax 31: 678.

Schlipkoter, H-W,; Winneke, G. (1980) Behavioral studies on the effects of ingested lead on the developing central nervous system of rats. In: Environmental quality of life: Lead Environmental Research Program 1976-80. Brussels, Luxembourg: Commission of the European Communities; pp. 127-134.

Schroeder, S.R.; Hawk, B. (1986) Child-caregiver environmental factors related to lead exposure and IQ to appear in: Toxic substances and mental retardation: neurobehavioral toxicology and teratology. (S.R. Schroeder, ed.); Washington, D.C.: AAMD Monograph Series (in press).

Schroeder, S.R.; Hawk, B.; Otto, D.A.; Mushak, P.; Hicks, R.E. (1985) Separating the effects of lead and social factors on IQ. Env. Res. 144-154.

Schuck, E.A.; Locke, J.K. (1970) Relationship of automotive lead particulates to certain consumer crops. Environ. Sci. Technol. 4: 324-330.

Schwartz, J. (1985a) Office of Policy Analysis, U.S. EPA, Washington, D.C. Lag time in the response of blood lead to air lead and its implications for averaging time. Memorandum to Jeff Cohen, Office of Air Quality Planning and Standards, U.S. EPA, RTP, N.C. August 8, 1985.

Schwartz, J. (1985b) Office of Policy Analysis, U.S. EPA, Washington, D.C. Memorandum on draft staff paper on lead, to Jeff Cohen, Office of Air Quality Planning and Standards, U.S. EPA, RTP, N.C., April 22, 1985.

Schwartz, J. (1985c) Office of Policy Analysis, U.S. EPA, Washington, D.C. Modeling the percent of children with high blood lead levels. Memorandum to Vic Hasselblad, Allan Marcus, Jeff Cohen. August 21, 1985.

Schwartz, J. (1985d) Office of Policy Analysis, U.S. EPA, Washington, D.C. Modeling the blood lead distribution in children. Memorandum to Jeff Cohen, Office of Air Quality Planning and Standards, U.S. EPA, RTP, N.C. September 4, 1985.

Scoppa, P.; Roumengous, M.; Penning, W. (1973) Hepatic drug metabolizing activity in lead-poisoned rats. Experentia 29: 970-972.

Secchi, G.; Alessio, L.; Cambiaghi, G. (1973) Na^+/K^+-ATPase activity of erythrocyte membrances: in urban populations not occupationally exposed to lead. Arch. Environ. Health 27: 399-400.

Secchi, G.C.; Erba, L.; Cambiaghi, G. (1974) Delta-aminolevulinic acid dehydratase activity of erythrocytes and liver tissue in man: relationship to lead exposure. Arch. Environ. Health 28: 130-132.

Sehmel, G.A. (1980) Particle and gas dry deposition: a review. Atmos. Environ. 14: 983-1011.

Selander, S.; Cramer, K. (1970) Interrelationships between lead in blood, lead in urine, and ALA in urine during lead work. Br. J. Ind. Med. 27: 28-39.

Selevan, S.G.; Landrigan, P.J.; Stern, F.B.; Jones, J.H. (1984) Mortality of lead smelter workers. Unpublished draft supplied by S.G. Selevan, Industrywide Studies Branch, National Institute for Occupational Safety and Health, Cincinnati, Ohio.

Seppalainen, A.M.; Hernberg, S. (1980) Subclinical lead neuropathy. Am. J. Ind. Med. 1: 413-420.

Seppalainen, A.M.; Hernberg, S. (1982) A follow-up study of nerve conduction velocities in lead exposed workers. Neurobehav. Toxicol. Teratol. 4: 721-723.

Seppalainen, A.M.; Hernberg, S.; Kock, B. (1979) Relationship between blood lead levels and nerve conduction velocities. Neurotoxicology 1: 313-332.

Seppalainen, A.M.; Hernberg, S.; Vesanto, R.; Kock, B. (1983) Early neurotoxic effects of occupational lead exposure: a prospective study. Neurotox. 4: 181 - 192.

Seppalainen, A.M.; Tola, S.; Hernberg, S.; Kock, B. (1975) Subclinical neuropathy at "safe" levels of lead exposure. Arch. Environ. Health 30: 180-183.

Settle, D.M.; Patterson, C.C. (1982) Magnitude and sources of precipitation and dry deposition fluxes of industrial and natural leads to the North Pacific at Eniewetok. J. Geophys. Res. 87:.8857-8869.

Shacklette, H.T.; Hamilton, J.C.; Boerngen, J.G.; Bowles, J.M. (1971) Elemental composition of surficial materials in the conterminous United States: an account of the amounts of certain chemical elements in samples of soils and other regoliths. Washington, D.C.: U.S. Department of the Interior, Geological Survey; Geological Survey professional paper no. 574-D.

Shaheen, S.J. (1984) Neuromaturation and behavior development: the case of childhood lead poisoning. Dev. Psych. 20: 542-550.

Shapiro, I.M.; Burke, A.; Mitchell, G.; Bloch, P. (1978) X-ray fluorescence analysis of lead in teeth of urban children: in situ correlation between the tooth lead level and the concentration of blood lead and free erythroporphyrins. Environ. Res. 17: 46-52.

Sharrett, A.R.; Carter, A.P.; Orheim, R.M.; Feinleib, M. (1982) Daily intake of lead, cadmium, copper, and zinc from drinking water: the Seattle study of trace metal exposure. Environ. Res. 28: 456-475.

Sheffet, A.; Thind, I.; Miller, A.M.; Louria, D.B. (1982) Cancer mortality in a pigment plant utilizing lead and zinc chromates. Arch. Environ. Health 37: 44-52.

Sherlock, J.; Smart, G.; Forbes, G.I.; Moore, M.R.; Patterson, W.J.; Richards, W.N.; Wilson, T.S. (1982) Assessment of lead intakes and dose-response for a population in Ayr exposed to a plumbsolvent water supply. Hum. Toxicol. 1: 115-122.

Shirahata, H.; Elias, R.W.; Patterson, C.C. (1980) Chronological variations in concentrations and isotopic compositions of anthropogenic atmospheric lead in sediments of a remote subalpine pond. Geochim. Cosmochim. Acta 44: 149-162.

Silbergeld, E.K. (1983) Experimental studies of lead neurotoxicity: implications for mechanisms, dose-response, and reversibility. In: Lead versus health: sources and effects of low level lead exposure, M. Rutter; R.R. Jones, eds. John Wiley & Sons, Ltd., Chichester, U.K.

Silbergeld, E.K.; Adler, H.S. (1978) Subcellular mechanisms of lead neurotoxicity. Brain Res. 148: 451-467.

Silbergeld, E.K.; Adler, H.S.; Costa, J.L. (1977) Subcellular localization of lead in synaptosomes. Res. Commun. Chem. Pathol. Pharmacol. 17: 715-725.

Silbergeld, E.K.; Fales, J.T.; Goldberg. A.M. (1974) Evidence for a junctional effect of lead on neuromusclar function. Nature (London) 247: 49-50.

Silbergeld, E.K.; Goldberg, A.M. (1975) Pharmacological and neurochemical investigations of lead-induced hyperactivity. Neuropharmacol. 14: 431-444.

Silbergeld, E.K.; Goldberg, A.M. (1980) Problems in experimental studies of lead poisoning. In: Lead toxicity, R. Singhal; J.A. Thomas, eds. Urban and Schwarzenberg, Baltimore.

Silbergeld, E.K.; Hruska, R.E.; Bradley, D.; Lamon, J.M.; Frykholm, B.C. (1982) Neurotoxic aspects of porphyrinopathies: lead and succinylacetone. Environ. Res. 29: 459-471.

Silbergeld, E.K.; Hruska, R.E.; Miller, L.P.; Eng, N. (1980) Effects of lead in vivo and in vitro on GABAergic neurochemistry. J. Neurochem. 34: 1712-1718.

Silbergeld, E.K.; Lamon, J.M. (1980) Role of altered heme synthesis in lead neurotoxicity. J. Occup. Med. 22: 680-684.

Silbergeld, E.K.; Miller, L.P.; Kennedy, S.; Eng, N. (1979) Lead, GABA, and seizures: effects of subencephalopathic lead exposure on seizure sensitivity and GABAergic function. Environ. Res. 19: 371-382.

Sillman, A.J.; Bolnick, D.A.; Bosetti, J.B.; Haynes, L.W.; Walter, A.E. (1982) The effects of lead and of cadmium on the mass photoreceptor potential: the dose-response relationship. Neurotoxicology 3: 179-194.

Silva, P.A.; Hughes, P.; Williams, S.; Faed, J. (1986) Blood lead, intelligence, reading attainment, and behaviour in eleven year old children in Dunedin, New Zealand. J. H. Child Psychology and Psychiatry (in press).

Silvasi, J. (1985) Control Programs Development Division, Office of Air Quality Planning and Standards, U.S. EPA, Research Triangle Park, N.C. Personal communication.

Silver, W.; Rodriguez-Torres, R. (1968) Electrocardiographic studies in children with lead poisoning. Pediatrics 41: 1124-1127.

Singer, R.; Valciukas, J.A.; Lilis, R. (1983) Lead exposure and nerve conduction velocity: the differential time course of sensory and motor nerve effects. Neurotox. 4: 193-202.

Sippel, A.J.A.; Geraci, J.R.; Hodson, P.V. (1983) Histopathological and physiological responses of rainbow trout (Salmo gairdneri Richardson) to sublethal levels of lead. Water Res. 17: 1115-1118.

Sirover, M.A.; Loeb, L.A. (1976) Infidelity of DNA synthesis in vitro: screening for potential metal mutagens or carcinogens. Science (Washington, D.C.) 194: 1434-1436.

Skogerboe, R.K. (1975) Analytical chemistry. In: Environmental contamination caused by lead. Washington, D.C.: National Science Foundation; pp. 187-203.

Slinn, W.G. (1982) Predictions for particle deposition to vegetative canopies. Atmos. Environ. 16: 1785-1794.

Smith, F.L., 2nd; Rathmell, T.K.; Marcil, G.E. (1938) The early diagnosis of acute and latent plumbism. Am. J. Clin. Pathol. 8: 471-508.

Smith, M.; Delves, T.; Lansdown, R.; Clayton, B.; Graham, P. (1983) The effects of lead exposure on urban children: the Institute of Child Health/ Southampton study. London, United Kingdom: Spastics International Medical Publications. (Developmental medicine and child neurology supps. 47.)

Smith, W.H. (1976) Lead contamination of the roadside ecosystem. J. Air Pollut. Control Assoc. 26: 753-766.

Smith, W.H. (1981) Air pollution and forests: interactions between air contaminants and forest ecosystems. New York, NY: Springer-Verlag.

Snee, R.D. (1982a) Development of an air quality standard for lead from community studies. Environ. sci. Technol. 16: 241-246.

Snee, R.D. (1982b) Silver Valley lead study: further analysis of the relationship between blood lead and air lead. J. Air Pollut. Control Assoc. 32: 170-175.

Spittler, T.M.; Feder, W.A. (1978) A study of soil contamination and plant uptake of lead in boston urban gardens. Presented at: Toxic element studies: food crops and urban vegetable gardens. A symposium sponsored by the New York City Gardening Program; June; The Bronx, NY. Ithaca, NY: Cornell University Cooperative Extension. Also in: Commun. Soil Sci. Plant Anal. 10: 1195-1210 (1979).

Spivey, G.H.; Brown, C.P.; Baloh, R.W.; Campion, D.S.; Valentine, J.L.; Massey, F.J., Jr.; Browdy, B.L.; Culver, B.D. (1979) Subclinical effects of chronic increased lead absorption--a prospective study. I: Study design and analysis of symptoms. J. Occup. Med. 21: 423-429.

Staessen, J.; Bulpitt, C.J.; Roels, H.; Bernard, A.; Fagard, A.; Joossens, J.V.; Lauwerys, R.; Lijnen, P.; Amery, A. (1984) Urinary cadmium and lead concentrations and their relation to blood pressure in a population with low exposure. Br. J. Ind. Med. 41: 241-248.

Stark, A.D.; Quah, R.F.; Meigs, J.W.; DeLouise, E.R. (1982) The relationship of environmental lead to blood-lead levels in children. Environ. Res. 27: 372-383.

Steenhout, A. (1982) Kinetics of lead storage on teeth and bones: an epidemiologic approach. Arch. Environ. Health 37: 224-231.

Steenhout, A.; Pourtois, M. (1981) Lead accumulation in teeth as a function of age with different exposures. Br. J. Ind. Med. 38: 297-303.

Stephens, M.C.C.; Gerber, G.B. (1981) Development of glycolipids and gangliosides in lead treated neonatal rats. Toxicol. Lett. 7: 373-378.

Stowe, H.E.; Goyer, R.A. (1971) The reproductive ability and progeny of F_1 lead-toxic rats. Fertil. Steril. 22: 755-760.

Stuik, E.J. (1974) Biological response of male and female volunteers to inorganic lead. Int. Arch. Arbeitsmed. 33: 83-97.

Stumpf, W.E.; Sar, M.; Grant, L.D. (1980) Autoradiographic localization of ^{210}Pb and its decay products in rat forebrain. Neurotoxicology 1: 593-606.

Sung, M.W.; Yang, W. J. (1979) Effects of some heavy metals (Al, Cd, Hg, and Pb) on ATP content in plant leaves. Korean J. Bot. 22: 107-113.

Swift, M.J.; Heal, O.W.; Anderson, J.M. (1979) Decomposition in terrestrial ecosystems. Los Angeles, CA: University of California Press. (Anderson, D.J.; Greig-Smith, P.; Pitelka, F.A., eds. Studies in ecology: v. 5.)

Tanaka, J.; Ichikuni, M. (1982) Monitoring of heavy metals in airborne particles by using bark samples of Japanese cedar collected from the metropolitan region of Japan. Atmos. Environ. 16: 2015-2018.

Taylor, D.; Nathanson, J.; Hoffer, B.; Olson, L.; Seiger, A. (1978) Lead blockade of norepinephrine-induced inhibition of cerebellar Purkinje neurons. J. Pharmacol. Exp. Ther. 206: 371-381.

Tepper, L.B.; Levin, L.S. (1975) A survey of air and population lead levels in selected American communities. In: Griffin, T.B.; Knelson, J.H., eds. Lead. New York, NY: Academic Press; pp. 152-195. (Coulston, F.; Korte, F., eds. Environmental quality and safety: suppl. v. 2).

Tera, O.; Schwartman, D.W.; Watkins, T.R. (1985) Identification of gasoline lead in children's blood using isotopic analysis. Arch. Env. Health 40: 120-123.

Ter Haar, G. (1970) Air as a source of lead in edible crops. Environ. Sci. Technol. 4: 226-229.

Ter Haar, G.; Aronow, R. (1974) New information on lead in dirt and dust as related to the childhood lead problem. Environ. Health Perspect. 7: 83-89.

Ter Haar, G.L.; Bayard, M.A. (1971) Composition of airborne lead particles. Nature (London) 232: 553-554.

Thrall, A.D.; Baptista, J.L.; Burton, C.S. (1984) An examination of air quality data completeness requirements. Prepared for: Monitoring and Reports Branch, Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Research Triangle Park, N.C.

Tola, S.; Hernberg. S.; Asp, S.; Nikkanen, J. (1973) Parameters indicative of absorption and biological effect in new lead exposure: a prospective study. Br. J. Ind. Med. 30: 134-141.

Tosteson, T.D.; Spengler, J.D.; Weker, R.A. (1982) Aluminum, iron, and lead content of respirable particulate samples from a personal monitoring survey. Environ. Int. 8: 265-268.

Triebig, G.; Nottbohm, L. (1983) Nerve conduction velocity study in workers chronically exposed to lead. In: International conference: heavy metals in the environment: v. 2; September; Heidelberg, West Germany. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 907-911.

Tsoukas, C.D.; Provvedini, D.M.; Manolagas, S.C. (1984) 1,25-dihydroxy-vitamin D_3: a novel immunoregulatory hormone. Science (Washington D.C.) 224: 1438-1439.

Tyler, D.D. (1984) Control Program Development Division, U.S. EPA, RTP, N.C. Source-oriented lead monitors and lead acid battery manufacturers. Technical Memorandum to Director, Air and Waste Management Division, U.S. EPA, Regions I-X.

Tyler, G. (1972) Heavy metals pollute nature, may reduce productivity. Ambio. 1: 52-59.

Tyler, G. (1978) Leaching rates of heavy metal ions in forest soil. Water Air Soil Pollut. 9: 137-148.

U.K. Central Directorate [United Kingdom Central Directorate on Environmental Pollution] (1982) The Glasgow duplicate diet study (1979/1980): a joint survey for the Department of the Environment and the Ministry of Agriculture Fisheries and Food. London, United Kingdom: Her Majesty's Stationery Office; pollution report no. 11.

U.S. Bureau of the Census (1982) 1980 census of population and housing: supplementary report: provisional estimates of social, economic, and housing characteristics: states and selected standard metropolitan statistical areas. Washington, D.C.: U.S. Department of Commerce; Bureau of the Census report no. PHC 80-S1-1. Available from: U.S. Department of Commerce, Bureau of the Census, Washington, D.C.

U.S. Bureau of Mines, Minerals Yearbook (1929-1983) Department of the Interior, Washington, D.C.

U.S. Department of Commerce (1968) Climatic atlas of the United States. Environmental Science Services Administration, Environmental Data Service. Reprinted 1977 National Oceanic and Atmospheric Administration, p. 43.

U.S. FDA [Food and Drug Administration] (1983) Market basket survey: preliminary results for lead analysis. Available for inspection at: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

U.S. FDA [Food and Drug Administration] (1984) Market basket survey: preliminary results for lead analysis. Available for inspection at: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

Urban, W.D. (1976) Analysis of blood lead levels of children surveyed in Pittsburgh, Pennsylvania: analytical methodologies and summary results. Washington, D.C.: U.S. Dept. of Commerce, National Bureau of Standards; report no. NBSIR76-1024. Available from NTIS, Springfield, VA; PB 255876.

Valentine, W.N.; Paglia, D.E. (1980) Erythrocyte disorders of purine and pyrimidine metabolism. Hemoglobin 4: 669-681.

Valentine, W.N.; Paglia, D.E.; Fink, K.; Madokoro, G. (1976) Lead poisoning: association with hemolytic anemia, basophilic stippling, erythrocyte pyrimidine 5'-nucleotidase deficiency, and intraerythrocytic accumulation of pyrimidines. J. Clin. Invest. 58: 926-932.

Vallee, B.L.; Ulmer, D.D. (1972) Biochemical effects of mercury, cadmium, and lead. Annu. Rev. Biochem. 41: 91-128.

van Rossum, G.D.V.; Kapoor, S.C.; Rabinowitz, M.J. (1985). Effects of inorganic lead in vitro on ion exchanges and respiratory metabolism of rat kidney cortex. Arch. Toxicol. 56: 175-181.

Victery, W.; Vander, A.J.; Markel, H.; Katzman, L.; Shulak, J.M.; Germain, C. (1982) Lead exposure, begun in in utero, decreases renin and angiotensin II in adult rats (41398). Proc. Soc. Exp. Biol. Med. 170: 63-67.

Wada, O.; Takeo, K.; Yano, Y.; Ono, T.; Nagahashi, M.; Seki, H. (1976) δ-Aminolevulinic acid dehydratase in low level lead exposure. Arch. Environ. Health 31: 211-215.

Wade, K. J.; Flanagan, J. T.; Currie, A.; Curtis, D. J. (1980) Roadside gradients of lead and zinc concentrations in surface-dwelling invertebrates. Environ. Pollut. Serv. B 1: 87-93.

Wallsten, T.S.; Whitfield, R.G. (1986) Estimating the risks of lead-induced health effects. Draft report prepared for U.S. EPA, Ambient Standards Branch, Strategies and Air Standards Division, Office of Air Quality Planning and Standards, Research Triangle Park, N.C. Argonne National Laboratory, Energy and Environmental Systems Division, Decision and System Sciences, January 1986.

Walter, S. D.; Yankel, A. J.; von Lindern, I. H. (1980) Age-specific risk factors for lead absorption in children. Arch. Environ. Health 35: 53-58.

Watson, A. P.; Van Hook, R. I.; Jackson, D. R.; Reichle, D. E. (1976) Impact of a lead mining smelting complex on the forest-floor litter arthropod fauna in the new lead belt region of southeast Missouri. Oak Ridge, TN: Oak Ridge National Laboratory, Environmental Sciences Division; Environmental Sciences Division publication no. 881. Available from: NTIS, Springfield, VA; ORNL/NSF/EATC-30.

Webb, R. C.; Winquist, R. J.; Victery, W.; Vander, A. J. (1981). In vivo and in vitro effects of lead on vascular reactivity in rats. Am. J. Physiol. 241: H211-H216.

Wedeen, R. P. (1982) Lead nephrotoxicity. In: Porter, G., ed. Nephrotoxic mechanisms of drugs and environmental toxins. New York, NY: Plenum Publishing Corp.; pp. 255-265.

Wedeen, R. P.; Mallik, D. K.; Batuman, V. (1979) Detection and treatment of occupational lead nephropathy. Arch. Intern. Med. 139: 53-57.

Wender, P. H. (1971) Minimal Brain Dysfunction in Children. Wiley-Interscience. New York.

Wershaw, R. L. (1976) Organic chemistry of lead in natural water systems. In: Lovering, T. G., ed. Lead in the environment. Washington, D.C.: U.S. Department of the Interior, Geological Survey: Geological Survey professional paper No. 957. Available from: GPO, Washington, D.C.; S/N 024-001-02911-1; pp. 13-16.

Wheeler, G. L.; Rolfe, G. L. (1979) The relationship between daily traffic volume and the distribution of lead in roadside soil and vegetation. Environ. Pollut. 18: 265-274.

Whetsell, W. O., Jr.; Kappas, A. (1981) Protective effect of exogenous heme against lead toxicity in organotypic cultures of mouse dorsal root ganglia (DRG): electon microscopic observations. J. Neuropathol. Exp. Neurol. 40: 334.

Whetsell, W. O., Jr.; Sassa, S.; Bickers, D.; Kappas, A. (1978) Studies on prophyrin-heme biosynthesis in organotypic cultures of chick dorsal root ganglion. I: Observations on neuronal and non-neuronal elements. J. Neuropathol. Exp. Neurol. 37: 497-507.

Whetsell, W. O., Jr.; Sassa, S.; Kappas, A. (1984) Porphyrin-heme biosynthesis in organotypic cultures of mouse dorsal root ganglia. J. Clin. Invest.: in press.

White, J. M.; Harvey, D. R. (1972) Defective synthesis of α and β globin chains in lead poisoning. Nature (London) 236: 71-73.

WHO [World Health Organization], United Nations Environmental Programme. (1977) Lead. Geneva, Switzerland: World Health Organization. (Environmental health criteria 3.)

Wildt, K.; Eliasson, R.; Berlin, M (1983) Effects of occupational exposure to lead on sperm and semen. Presented at: A joint meeting of the Rochester conference and scientific committee (PCIAOH) on the toxicology of metals: reproductive and development toxicity of metals; May; Rochester, NY.

Williams, B. J.; Griffith, W. H., III; Albrecht, C. M.; Pirch, J. H.; Hejtmancik, M. R., Jr. (1977b) Effects of chronic lead treatment on some cardiovascular responses to norepinephrine in the rat. Toxicol. Appl. Pharmacol. 40: 407-413.

Williams, B. J.; Griffith, W. H.; Albrecht, C. M.; Pirch, J. H.; Hejtmancik, M. R., Jr.; Nechay, B. R. (1977a) Cardiac effect of chronic lead poisoning. In: Brown, S. S., ed. Clinical chemistry and chemical toxicology of metals. New York, NY: Elsevier/North-Holland Biomedical Press; pp. 127-130.

Williams, M. K.; King, E.; Walford, J. (1969) An investigation of lead absorption in an electric accumulator factory with the use of personal samplers. Br. J. Ind. Med. 26: 202-216.

Williams, S. T.; McNeilly, T.; Wellington, E. M. H. (1977c) The decomposition of vegetation growing on metal mine waste. Soil Biol. Biochem. 9: 271-275.

Williamson, P.; Evans, P. R. (1972) Lead: levels in roadside invertebrates and small mammals. Bull. Environ. Contam. Toxicol. 8: 280-288.

Windebank, A.J.; McCall, J.T.; Hunder, H.G.; Dyck, P.J. (1980) The endoneurial content of lead related to the onset and severity of segmental demyelination. J. Neuropathol. Exp. Neurol. 39: 692-699.

Winneke, G. (1980) Non-recovery of lead-induced changes of visual evoked potentials in rats. Toxicol. Lett. Spec. Iss. 1: 77.

Winneke, G.; Beginn, U.; Ewert, T.; Havestadt, C.; Kramer, U.; Krause, C.; Thron, H. L.; Wagner, H. M. (1984) Studie zur Erfassung subklinischer Bleiwirkungen auf das Nervensystem bei Kindern mit bekannter pranataler Exposition in Nordenham. [Study on the determination of subclinical lead effects on the nervous system of Nordenham children with known pre-natal exposure.] BGA-Berichte: in press.

Winneke, G.; Brockhaus, A.; Baltissen, R. (1977) Neurobehavioral and systemic effects of longterm blood lead-elevation in rats. I: Discrimination learning and open field-behavior. Arch. Toxicol. 37: 247-263.

Winneke, G.; Hrdina, K-G.; Brockhaus, A. (1982a) Neuropsychological studies in children with elevated tooth-lead concentrations. Part I: Pilot study. Int. Arch. Occup. Environ. Health 51: 169-183.

Winneke, G.; Kramer, U.; Brockhaus, A.; Ewers, U.; Kujanek, G.; Lechner, H.; Janke, W. (1983) Neuropsychological studies in children with elevated tooth lead concentrations. Part II: Extended study. Int. Arch. Occup. Environ. Health 51: 231-252.

Winneke, G.; Lilienthal, H.; Werner, W. (1982b) Task dependent neurobehavioral effects of lead in rats. Arch. Toxicol. Suppl. 5: 84-93.

Wintrobe, M.W. (1979) Clinical Hematology, (Sixth Ed) Lea and Febiger, Philadelphia. pp. 348-350.

Wixson, B. G. (1978) Biogeochemical cycling of lead in the New Lead Belt of Missouri. In: The biogeochemistry of lead in the environment, Part A: Ecological cycles, J. O. Nriago, ed. Elsevier/North-Holland Biomedical Press, New York.

Wolnik, K. A.; Fricke, F. L.; Capar, S. G.; Braude, G. L.; Meyer, M. W.; Satzger, R. D.; Bonnin, E. (1983) Elments in major raw agricultural crops in the United States: 1. Cadmium and lead in lettuce, peanuts, potatoes, soybeans, sweet corn, and wheat. J. Agric. Food Chem. 31: 1240-1244.

Wong, M. H.; Bradshaw, A. D. (1982) A comparison of the toxicity of heavy metals, using root elongation of rye grass, Lolium perenne. New Phytol. 91: 255-261.

Wong, P. T. S.; Silverberg, B. A.; Chau, Y. K.; Hodson, P. V. (1978) Lead and the aquatic biota. In: Nriagu, J. O., ed. The biogeochemistry of lead in the environment. Part B: Biological effects. Amsterdam, The Netherlands: Elsevier/North-Holland Biomedical Press; pp. 279-342.

Worth, D.; Matranga, A.; Lieberman, M.; DeVos, E.; Karelekas, P.; Ryan, C.; Craun, C. (1981) Lead in drinking water: the contribution of household tap water to blood lead levels. In: Lynam, D. R.; Piantanida, L. G.; Cole, J. F., eds. Environmental lead: proceedings of the second international symposium on environmental lead research; December 1978; Cincinnati, OH. New York, NY: Academic Press; pp. 199-225.

Wyrobek, A. J.; Bruce, W. R. (1978) The induction of sperm-shape abnormalities in mice and humans. In: Hollaender, A.; de Serres, F. J., eds. Chemical mutagens: principles and methods for their detection: vol. 5. New York, NY: Plenum Press; pp. 257-285.

Yaffe, Y.; Flessel, C. P.; Wesolowski, J. J.; Del Rosario, A.; Guirguis, G. N.; Matias V.; DeGarmo, T. E.; Coleman, G. C.; Gramlich, J. W.; Kelly, W. R. (1983) Identification of lead sources in California children using the stable isotope ration technique. Arch. Env. Health 38: 237-245.

Yankel, A. J.; Von Lindern, I. H.; Walter, S. D. (1977) The Silver Valley lead study: the relationship of childhood lead poisoning and environmental exposure. J. Air Pollut. Control Assoc. 27: 763-767.

Yarn, J. (1984) Control Programs Development Division, Office of Air Quality Planning and Standards, U.S. EPA, RTP, N.C. Personal communication based on analysis of available air quality data up until summer, 1984 in SAROAD data system.

Yocom, J. E. (1982) Indoor-outdoor air quality relationships: a critical review. J. Air Pollut. Control Assoc. 32: 500-520.

Yocom, J. E.; Clink, W. L.; Cote, W. A. (1971) Indoor/outdoor air quality relationships. J. Air Pollut. Control Assoc. 21: 251-259.

Youroukos, S.; Lyberatos, C.; Philipidou, A.; Gardikas, C.; Tsomi, A. (1978) Increased blood lead levels in mentally retarded children in Greece. Arch. Env. Health 33: 297-300.

Yule, W.; Lansdown, R. (1983) Lead and children's development: recent findings. Presented at: International conference: management and control of heavy metals in the environment; September; Heidelberg, West Germany. Edinburgh, United Kingdom: CEP Consultants, Ltd.

Yule, W.; Lansdown, R.; Hunter, J.; Urbanowicz, M. A.; Clayton, B.; Delves, T. (1983) Blood lead concentrations in school age children, intelligence, attainment and behaviour. Background information to a paper presented at the Annual Conference of the British Psychological Society at the University of York; April 1983; York, United Kingdom. Available for inspection at: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

Yule, W.; Lansdown, R.; Millar, I. B.; Urbanowicz, M-A. (1981) The relationship between blood lead concentrations, intelligence and attainment in a school population: a pilot study. Dev. Med. Child Neurol. 23: 567-576.

Yule, W.; Urbanowicz, M-A.; Lansdown, R.; Millar, I. B. (1984) Teachers' ratings of children's behavior in relation to blood lead levels. British Journal of Develomental Psychology: in press.

Zenick, H.; Pecorraro, F.; Price, D.; Saez, K.; Ward, J. (1979) Maternal behavior during chronic lead exposure and measures of offspring development. Neurobehav. Toxicol. 1: 65-71.

Ziegler, E. E.; Edwards, B. B.; Jensen, R. L.; Mahaffey, R. R.; Fomon, S.J. (1978) Absorption and retention of lead by infants. Pediatr. Res. 12: 29-34.

Zielhuis, R. L. (1975) Dose-response relationships for organic lead. Int. Arch. Occup. Health 35: 1-18.

Zielhuis, R. L.; del Castilho, P.; Herber, R. F. M.; Wibowo, A. A. E.; Salle, H. J. A. (1979) Concentrations of lead and other metals in blood of two and three year-old children living near a secondary smelter. Int. Arch. Occup. Environ. Health 42: 231-239.

Zimdahl, R. L.; Hassett, J. J. (1977) Lead in soil. In: Lead in the Environment: A report and analysis of research at Colorado State University, University of Illinois, and University of Missouri (W.R. Boggess, ed.); Washington, D.C.: National Science Foundation: NSF report no. NSF/RA-770214; pp. 93-98.

Zimdahl, R. L.; Skogerboe, R. K. (1977) Behavior of lead in soil. Environ. Sci. Technol. 11: 1201-1207.

Zimmerman-Tansella, C.; Campara, P.; D'Andrea, F.; Savonitto, C.; Tansella, M. (1983) Psychological and physical compliants of subjects with low exposure to lead. Hum. Toxicol. 2: 615-623.

Zurlo, N.; Griffini, A. M. (1973) Lead contents in foods and beverages consumed in Milan. In: Proceedings, international symposium on the environmentl health aspects of lead; October, 1972; Amsterdam, The Netherlands. Luxembourg: Commission of The European Communities; pp. 93-98.

REFERENCES

Adenbojo, F.O. (1974) Hematologic status of urban black children in Philadelphia: emphasis on the frequency of anemia and elevated blood lead levels. Clin. Pediatr. (Philadelphia) 13: 874-888.

Albahary, C. (1972) Lead and hemopoiesis: the mechanism and consequences of the erythropathy of occupational lead poisoning. Am. J. Med. 52: 367-378.

Alexander, F.W.; Delves, H.T. (1981) Blood lead levels during pregnancy. Int. Arch. Occup. Environ. Health 48: 35-39.

Alexander, F.W.; Delves, H.T.; Clayton, B.E. (1973) The uptake and excretion by children of lead and other contaminants. In: Barth, D.; Berlin, A.; Engel, R.; Recht, P.; Smeets, J., eds. Environmental health aspects of lead proceedings, international symposium: October 1972; Amsterdam, The Netherlands. Luxembourg: Commission of the European Communities, Centre for Information and Documentation. pp. 319-331.

Alfano, D.P.; Petit, T.L. (1982) Neonatal lead exposure alters the dendritic development of hippocampal dentate granule cells. Exp. Neurol. 75: 275-288.

Altman, P.L.; Dittmer, D.S. (1971) Respiration and Circulation. Fed. Am. Soc. for Exp. Biol., Bethesda, MD, pp. 40-41 and 78-84.

Alvares, A.P.; Fischbein, A.; Sassa, S.; Anderson, K.E.; Kappas, A. (1976) Lead intoxication: effects on cytochrome P-450-mediated hepatic oxidations. Clin. Pharmacol. Ther. 19: 183-190.

Alvares, A.P.; Kapelner, S.; Sassa, S.; Kappas, A. (1975) Drug metabolism in normal children, lead-poisoned children, and normal adults. Clin. Pharmacol. Ther. 17: 179-183.

American Psychiatric Association (1980) Diagnostic and statistical manual of mental disorders (3rd ed.); pp. 41-45.

Angle, C.R. (1985) Personal communication to Donna Sledge, Office of Air Quality Planning and Standards, U.S. EPA, Durham, N.C. July 27, 1985.

Angle, C.R.; Marcus, A.; Cheng, I-H, McIntire, M.S. (1984) Omaha childhood blood lead and environmental lead: a linear total exposure model. Environ. Res. 35: in press.

Angle, C.R.; McIntire, M.S. (1978) Low level lead and inhibition of erythrocyte pyrimidine nucleotidase. Environ. Res. 17: 296-302.

Angle, C.R.; McIntire, M.S. (1979) Environmental lead and children: the Omaha study. J. Toxicol. Environ. Health 5: 855-870.

Angle, C.R.; McIntire, M.S. (1982) Children, the barometer of environmental lead. Adv. Pediatr. 27: 3-31.

Angle, C.R.; McIntire, M.S.; Stelmark, K.L. (1975) High urban lead and decreased red blood cell survival. Intl. Conf. on Heavy Metals in the Environment, Toronto, Ont. Oct. 27-31, 1975, pp. 87-104.

Angle, C.R.; McIntire, M.S.; Swanson, M.S.; Stohs, J.J. (1982) Erythrocyte nucleotides in children - increased blood lead and cytidine triphosphate. Pediatr. Res. 16: 331-334.

Annest, J.L., Mahaffey, K.R., Cox, D.H., Roberts, J. (1982) Blood lead levels for persons 6 months - 74 years of age: United States, 1976-80, Hyattsville, MD: U.S. Department of Health and Human Services; DHHS pub.no. (PHS) 82-1250. (Advance data from vital and health statistics of the National Center for Health Statistics: No 79).

Annest, J.L.; Pirkle, J.L.; Makug, D.; Neese, J.W.; Bayse, D.D.; Kovar, M.G. (1983) Chronological trend in blood lead levels between 1976 and 1980. N. Engl. J. Med. 308: 1373-1377.

Antonovics, J.; Bradshaw, A.D.; Turner, R.G. (1971) Heavy metal tolerance in plants. Adv. Ecol. Res. (London) 7: 1-85.

Araki, S.; Honma, T. (1976) Relationships between lead absorption and peripheral nerve conduction velocities in lead workers. Scand. J. Work. Environ. Health 4: 225-231.

Araki, S.; Ushio, K. (1982) Assessment of the body burden of chelatable lead: a model and its application to lead workers. Br. J. Ind. Med. 39: 157-160.

Atkins, D.P.; Trueman, I.C.; Clarke, C.B.; Bradshaw, A.D. (1982) The evolution of lead tolerance by Festuca rubra on a motorway verge. Environ. Pollut. Ser. A 27: 233-241.

Averill, D.R., Jr.; Needleman, H.L. (1980) Neonatal lead exposure retards cortical synaptogenesis in the rat. In: Needleman, H.L., ed. Low level lead exposure: the clinical implications of current research. New York, N.Y.: Raven Press; pp. 201-210.

Azar, A.; Snee, R.D.; Habibi, K. (1975) An epidemiologic approach to community air lead exposure using personal air samplers. In: Lead. Environ. Qual. Saf. Suppl. 2: 254-290.

Azar, A.; Trochimowicz, H.J.; Maxfield, M.E. (1973) Review of lead studies in animals carried out at Haskell Laboratory: two year feedings study and response to hemmorhage study. In Barth, D.; Berlin, A.; Engel, R.; Recht, P.; Smeets, J., eds. Environmental health aspects of lead: proceedings, international symposium; October 1972; Amsterdam, The Netherlands. Luxembourg: Commission of the European Communities, Centre for Information and Documentation; pp. 199-210.

Babich, H.; Stotzky, G. (1979) Abiotic factors affecting the toxicity of lead to fungi. Applied and Environmental Microbiology 38: 506-513.

Baker, E.L.; Goyer, R.A.; Fowler, B.A.; Khettry, U.; Bernard, D.B.; Adler, S.; White, R.D.; Babayan, R.; Feldman, R.G. (1980) Occupational lead exposure, nephropathy, and renal cancer. Am. J. Ind. Med. 1: 139-148.

Baker, E.L., Jr.; Landrigan, P.J.; Barbour, A.G.; Cox, D.H., Folland, D. S.; Ligo, R.N.; Throckmorton, J. (1979) Occupational lead poisoning in the United States: clinical and biochemical findings related to blood lead levels. Br. J. Ind. Med. 36: 314-322.

Baloh, R.W. (1974) Laboratory diagnosis of increased lead absorption. Arch. Environ. Health 28: 198-208.

Baloh, R.; Sturm, R.; Green, B.; Gleser, G. (1975) Neuropsychological effects of chronic asymptomatic increased lead absorption: a controlled study. Arch. Neurol. 32: 326-330.

Barltrop, D. (1966) The prevalence of pica. Am. J. Dis. Child. 112: 116-123.

Barltrop, D. (1969) Transfer of lead to the human fetus. In: Barltrop, D.; Burland, W.L., eds. Mineral metabolism in pediatrics. Philadelphia, PA; Davis Co.; pp. 135-151.

Barltrop, D.; Barrett, A.J.; Dingle, J.T. (1971) Subcellular distribution of lead in the rat. J. Lab. Clin. Med. 77: 705-712.

Barltrop, D.; Meek, F. (1975) Absorption of different lead compounds. Postgrad. Med. J. 51: 805-809.

Barltrop, D.; Strehlow, C.D.; Thornton, I.; Webb, J.S. (1975) Absorption of lead from dust and soil. Postgrad. Med. J. 51: 801-804.

Barrett, J.; Livesey, P.J. (1985) Lead induced alterations in maternal behavior and offspring development in the rat. Neurobehav. Toxicol. Teratol. 5: 557-563.

Barry, P. S. I. (1975) A comparison of concentrations of lead in human tissues. Br. J. Ind. Med. 32: 119-139.

Barry, P.S.I. (1981) Concentrations of lead in the tissues of children. Br. J. Ind. Med. 38: 61-71.

Barton, J.C.; Conrad, M.E.; Nuby, S.; Harrison, L. (1978) Effects of iron on the absorption and retention of lead. J. Lab. Clin. Med. 92: 536-547.

Batschelet, E.; Brand, L.; Steiner, A. (1979) On the kinetics of lead in the human body. J. Math. Biol. 8: 15-23.

Battye, W. (1984) Lead monitoring data analysis. Technical memorandum to John Haines, U.S. EPA, Office of Air Quality Planning and Standards, Durham, N.C. GCA Corporation, Technology Division, October 25, 1984.

Battye, W. (1985a) Lead concentration frequency distributions and trends for 1980 to 1983. Technical memorandum to John Haines and Jeff Cohen, U.S. EPA, Office of Air Quality Planning and Standards, Durham, N.C. GCA Corporation, Technology Division, February 25, 1985.

Battye, W. (1985b) Predicted mobile source lead impact for 1990 and 1995. Technical memorandum to John Haines and Jeff Cohen, U.S. EPA, Office of Air Quality Planning and Standards, Durham, N.C. GCA Corporation, Technology Division, April, 1985.

Battye, W. (1985c) Estimated numbers of children residing near lead point sources. Technical memorandum to John Haines and Jeff Cohen, U.S. EPA, Office of Air Quality Planning and Standards, Durham, N.C. GCA Corporation, Technology Division, April, 1985.

Battye, W. (1985d) Calculation of urban mobile source background concentrations for the lead RIA exposure analysis. Technical memorandum to John Haines, U.S. EPA, Office of Air Quality Planning and Standards, Durham, N.C. GCA Corporation, Technology Division, November 20, 1985.

Battye, W.; Battye, R.; Browne, N.; Clowers, M.; Eichinger, J.; Viconovic, G. (1985) Cost assessment of regulatory alternatives for lead national ambient air quality standards. Revised draft report prepared for U.S. EPA, Ambient Standards Branch, Strategies and Air Standards Division, Office of Air Quality Planning and Standards, Research Triangle Park, N.C. GCA Corporation, Technology Division, GCA-TR-83-105G, July 1985.

Batuman, V.; Landy, E.; Maesaka, J.K.; Wedeen, R.P. (1983) Contribution of lead to hypertension with renal impairment. N. Engl. J. Med. 309: 17-21.

Batuman, V.; Maesaka, J.K.; Haddad, B.; Tepper, E.; Landry, E.; Wedeen, R.P. (1981) The role of lead in gout nephropathy. N. Engl. J. Med. 304: 520-523.

Bauman, S.E.; Williams, E.T.; Finston, H.L.; Ferrand, E.F.; Sontowski, J. (1982) Street level versus rooftop sampling: carbon monoxide and aerosol in New York City. Atmosph. Environ. 16: 2489-2496.

Beattie, A.D.; Moore, M.R.; Goldberg, A.; Finlayson, M.J.W.; Graham, J. F.; Mackie, E.M.; Main, J.C.; McLaren, D.A.; Murdoch, K.M.; Stewart, G.T. (1975) Role of chronic low-level lead exposure in the aetiology of mental retardation. Lancet 1(7907): 589-592.

Beevers, D.G.; Erskine, E.; Robertson, M.; Beattie, A.D.; Campbell, B.C.; Goldberg, A.; Moore, M.R.; Hawthorne, V.M. (1976) Blood-lead and hypertension. Lancet 2(7975): 1-3.

Bellinger, D.; Leviton, A.; Waternaux, C.; Allred, E. (1985) Methodological issues in modeling the relationship between low level lead exposure and infant development; examples from the Boston lead study. Environ. Res. 38: 119-129.

Bellinger, D.; Needleman, M.C., Bromfield, R.; Nimtz, M. (1984) A followup study of the academic attainment and classroom behavior of children with elevated dentine lead levels. Biol. Trace Element Res. 6: 207 - 223.

Beloian, A.; McDowell, M. (1981) Estimates of lead intakes among children up to 5 years of age, 1973-1978 and 1980. Washington, DC: U.S. Food and Drug Administration, Bureau of Foods; Division of Nutrition final internal report. Available from: U.S. Food and Drug Administration, Bureau of Foods, Washington, DC.

Benignus, V.A.; Otto, D.A.; Muller, K.E.; Seiple, K.J. (1981) Effects of age and body lead burden on CNS function in young children: II. EEG spectra. Electroencephalogr. Clin. Neurophysiol. 52: 240-248.

Berk, J.V.; Young, R.A.; Brown, S.R.; Hollowell, C.D. (1981) Impact of energy-conserving retrofits on indoor air quality in residential housing. For presentation at: 74th annual meeting of the Air Pollution Control Association; June; Philadelphia, PA. Pittsburgh, PA: Air Pollution Control Association; paper no. 81-22.1.

Bernard, S.R. (1977) Dosimetric data and metabolic model for lead. Health Phys. 32: 44-46.

Bethea, R.M.; Bethea, N.J. (1975) Consequences of lead in the ambient environment: an analysis. Residue Reviews 54: 55-77.

Betts, P.R.; Astley, R.; Raine, D.N. (1973) Lead intoxication in children in Birmingham. Br. Med. J. 1(5850): 402-406.

Bhalla, A.K.; Amento, E.P.; Clemens, T.L.; Holick, M.F.; Krane, S.M. (1983) Specific high-affinity receptors for 1,25-dihydroxyvitamin D_3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. J. Clin. Endocrinol. Metab. 57: 1308-1310.

Biesinger, K.E.; Christensen, G.M. (1972) Effects of various metals on survival, growth, reproduction, and metabolism of Daphnia magna. J. Fish. Res. Board Can. 29: 1691-1700.

Biggins, P.D.E.; Harrison, R.M. (1978) Identification of lead compounds in urban air. Nature (London) 272: 531-532.

Biggins, P.D.E.; Harrison, R.M. (1979) Atmospheric chemistry of automotive lead. Environ. Sci. Technol. 13: 558-565.

Biller, W.F.; Feagans, T.B. (1981) Statistical forms of National Ambient Air Quality Standards. Presented at Environetrics 1981 Conference (April 8-10), Alexandria, Va.

Billick, I.H.; Curran, A.S.; Shier, D.R. (1979) Analysis of pediatric blood lead levels in New York City for 1970-1976. Environ. Health Perspect. 31: 183-190.

Billick, I.H.; Curran, A.S.; Shier, D.R. (1980) Relation of pediatric blood lead levels to lead in gasoline. Environ. Health Perspect. 34: 213-217.

Billick, I.H.; Gray, V.E. (1978) Lead based paint poisoning research: review and evaluation 1971-1977. Washington, DC: U.S. Department of Housing and Urban Development, Office of Policy Development and Research; HUD report no. HUD 0000809. Available from: NTIS, Springfield, VA; PB80-136849.

Bisessar, S. (1982) Effect of heavy metals on microorganisms in soils near a secondary lead smelter. Water Air Soil Pollut. 17: 305-308.

Bjorklund, H.; Lind, B.; Piscator, M.; Hoffer, B.; Olson, L. (1981) Lead, zinc, and copper levels in intraocular brain tissue grafts, brain, and blood of lead-exposed rats. Toxicol. Appl. Pharmacol. 60: 424-430.

Blake, K.C.H. (1976) Absorption of ^{203}Pb from gastrointestinal tract of man. Environ. Res. 11: 1-4.

Bordo, B.M.; Filippini, G.; Massetto, N.; Musicco, M.; Boeri, R. (1982) Electrophysiological study of subjects occupationally exposed to lead and with low levels of lead poisoning. Scand. J. Work Environ. Health 8 (Suppl. 1): 142-147.

Borgmann, U.; Kramar, O.; Loveridge, C. (1978) Rates of mortality, growth, and biomass production of Lymnaea palustris during chronic exposure to lead. J. Fish. Res. Board Can. 35: 1109-1115.

Bornschein, R.; Pearson, D.; Reiter, L. (1980) Behavioral effects of moderate lead exposure in children and animal models: part 2, animal studies. CRC Crit. Rev. Toxicol. 8: 101-152.

Botts, R.P. (1977) The short-term effects of lead on domestic and wild animals. Corvallis, OR: Corvallis Environmental Research Laboratory; EPA report no. EPA-600/3-77-009. Available from: NTIS, Springfield, VA; PB 272099.

Bradley, J.E.; Baumgartner, R.J. (1958) Subsequent mental development of children with lead encephalopathy, as related to type of treatment. J. Pediatr. (St. Louis) 53: 311-315.

Bradley, J.E.; Powell, A.E.; Niermann, W.; McGrady, K.R.; Kaplan, E. (1956) The incidence of abnormal blood levels of lead in a metropolitan pediatric clinic: with observation on the value of coproporphyrinuria as a screening test. J. Pediatr. (St. Louis) 49: 1-6.

Brennan, M.J.W.; Cantrill, R.C. (1979) §-Aminolaevulinic acid is a potent agonist for GABA autoreceptors. Nature (London) 280: 514-515.

Brown, D.R. (1975) Neonatal lead exposure in the rat: decreased learning as a function of age and blood lead concentrations. Toxicol. Appl. Pharmacol. 32: 628-637.

Brown, R.S.; Hingerty, B.E.; Dewa , J.C.; Klug, A. (1983) Pb(II) - catalysed cleavage of the sugar-phosphate backbone of yeast + RNA - implications for lead toxicity and self-splicing RNA. Nature 303: 543-546.

Brunekreef, B.D. (1984) The relationship between air lead and blood lead in children: a critical review. Sci. Total Environ. 38: 79-123.

Brunekreef, B.; Noy, D.; Biersteker, K.; Boleij, J. (1983) Blood lead levels of Dutch city children and their relationship to lead in the environment. J. Air Pollut. Control Assoc. 33: 872-876.

Brunekreef, B.; Veenstra, S.J.; Biersteker, K.; Boleij, J.S.M. (1981) The Arnhem lead study: 1. lead uptake by 1- to 3-year-old children living in the vicinity of a secondary lead smelter in Arnhem, The Netherlands. Environ. Res. 25: 441-448.

Buchtal, F.; Behse, F. (1981) Nerve conduction and nerve biopsy in men exposed to lead. In: Lynam, D.R.; Piantanida, L.G.; Cole, J.R., eds. Environmental lead. New York, N.Y.: Academy Press; pp. 69-94.

Bull, K.R.; Every, W.J.; Freestone, P.; Hall, J.R.; Osborn, D. (1983a) Alkyl lead pollution and bird mortalities on the Mersey Estuary, UK, 1979-1981. Environ. Pollut. Ser. A 31: 239-259.

Bull, R.J. (1980) Lead and energy metabolism. In: Singhal, P.L.; Thomas, J.A., eds. Lead toxicity. Baltimore, MD: Urban and Schwarzenberg, Inc.; pp. 119-168.

Bull, R.J. (1983) Delayed metabolic maturation of the cerebral cortex of rat pups derived from lead-treated dams. J. Toxicol. Environ. Health 11: 211-225.

Bull, R.J.; Lutkenhoff, S.D.; McCarty, G.E.; Miller, R.G. (1979) Delays in the postnatal increase of cerebral cytochrome concentrations in lead-exposed rats. Neuropharmacology 18: 83-92..

Bull, R.J.; McCauley, P.T.; Taylor, D.H.; Croften, K.M. (1983) The effects of lead on the developing central nervous system of the rat. Neurotoxicology 4: 1-18.

Bull, R.J.; Stanaszek, P.M.; O'Neill, J.J.; Lutkenhoff, S.D. (1975) Specificity of the effects of lead on brain energy metabolism for substrates donating a cytoplasmic reducing equivalent. Environ. Health Perspect. 12: 89-95.

Burchfiel, J.L.; Duffy, F.H.; Bartels, P.H.; Needleman, H.L. (1980) The combined discriminating power of quantitative electroencephalography and neuropsychologic measures in evaluating central nervous system effects of lead at low levels. In: Needleman, H.L., ed. Low level lead exposure: the clinical implications of current research. New York, NY: Raven Press; pp. 75-89.

Bureau of the Census (1983) Census of Housing: Components of inventory change, United States and regions. Washington, D.C.: U.S. Dept. of Commerce.

Bushnell, P.J.; Bowman, R.E. (1979) Reversal learning deficits in young monkeys exposed to lead. Pharmacol. Biochem. Behav. 10: 733-742.

Bushnell, P.J.; Bowman, R.E.; Allen, J.R.; Marlar, R.J. (1977) Scotopic vision deficits in young monkeys exposed to lead. Science (Washington D.C.) 196: 333-335.

Byers, R.K.; Lord, E.E. (1943) Late effects of lead poisoning on mental development. Am. J. Dis. Child. 66: 471-494.

Camerlynck, R.; Kiekens, L. (1982) Speciation of heavy metals in soils based on charge separation. Plant Soil 68: 331-339.

Campbell, J.B.; Woolley, D.E.; Vijakan, V.K.; Overmann, S.R. (1982) Morphometric effects of postnatal lead exposure on hippocampal development of the 15-day-old rat. Dev. Brain Res. 3: 595-612.

Carpenter, S.J.; Ferm, V.H. (1977) Embryopathic effects of lead in the hamster: a morphologic analysis. Lab. Invest. 37: 369-385.

Castellino, N.; Aloj, S. (1969) Intracellular distribution of lead in the liver and kidney of the rat. Br. J. Ind. Med. 26: 139-143.

Casto, B.C.; Meyers, J.; Dipaolo, J.A. (1979) Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 39: 193-198.

Cavalleri, A.; Baruffini, A.; Minoia, C.; Bianco, L. (1981) Biological response of children to low levels of inorganic lead. Environ. Res. 25: 415-423.

CDC [Center for Disease Control] (1978) Preventing Lead Poisoning in Young Children. U.S. Department of Health, Education, and Welfare. April, 1978.

CDC [Centers for Disease Control] (1985) Preventing Lead Poisoning in Young Children. U.S. Department of Health and Human Services. January, 1985.

Cerklewski, F.L.; Forbes, R.M. (1976) Influence of dietary zinc on lead toxicity in the rat. J. Nutr. 110: 1453-1457.

Chamberlain, A.C. (1983) Effect of airborne lead on blood lead. Atmos. Environ. 17: 677-692.

Chamberlain, A.C.; Heard, M.J. (1981) Lead tracers and lead balances. In: Lynam, D.R.; Piantanida, L.G.; Cole, J.F., eds. Environmental lead: proceedings of the second international symposium on environmental lead research; December 1978; Cincinnati, OH. New York, NY: Academic Press; pp. 175-198.

Chamberlain, A.C.; Heard, M.J.; Little, P.; Newton, D.; Wells, A.C.; Wiffen, R.D. (1978) Investigations into lead from motor vehicles. Harwell, United Kingdom: United Kingdom Atomic Energy Authority; report no. AERE-R9198.

Chan, T.L.; Lippmann, M. (1980) Experimental measurements and empirical modelling of the regional deposition of inhaled particles in humans. Am. Ind. Hyg. Assoc. J. 41: 399-408.

Charney, E.; Kessler, B.; Farfel, M.; Jackson, D. (1983) Childhood lead poisoning: a controlled trial of the effect of dust-control measures on blood lead levels. N. Engl. J. Med. 309: 1089-1093.

Chesney, R.W.; Rosen, J.F.; DeLuca, H.F. (1983) Disorders of calcium metabolism in children. In: Chiumello, G.; Sperling, M., eds. Recent progress in pediatric endocrinology. New York, NY: Raven Press; pp. 5-24.

Cheung, W.Y. (1980) Calmodulin plays a pivotal role in cellular regulation. Science (Washington, D.C.) 207: 19-27.

Chisolm, J.J., Jr. (1965) Chronic lead intoxication in children. Dev. Med. Child Neurol. 7: 529-536.

Chisolm, J.J., Jr. (1981) Dose-effect relationships for lead in young children: evidence in children for interactions among lead, zinc and iron. In: Lynam, D.R.; Piantanida, L.G.; Cole, J.R., eds. Environmental lead: proceedings of the second international symposium on environmental lead research; December 1978; Cincinnati, OH. New York, NY: Academic Press; pp. 1-7.

Chisolm, J.J., Jr. (1984) The continuing hazard of lead exposure and its effects on children. Neurotox. 5: 23-42.

Chisolm, J.J., Jr.; Barltrop, D. (1979) Recognition and management of children with increased lead absorption. Arch. Dis. Child. 54: 249-262.

Chisolm, J.J., Jr.; Harrison, H.E. (1956) Quantitative urinary coproporphyrin excretion and its relation to edathamil calcium disodium administration in children with acute lead intoxication. J. Clin. Invest. 35: 1131-1138.

Chisolm, J.J., Jr.; Mellits, E.D.; Barrett, M.B. (1976) Interrelationships among blood lead concentration, quantitative daily ALA-U and urinary lead output following calcium EDTA. In: Nordberg, G.F.,; ed. Proceedings of third meeting of the subcommittee on the toxicology of metals under the Permanent Commisssion and International Association on Occupational Health; November 1974; Tokyo, Japan. Amsterdam, The Netherlands: Elsevier Publishing Co.; pp. 416-433.

Chisolm, J.J., Jr.; Mellits, E.D.; Quaskey, S.A. (1985) The relationship between the level of lead absorption in children and the age, type, and condition of housing. Env. Res. 38: 31-45.

Choie, D.D.; Richter, G.W. (1974a) Cell proliferation in mouse kidney induced by lead. I: Synthesis of deoxyribonucleic acid. Lab. Invest. 30: 647-651.

Choie, D.D., Richter, G.W. (1974b) Cell proliferation in mouse kidney induced by lead: II: Synthesis of ribonucleic acid and protein. Lab. Invest. 30: 652-656.

Chow, C.P.; Cornish, H.H. (1978) Effects of lead on the induction of hepatic microsomal enzymes by phenobarbital and 3,4-benzpyrene. Toxicol. Appl. Pharmacol. 43: 219-228.

Chow, T.J.; Snyder, C.B.; Earl, J.L. (1975) Isotope ratios of lead as pollutant source indicators. Proceedings of the symposium on isotope ratios as pollutant source and behavior indicators; Vienna, Austria; IAEA.

Christensen, G.; Hunt, E.; Fiandt, J. (1977) The effect of methylmercuric chloride, cadmium chloride, and lead nitrate on six biochemical factors of the brook trout (Salvelinus fontinalis). Toxicol. Appl. Pharmacol. 42: 523-530.

Clark, D.R., Jr. (1979) Lead concentrations: bats vs. terrestrial small mammals collected near a major highway. Environ. Sci. Technol. 13: 338-341.

Clark, S.A.; Stumpf, W.E.; Sar, M. (1981) Effect of 1,25-dihydroxyvitamin D_3 on insulin secretion. Diabetes 30: 382-386.

Clark, S.; Bornschein, R.L.; Succop, P.; Quehee, S.S.; Hammond, P.B.; Peace, B. (1984) Condition and type of housing as indicator of potential environmental lead exposure and pediatric blood lead levels. Env. Res. 38: 46-53.

Cohen, A.F.; Cohen, B.L. (1980) Protection from being indoors against inhalation of suspended particulate matter of outdoor origin. Atmos. Environ. 14: 183-184.

Colombo, A.; Fantechi, R. (1983) Isotopic lead experiment: a dynamic analysis of the isotopic lead experiment results. Luxembourg: Commission of the European Communities.

Committee on Public Works, U.S. Senate (1974) A legislative history of the clean air act amendments. Volume I. Serial No. 93-18. U.S. Government Printing Office, Washington, D.C. prepared by the Environmental Policy Division of the Congressional Research Service of the Library of Congress.

Cook, J.A.; Marconi, E.A.; Di Luzio, N.R. (1974) Lead, cadmium, endotoxin interaction: effect on mortality and hepatic function. Toxicol. Appl. Pharmacol. 28: 292-302.

Cools, A.; Salle, J.A.; Verberk, M.M; Zielhuis, R.L. (1976) Biochemical response of male volunteers ingesting inorganic lead for 49 days. Int. Arch. Occup. Environ. Health 38: 129-139.

Cooper, G.P.; Fox, D.A.; Howell, W.E.; Laurie, R.D.; Tsang, W.; Lewkowski, J.P. (1980) Visual evoked responses in rats exposed to heavy metals. In: Merigan, W.H.; Weiss, B., eds. Neurotoxicity of the visual system. New York, NY: Raven Press; pp. 203-218.

Cooper, G.P.; Manalis, R.S. (1974) Effects of polyvalent cations on synaptic transmission in frog neuromuscular junction and frog sympathetic ganglion. In: Xintaras, C.; Johnson, B.L.; de Groot, I., eds. Behavioral toxicology: early detection of occupational hazards. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health; DHEW (NIOSH) publication no. 74-126; pp. 267-276.

Cooper, W.C. (1981) Mortality in employees of lead production facilities and lead battery plants, 1971-1975. In: Lynam, D.R.; Piantanida, L.G.; Cole, J.F., eds. Environmental lead: proceedings of the second international symposium on environmental lead research; December 1978; Cincinnati, OH. New York, NY: Academic Press; pp. 111-143.

Cooper, W.C. (1984) Mortality in employees of lead battery plants and lead production plants, 1947 - 1980: final report. Project LH-157. New York NY: The International Lead Zinc Research Organization, Inc.

Cooper, W.C.; Gaffey, W.R. (1975) Mortality of lead workers. In: Cole, J.F., ed. Proceedings of the 1974 conference on standards of occupational lead exposure; February 1974; Washington, D.C. J. Occup. Med. 17: 100-107.

Corrin, M.L.; Natusch, D.F.S. (1977) Physical and chemical characteristics of environmental lead. In: Lead in the environment; a report and analysis of research at Colorado State University, University of Illinois, and University of Missouri, (W.R. Boggess, ed.); Washington, D.C.: National Science Foundation; NSF report no. NSF/RA-770214; pp. 7-32.

Cory-Slechta, D.A.; Thompson, T. (1979) Behavioral toxicity of chronic post-weaning lead exposure in the rat. Toxicol. Appl. Pharmacol. 47: 151-159.

Cory-Schlechta, D.A.; Weiss, B.; Cox, C. (1983) Delayed behavioral toxicity of lead with increasing exposure concentration. Toxicol. Appl. Pharmacol 71: 342-352.

Cory-Schlechta, D.A.; Weiss, B.; Cox, C. (1985) Performance and exposure indices of rats exposed to low concentrations of lead. Toxicol. Appl. Pharmacol, 78: 291-299.

Costa, L.G.; Fox, D.A. (1983) A selective decrease of cholinergic muscarinic receptors in the visual cortex of adult rats following developmental lead exposure. Brain Res. 276: 259-266.

Cotes, J.E. (1979) Lung function assessment and application in medicine. Blackwell Scientific Publications, London, England. pp. 265-284.

Cramer, K.; Dahlberg, L. (1966) Incidence of hypertension among lead workers: a follow-up study based on regular control over 20 years. Br. J. Ind. Med. 23: 101-104.

Cramer, K.; Goyer, R.A.; Jagenburg, R.; Wilson, M.H. (1974) Renal ultra-structure, renal function, and parameters of lead toxicity in workers with different periods of lead exposure. Br. J. Ind. Med. 31: 113-127.

Crofton, K.M.; Taylor, D.H.; Bull, R.J.; Sivulka, D.J.; Lutkenhoff, S.D. (1980) Developmental delays in exploration and locomotor activity in male rats exposed to low level lead. Life Sci. 26: 823-831.

Crump, D.R.; Barlow, P.J. (1982) Factors controlling the lead content of a pasture grass. Environ. Pollut. Ser. B 3: 181-192.

Cumings, J.N. (1959) Heavy metals and the brain. Part 3: Lead. Springfield, IL: Thomas; pp. 93-155.

Dacre, J.C.; Ter Haar, G.L. (1977) Lead levels in tissues from rats fed soils containing lead. Arch. Environ. Contam. Toxicol. 6: 111-119.

Dagg, J.H.; Goldberg, A.; Lochhead, A.; Smith, J.A. (1965) The relationship of lead poisoning to acute intermittent porphyria. Q.J. Med. 34: 163-175.

Daines, R.H.; Motto, H.; Chilko, D.M. (1970) Atmospheric lead: its relationship to traffic volume and proximity to highways. Environ. Sci. Technol. 4: 318-322.

Dalpra, L.; Tibiletti, M.G.; Nocera, G.; Giulotto, P.; Auriti, L.; Carnelli, V.; Simoni, G. (1983) SCE analysis in children exposed to lead emission from a smelting plant. Mutation Res. 120: 249-256.

David, O.J.; Hoffman, S.P.; Clark, J.; Grad, G.; Sverd, J. (1983) The relationship of hyperactivity to moderately elevated lead levels. Arch. Env. Health 38: 341-346.

David, O.J.; Hoffman, S.P., Sverd, J.; Clark, J. (1977) Lead and hyperactivity: lead levels among hyperactive children. J. Abnorm. Child Psychol. 5: 405-416.

David, O.J.; Hoffman, S.P.; Sverd, J.; Clark, J.; Voeller, K. (1976) Lead and hyperactivity: behavioral response to chelation: a pilot study. Am. J. Psychiatry 133: 1155-1158.

David, O.J., Katz, S.; Arcoleo, C.G.; Clark, J. (1985) Chelation therapy in children as treatment of sequelae in severe lead toxicity. Arch. Environ. Health. 40: 109-113.

David, O.J.; Wintrob, H.L.; Arcoleo, C.G. (1982) Blood lead stability. Arch. Environ. Health 37: 147-150.

Davidson, C.I. (1977) The deposition of trace metal-containing particles in the Los Angeles area. Powder Technology 18: 117-126.

Davidson, C.I.; Chu, L.; Grimm, T.C.; Nasta, M.A.; Qamoos, M.P. (1981c) Wet and dry deposition of trace elements onto the Greenland ice sheet. Atmos. Environ. 15: 1429-1437.

Davidson, C.I.; Goold, W.D.; Mathison, T.P.; Wiersma, G.B.; Brown, K.W.; Reilly, M.T. (1985) Airborne trace elements in Great Smoky Mountains, Olympic, and Glacier National Parks. Environ. Sci. Technol. 19(1): 27-35.

Davidson, C.I.; Graimm, T.C.; Nasta, M.A. (1981b) Airborne lead and other elements derived from local fires in the Himalayas. Science (Washington, D.C.) 214: 1344-1346.

Davidson, C.I.; Miller, J.M.; Pleskow, M.A. (1982) The influence of surface structure on predicted particle dry deposition to natural grass canopies. Water Air Soil Pollut. 18: 25-43.

Davidson, C.I.; Osborn, J.F. (1984) The sizes of airborne trace metal-containing particles. In: Nriagu, J.O.; Davidson, C.I., eds. Toxic Metals in the Air. New York, NY: Wiley.

Davies, P.H.; Goettl, J.P., Jr.; Sinley, J.R.; Smith, N.F. (1976) Acute and chronic toxicity of lead to rainbow trout Salmo gairdneri, in hard and soft water. Water Research 10: 199-206.

Day, J.P.; Fergusson, J.E.; Chee, T.M. (1979) Solubility and potential toxicity of lead in urban street dust. Bull. Environ. Contam. Toxicol. 23: 497-502.

Day, J.P.; Hart, M.; Robinson, M.S. (1975) Lead in urban street dust. Nature (London) 253: 343-345.

D.C. Cir. (1980) Lead Industries Association, Inc. v. EPA. F.2d, 14 ERC 1906 (D.C. Cir.) Cert. Denied 49 U.S.L.W. 3428 December 8, 1980.

D.C. Cir. (1981) American Petroleum Institute v. Costle, Nos. 79-1104 et al. (D.C. Cir.) September 3, 1981.

de la Burde, B.; Choate, M.S., Jr. (1972) Does asymptomatic lead exposure in children have latent sequelae? J. Pedistr. (St. Louis) 81: 1088-1091.

de la Burde, B.; Choate, M.S., Jr. (1975) Early asymptomatic lead exposure and development at school age. J. Pediatr. (St. Louis) 87: 638-642.

Der, R.; Fahim, Z.; Hilderbrand, D.; Fahim, M. (1974) Combined effect of lead and low protein diet on growth, sexual development, and metabolism in female rats. Res. Commun. Chem. Pathol. Pharmacol. 9: 723-738.

DeSilva, P.E. (1981) Determination of lead in plasma and studies on its relationship to lead in erythrocytes. Br. J. Ind. Med. 38: 209-217.

DHSS [U.S. Department of Health and Human Services] (1984) Blood lead levels for persons ages 6 months-74 years: United States, 1976-1980. Data from the National Health and Nutrition Examination Survey, Series 11, No. 233, Public Health Service, National Center for Health Statistics, Hyattsville, Md., DHSS Publication No. (PHS) 84-1683, August, 1984.

Diemel, J.A.L.; Brunekreef, B.; Boleij, J.S.M.; Biersteker, K.; Veenstra, S.J. (1981) The Arnhem lead study: II. indoor pollution, and indoor/outdoor relationships. Environ. Res. 25: 449-456.

Dietrich, K.N.; Krafft, K.M.; Pearson, D.T.; Bornschein, R.L.; Hammond, P.B.; Succop, P.A. (1985) Postnatal lead exposure and early sensorimotor development. Environ. Res. 38: 130-136.

Dietrich, K.N.; Pearson, D.T., Krafft, K.M., Hammond, P.B.; Bornschein, R.L.; Succop, P.A. (1984) Lead exposure and early sensorimotor development. Presented at: Gatlinburg conference on research in mental retardation and development disabilities; March; Gatlinburg, TN. Available for inspection at: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

Dingwall-Fordyce, I.; Lane, R.E. (1963) A follow-up study of lead workers. Br. J. Ind. Med. 20: 313-315.

Dipaolo, J.A.; Nelson, R.L.; Casto, B.C. (1978) In vitro neoplastic transformation of Syrian hamster cells by lead acetate and its relevance to environmental carcinogenesis. Br. J. Cancer 38: 452-455.

Dobbing, J. (1974) The later growth of the brain and its vulnerability. Pediatrics 53: 2-6.

DOE [Department of the Environment] (1983) European Community Screening Program for Lead: United Kingdom Results for 1981, Pollution Report 18.

Doelman, P. (1978) Lead and terrestrial microbiota. In: Nriagu, J.O., ed. The biogeochemistry of lead in the environment. Part B: Biological effects. Amsterdam, The Netherlands: Elsevier/North-Holland Biomedical Press; pp. 343-353.

Doelman, P.; Haanstra, L. (1979a) Effects of lead on the decomposition of organic matter. Soil Biol. Biochem. 11: 481-485.

Doelman, P.; Haanstra, L. (1979b) Effects of lead on the soil bacteria microflora. Soil Biol. Biochem. 11: 487-491.

Doershuk, C.F.; Downs, T.D.; Matthews, L.W.; Lough, M.D. (1970). A method for ventilatory measurements in subjects 1 month-5 years of age: normal results and observations in disease. Pediat. Res. 4: 165-174.

Donovan, M.P.; Schein, L.G.; Thomas, J.A. (1980) Inhibition of androgen-receptor interaction in mouse prostrate gland cytosol by divalent metal ions. Mol. Pharmacol. 17: 156-162.

Dorn, C.R.; Pierce, J.D.; Phillips, P.E.; Chase, G.R. (1976) Airborne Pb, Cd, Zn and Cu concentration by particle size near a Pb smelter. Atmos. Environ. 10: 443-446.

Dresner, D.L.; Ibrahim, N.G.; Mascharenhas, B.R.; Levere, R.D. (1982) Modulation of bone marrow heme and protein synthesis by trace elements. Environ. Res. 28: 55-66.

Drill, S.; Konz, J.; Mahar, H.; Morse, M. (1979) The environmental lead problem: an assessment of lead in drinking water from a multi-media perspective. Washington, D.C.: U.S. Environmental Protection Agency; EPA report no. EPA-570/9-79-003. Available from NTIS, Springfield, VA; PB 296556.

Dubas, T.C.; Stevenson, A.; Singhal, R.L.; Hrdina, P.D. (1978) Regional alterations of brain biogenic amines in young rats following chronic lead exposure. Toxicology 9: 185-190.

Duce, R.A.; Hoffman, G.L.; Zoller, W.H. (1975) Atmospheric trace metals at remote northern and southern hemisphere sites: pollution or natural? Science (Washington, D.C.) 187: 59-61.

Duggan, M.J. (1983) The uptake and excretion of lead by young children. Arch. Env. Health 38: 246-247.

Duggan, M.J.; Williams, S. (1977) Lead-in-dust in city streets. Sci. Total Environ. 7: 91-97.

Dzubay, T.G.; Stevens, R.K. (1973) Applications of X-ray fluorescence to particulate meaaurements. In: Second joint conference on sensing of environmental pollutants; December; Washington, D.C. Pittsburgh, PA: Instrument Society of America; pp. 211-216.

Edelstein, S.; Fullmer, C.S.; Wasserman, R.H. (1984) Gastrointestinal absorption of lead in chicks: involvement of the cholecalciferol endocrine system. In press.

Edwards, H.W.; Rosenvold, R.J.; Wheat, H.G. (1975) Sorption of organic lead vapor on atmospheric dust particles. In: Trace substances in environmental health--IX; proceedings of University of Missouri's 9th annual conference on trace substances in environmental health (D.D. Hemphill, ed); June; Columbia, MO. University of Missouri-Columbia; pp. 197-206.

Elias, R.W.; Davidson, C.I. (1980) Mechanisms of trace element deposition from the free atmosphere to surfaces in a remote high sierra canyon. Atmospheric Environment (14): 1427-1432.

Emmerson, B.T. (1973) Chronic lead nephropathy. Kidney Int. 4: 1-5.

EPA [U.S. Environmental Protection Agency] (1977) Air quality criteria for lead. Research Triangle Park, NC: U.S. Environmental Protection Agency, Criteria and Special Studies Office; EPA report no. EPA-600/8-77-017. Available from: NTIS, Springfield, VA; PB 280411.

EPA [U.S. Environmental Protection Agency] (1984a) Air Quality Criteria for Lead. Environmental Criteria and Assessment Office, Office of Research and Development, Research Triangle Park, N.C. EPA 600/8-83-028 a-d, August-September 1984.

EPA [U.S. Environmental Protection Agency] (1984b) Philadelphia roadway study. Environmental Monitoring Systems Laboratory, Research Triangle Park, N.C.; EPA report no. EPA-600/4-84-070.

EPA [U.S. Environmental Protection Agency] (1985a) Draft. Recommended Maximum Contaminant level (RMCL) Proposal for Revised National Primary Drinking Water Regulations. Expected in Federal Register, June, 1985.

EPA [U.S. Environmental Protection Agency] (1985b) Regulation of Fuels and Additives; Gasoline Lead Content; Final Rule and Supplemental Notice of Proposed Rulemaking. March 7, 1985, 40 CFR Part 80.

EPA [U.S. Environmental Protection Agency] (1985c) Costs and Benefits of Reducing Lead in Gasoline. Final Report, Office of Policy Analysis, Office of Policy, Planning and Evaluation, Washington, D.C.

Erenberg, G.; Rinsler, S.S.; Fish, B.G. (1974) Lead neuropathy and sickle cell disease. Pediatrics 54: 438-441.

Ernhart, C.B. (1983) Response to Appendix 12-C: independent peer-review of selected studies concerning neurobehavioral effects of lead exposures in nominally asymptomatic children: official report of findings and recommendations of an interdisciplinary expert review committee. Available for inspection at: U.S. EPA, Central Docket Section, Washington, D.C.; docket no. ECAO-CD-81-2 II A.E.C.1.30.

Ernhart, C.B. (1984) Comments on Chapter 12, Air Quality Criteria for Lead. Available for inspection at U.S. EPA, Central Docket Section, Washington, D.C.; docket no. ECAO-CD-81-2 II A.E.C.1.30.

Ernhart, C.B.; Landa, B.; Schell, N.B. (1981) Subclinical levels of lead and developmental deficit - a multivariate follow-up reassessment. Pediatrics 67: 911-919.

Ewers, U.; Stiller-Winkler, R.; Idel, H. (1982) Serum immunoglobulin, complement C3, and salivary IgA levels in lead workers. Environ. Res. 29: 351-357.

Ewing, B.B.; Pearson, J.A. (1974) Lead in the environment. In: Advances in environmental science and technology (J. Pitts and R. Metcalf, eds.); New York: John Wiley and Sons; pp. 1-126.

Facchetti, S.; Geiss, F. (1982) Isotopic lead experiment: status report. Luxembourg: Commission of the European Communities; Publication no. EUR 8352 EN.

Farfel, M.R. (1985) Reducing lead exposure in children. Ann. Rev. Public Health 6: 333-360.

Farras, W.R. (1975) Effect of plumbous ion on messenger RNA. Chem. Biol. Interactions 11: 253-263.

Feldman, R.G.; Hayes, M.K.; Younes, R.; Aldrich, F.D. (1977) Lead neuropathy in adults and children. Arch. Neurol. 34: 481-488.

Fischbein, A.; Thornton, J.; Blumberg, W.E.; Bernstein, J.; Valciukas, J.A.; Moses, M.; Davidow, B.; Kaul, B.; Sirota, M.; Selikoff, I.J. (1980) Health status of cable splicers with low-level exposure to lead: results of a clinical survey. Am. J. Public Health 70: 697-700.

Fjerdingstad, E.J.; Danscher, G.; Fjerdingstad, E. (1974) Hippocampus: selective concentration of lead in the normal rat brain. Brain Res. 80: 350-354.

Flynn, J.R. (1984) The mean IQ of Americans: massive gains 1932 to 1978. Psych. Bull. 95: 29-51.

Forbes, R.M.; Sanderson, G.C. (1978) Lead toxicity in domestic animals and wildlife. In: Nriagu, J.O. ed. The biogeochemistry of lead in the environment. Part B: Biological effects. Amsterdam, The Netherlands: Elsevier/North-Holland Biomedical Press; pp. 225-277.

Fowler, B.A.; Kimmel, C.A.; Woods, J.S.; McConnell, E.E.; Grant, L.D. (1980) Chronic low-level lead toxicity in the rat: III. an integrated assessment of long-term toxicity with special reference to the kidney. Toxicol. Appl. Pharmacol. 56: 59-77.

Fowler, B.A.; Squibb, K.S.; Oskarsson, A. (1981b) Mitochondrial membrane potential and energy-linked membrane transformation: inhibition by Pb binding in vitro. J. Cell Biol. 91: 287a.

Fowler, B.A.; Squibb, K.S.; Oskarsson, A.; Taylor, J.A.; Carver, G.T. (1981a) Lead-induced alteration of renal mitochondrial membrane structure and function. Toxicologist 1: 19.

Fox, D.A.; Lewkowski, J.P.; Copper, G.P. (1977) Acute and chronic effects of neonatal lead exposure on development of the visual evoked response in rats. Toxicol. Appl. Pharmacol. 40: 449-461.

Fox, D.A.; Overmann, S.R.; Woolley, D.E. (1979) Neurobehavioral ontogeny of neonatally lead-exposed rats: II. maximal electroshock seizures in developing and adult rats. Neurotoxicology 1: 149-170.

Fox, D.A.; Sillman, A.J. (1979) Heavy metals affect rod, but not cone, photoreceptors. Science (Washington, D.C.) 206: 78-80.

Fox, D.A.; Wright, A.A. (1982) Evidence that low-level developmental lead exposure produces toxic amblyopia. Soc. Neurosci. Abstr. 8: 81.

Fox, D.A.; Wright, A.A.; Costa, L.G. (1982) Visual acuity deficits following neonatal lead exposure: cholinergic interactions. Neurobehav. Toxicol. Teratol. 4: 689-693.

FR [Federal Register] Vol. 50, No. 145, July 29, 1985, pp. 30791-30792.

Fugas, M.; Saric, M. (1979) Health study of a lead-exposed population. In: Lynam, D.R.; Piatanida, L.G.; Cole, J.F., eds. Environmental lead: proceedings of the second international symposium on environmental lead research; December 1978; Cincinnati, OH. New York, NY: Academic Press.

Galke, W.A.; Hammer, D.I.; Keil, J.E.; Lawrence, S.W. (1975) Environmental determinants of lead burdens in children. In: Hutchinson, T.C.; Epstein, S.; Page, Al. L.; Van Loon, J.; Davey, T.; eds. International conference on heavy metals in the environment: symposium proceedings, vol. 3; October; Toronto, ON, Canada. Toronto; ON, Canada: Institute for Environmental Studies; pp. 53-74. See also: Washington, DC: U.S. Environmental Protection Agency; EPA report no. EPA-600/J-78-022 1975. Available from: NTIS, Springfield, VA; PB 283567.

Galloway, J.N.; Eisenreich, S.J.; Scott, B.C., eds. (1980) Toxic substances in atmospheric deposition: a review and assessment. National Atmospheric Deposition Program Rep. NC-141.

Galloway, J.N.; Thornton, J.D.; Norton, S.A.; Volchok, H.L.; McLean, R.A. (1982) Trace metals in atmospheric deposition: a review and assessment. Atmospheric Environment 16(7): 1677-1700.

Gant, V.A. (1938) Lead poisoning. Ind. Med. 7: 679-699.

Garland, C.J.; Wilkins, D.A. (1981) Effect of calcim on the uptake and toxicity of lead in Hordeum vulgare L. and Festuca ovina L. New Phytol. 87: 581-593.

Garty, J.; Fuchs, C. (1982) Heavy metals in the lichen Ramalina duriaei transplanted in bio-monitoring stations. Water Air Soil Pollut. 17: 175-183.

Gelman, B.B.; Michaelson I.A.; Bus, J.S. (1978) The effect of lead on oxidative hemolysis and erythrocyte defense mechanisms in the rat. Toxic. Appl. Pharmacol. 45: 119-129.

General Electric Company (1972) Indoor-outdoor carbon monoxide pollution study. Research Triangle Park, NC: U.S. EPA, National Environmental Research Center, Quality Assurance and Environmental Monitoring Laboratory; EPA report no. EPA-R4-73-020. Available from NTIS, Springfield, VA; PB 220428.

Gerber, G.B.; Maes, J. (1978) Heme synthesis in the lead-intoxicated mouse embryo. Toxicology 9: 173-179.

Gerber, G.B.; Maes, J.; Gilliavod, N.; Casale, G. (1978) Brain biochemistry of infant mice and rats exposed to lead. Toxicol. Lett. 2: 51-63.

Getz, L.L.; Haney, A.W.; Larimore, R.W.; McNurney, J.W.; Leland, H.V.; Price, P.W.; Rolfe, G.L.; Wortman, R.L.; Hudson, J.L.; Solomon, R.L.; Reinbold, K.A. (1977) Transport and distribution in a watershed ecosystem. In: Boggess, W.R., ed. Lead in the environment. National Science Foundation; NSF report no. NSF/RA-770214; pp. 105-134.

Gilbert C.; Tuthill, R.W.; Calabrese, E.J.; Peters, H.A. (1979) A comparison of lead hazards in the housing environment of lead poisoned children versus nonpoisoned controls. J. Environ. Sci. Health A14: 145-168.

Gillberg, C.; Norem, J.G., Wahlstrom, J.; Rusmussen, P. (1982) Heavy metals and neurophyschiatric disorders in 6-year old children: aspects of dental lead and cadmium. Acta. Paedo. Psychiat. 48: 253-263.

Gilsinn, J. (1972) Estimates of the nature and extent of lead paint poisoning in the United States. NBS Tech Note 764: National Bureau of Standards, Washington, D.C., December, 1972.

Gish, C.D.; Christensen, R.E. (1973) Cadmium, nickel, lead, and zinc in earthworms from roadside soil. Environ. Sci. Technol. 7: 1060-1062.

Gittelman, R.; Eskenazi, B. (1983) Lead and hyperactivity revisited: an investigation of nondisadvantaged children. Arch. Gen. Psychiatry 40: 827-833.

Gmerek, D.E.; McCafferty, M.R.; O'Neill, K.J.; Melamed, B.R.; O'Neill, J.J. (1981) Effect of inorganic lead on rat brain mitochondrial respiration and energy production. J. Neurochem. 36: 1109-1113.

Goddard, G.A.; Robinson, J.D. (1976) Uptake and release of calcium by rat brain synaptosomes. Brain Res. 110: 331-350.

Goldman, D.; Hejtmancik, M.R., Jr.; Williams, B.J.; Ziegler, M.G. (1980) Altered noradrenergic systems in the lead-exposed neonatal rat. Neurobehav. Toxicol. 2: 337-343.

Goldstein, G.W.; Asbury, A.K.; Diamond, I. (1974) Pathogenesis of lead encephalopathy: uptake of lead and reaction of brain capillaries. Arch. Neurol. (Chicago) 31: 382-389.

Govoni, S.; Lucchi, L.; Battaini, F.; Spano, P.F.; Trabucchi, M. (1984) Chronic lead treatment affects dopaminergic control of prolactin secretion in rat pituitary. Toxicol. Lett. 20: 237-241.

Govoni, S.; Montefusco, O.; Spano, P.F.; Trabucchi, M. (1978) Effect of chronic lead treatment on brain dopamine synthesis and serum prolactin release in the rat. Toxicol. Lett. 2: 333-337.

Goyer, R.A. (1968) The renal tubule in lead poisoning: 1. mitochondrial swelling and aminoaciduria. Lab. Invest. 19: 71-77.

Goyer, R.A.; Moore, J.F. (1974) Cellular effects of lead. Adv. Exp. Med. Biol. 48: 447-462.

Graham, D.L.; Kalman, S.M. (1974) Lead in forage grass from a suburban area in northern California. Environ. Pollut. 7: 209-215.

Grandjean, P. (1978) Regional distribution of lead in human brains. Toxicol. Lett. 2: 65-69.

Grandjean, P.; Lintrup, J. (1978) Erythrocyte-Zn-protoporphyrin as an indicator of lead exposure. Scand. J. Clin. Lab. Invest. 38: 669-675.

Grandjean, P.; Wulf, H.C.; Niebuhr, E. (1983) Sister chromatid exchange in response to variations in occupational lead exposure. Environ. Res. 32: 199-204.

Granick, J.L.; Sassa, S.; Granick, S.; Levere, R.D.; Kappas, A. (1973) Studies in lead poisoning: II. correlation between the ratio of activated to inactivated d-aminolevulinic acid dehydratase of whole blood and the blood lead level. Biochem. Med. 8: 149-159.

Granick, J.L.; Sassa, S.; Kappas, A. (1978) Some biochemical and clinical aspects of lead intoxication. Adv. Clin. Chem. 20: 288-339.

Grant, L.D.; Kimmel, C.A.; West, G.L.; Martinez-Vargas, C.M.; Howard, J.L. (1980) Chronic low-level lead toxicity in the rat: II. effects on postnatal physical and behavioral development. Toxicol. App. Pharmacol. 56: 42-58.

Griffin, T.B.; Coulston, F.; Wills, H.; Russell, J.C.; Knelson, J.H. (1975) Clinical studies on men continuously exposed to airborne particulate lead. In: Griffin, T.B.; Knelson, J.H., eds. Lead. New York, NY: Academic Press; pp. 221-240. (Coulston, F.; Korte, F., eds. Environmental quality and safety: supplement v. 2).

Gross, S.B. (1981) Human oral and inhalation exposures to lead: summary of Kehoe balance experiments. J. Toxicol. Environ. Health 8: 333-337.

Gross, S.B.; Pfitzer, E.A. (1974) Influence of pathological change on lead in human tissues. In: Hemphill, D.D., ed. Trace substances in environmental health - VIII: [proceedings of University of Missouri's 8th annual conference on trace substances in environmental health]: June; Columbia, MO: University of Missouri-Columbia; pp. 335-340.

Gross, S.B.; Pfitzer, E.A.; Yeager, D.W.; Kehoe, R.A. (1975) Lead in human tissues. Toxicol. Appl. Pharmacol. 32: 638-651.

Gross-Selbeck, E.; Gross-Selbeck, M. (1981) Changes in operant behavior of rats exposed to lead at the accepted no-effect level. Clin. Toxicol. 18: 1247-1256.

Habermann, E.; Crowell, K.; Janicki, P. (1983) Lead and other metals can substitute for Ca^{+2} in calmodulin. Arch. Toxicol. 54: 61-70.

Habibi, K.; Jacobs, E.S.; Kunz, W.G., Jr.; Pastell, D.L. (1970) Characterization and control of gaseous and particulate exhaust emissions from vehicles. Presented at 5th technical meeting of the Air Pollution Control Association, West Coast section; October: San Francisco, CA. Pittsburgh, PA: Air Pollution Control Association.

Haenninen, H.; Hernberg, S.; Mantere, P.; Vesanto, R.; Jalkanen, M. (1978) Psychological performance of subjects with low exposure to lead. J. Occup. Med. 20: 683-689.

Haenninen, H.; Mantere, P.; Hernberg, S.; Seppalainen, A.M.; Kock, B. (1979) Subjective symptoms in low-level exposure to lead. Neurotoxicology 1: 333-347.

Halpern, M. (1978) Indoor/outdoor air pollution continuity relationships. J. Air Pollut. Control Assoc. 28: 689-691.

Hambidge, R.M. (1977) The role of zinc and other trace metals in pediatric nutrition and health. Pediatr. Clin. North Am. 24: 95-106.

Hammond, P.B.; Bornschein, R.L.; Succop, P. (1984) Dose-effect and dose-response relationships of blood lead to erythrocyte protoporphyrin in young children. Environ. Res.: in press.

Hammond, P.B.; O'Flaherty, E.J.; Gartside, P.S. (1981) The impact of air-lead on blood-lead in man - a critique of the recent literature. Food Cosmet. Toxicol. 19: 631-638.

Hammond, P.B.; O'Flaherty, E.J.; Gartside, P.S. (1982) Letter: Impact of air-lead on blood lead in man. Fd. Chem. Toxic. 20: 493.

Hampp, R.; Lendzian, K. (1974) Effect of lead ions on chlorophyll synthesis. Naturwissenschaften 61: 218-219.

Harlan, W.R.; Landis, J.R.; Schmouder, R.L.; Goldstein, N.G.; Harlan, L.C. (1985) Blood lead and blood pressure: relationship in the adolescent and adult U.S. population. JAMA 253: 530-534.

Harley, N.H.; Kneip, T.H. (1985) An integrated metabolic model for lead in humans of all ages. Final report to the U.S. EPA, Contract No. B44899 with New York University School of Medicine, Dept. of Environmental Medicine, January 30, 1985.

Harrison, R.M. (1979) Toxic metals in street and household dusts. Sci. Total Environ. 11: 89-97.

Harrison, R.M.; Laxen, D.P.H.; Birch, J. (1979) Tetraalkylead in air: sources, sinks and concentrations. In: International conference: management and control of heavy metals in the environment; September; London, United Kingdom. Edinburgh, United Kingdom: CEP Consultants, Ltd., pp. 257-261.

Hartwell, T.D.; Handy, R.W.; Harris, B.S.; Williams, S.R.; Gehlbach, S.H. (1983) Heavy metal exposure in populations living around zinc and copper smelters. Arch. Environ. Health 38: 284-295.

Harvey, P.; Hamlin, M.; Kumar, R. (1983) The Birmingham blood lead study. Presented at: annual conference of the British Psychological Society, symposium on lead and health: some psychological data; April; University of York, United Kingdom. Available for inspection at: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

Harvey, P.G.; Hamlin, M.W.; Kumar, R.; Delves, H.T. (1984) Blood lead, behaviour and intelligence test performance in pre-school children. Sci. Total Environ.: in press.

Hasan, J.; Vihko, V.; Hernberg, S. (1967) Deficient red cell membrane / $NA^+ + K^+$ /-ATPase in lead poisoning. Arch. Environ. Health 14: 313-318.

Hastings, L.; Cooper, G.P.; Bornschein, R.L.; Michaelson, I.A. (1977) Behavioral effects of low level neonatal lead exposure. Pharmacol. Biochem. Behav. 7: 37-42.

Hastings, L.; Cooper, G.P.; Bornschein, R.L.; Michaelson, I.A. (1979) Behavioral deficits in adult rats following neonatal lead exposure. Neurobehav. Toxicol. 1: 227-231.

Hayashi, M. (1983a) Lead toxicity in the pregnant rat. I. The effects of high-level lead on α-ALAD activity in maternal and fetal blood or tissues. Environ. Res. 30: 152-160.

Hayashi, M. (1983b) Lead toxicity in the pregnant rat. II. Effects of low-level lead on β-ALAD activity in maternal and fetal blood or tissues. Indust. Health 21: 127-135.

Hayes, S.R., Mahoney, L.A.; Permutt, T.J., Thrall, A.D., Weir, B.R., Burton, C.S. (1985). An evaluation of alternative forms of the National Air Quality Standards for Lead. Prepared for the Office of Air Quality Planning and Standards and Office of Policy Analysis, U.S. EPA.

Heard, M.J.; Chamberlain, A.C. (1982) Effect of minerals and food on uptake of lead from the gastrointestinal tract in humans. Hum. Toxicol. 1: 411-415.

Heard, M.J.; Chamberlain, A.C. (1984) Uptake of Pb by human skelton and comparative metabolism of Pb and alkaline earth elements. Health Physics 47: 857-862.

Hem, J.D. (1976) Inorganic chemistry of lead in water. In: Lovering, T.G., ed. Lead in the environment. Washington, D.C.: U.S. Department of the Interior, Geological Survey: Geological Survey professional paper no. 957. Available from: GPO, Washington, D.C.; S/N: 024-001-02911-1; pp. 5-11.

Herber, R.F.M. (1980) Estimation of blood lead values from blood porphyrin and urinary δ-aminolevulinic acid levels in workers. Int. Arch. Occup. Environ. Health 45: 169-179.

Hernberg, S.; Nikkanen, J. (1970) Enzyme inhibition by lead under normal urban conditions. Lancet 1 (7637): 63-64.

Hiasa, Y.; Ohshima, M.; Yoshiteru, K.; Fujita, T.; Yuasa, T.; Miyashiro, A. (1983) Basic lead acetate: promoting effect on the development of renal tubular cell tumors in rats treated with N-ethyl-N-hydroxyethylnitrosamine. J. Nat. Cancer Inst. 70: 761-765.

Hilderbrand, D.C.; Der, R.; Griffin, W.T.; Fahim, M.S. (1973) Effect of lead acetate on reproduction. Am. J. Obstet. Gynecol. 115: 1058-1065.

Hodson, P.V. (1979) Factors affecting the sublethal toxicity of lead to fish. In: International conference: management and control of heavy metals in the environment; September; London, United Kingdom. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 135-138.

Hodson, P.V.; Blunt, B.R.; Jensen, D.; Morgan, S. (1979) Effect of fish age on predicted and observed chronic toxicity of lead to rainbow trout in Lake Ontario water. J. Great Lakes Res. 5: 84-89.

Hodson, P.V.; Blunt, B.R.; Spry, D.J. (1978a) Chronic toxicity of water-borne and dietary lead to rainbow trout (Salmo gairdneri) in Lake Ontario water. Water Res. 12: 869-878.

Hodson, P.V.; Blunt, B.R.; Spry, D.J. (1978b) pH-induced changes in blood lead of lead-exposed rainbow trout. J. Fish. Res. Board Can. 35: 437-445.

Hoffman, W.; Steinhausler, F.; Pohl, E. (1979) Dose calculations for the respiratory tract from inhaled natural radioactive nuclides as a function of age; I. compartmental deposition, retention, and resulting dose. Health Physics 37: 517-532.

Holtzman, D.; Shen Hsu, J. (1976) Early effects of inorganic lead on immature rat brain mitochrondrial respiration. Pediatr. Res. 10: 70-75.

Holtzman, D.; Shen Hsu, J.; Mortell, P. (1977) Effects of inorganic lead on isolated rat brain mitochondrial respiration. Pediatr. Res. 11: 407.

Holtzman, D.; Shen Hsu, J; Mortell, P. (1978) In vitro effects of inorganic lead on isolated rat brain mitochondrial respiration. Neurochem. Res. 3: 195-206.

Hubermont, G.; Buchet, J-P; Roels, H.; Lauwerys, R. (1976) Effect of short-term administration of lead to pregnant rats. Toxicology 5: 379-384.

Hughes, M.K. (1981) Cycling of trace metals in ecosystems. In: Lepp, N.W., ed. Effect of heavy metal pollution on plants. Vol. 1: Effects of trace metals on plant function. Barking, United Kingdom: Applied Science Publishers, Ltd.; pp. 95-118. (Mellanby, K., ed. Pollution monitoring series.)

Hunt, W.F., Jr. (1985) Comparison of four alternative lead air quality standards using modeled data at a secondary lead smelter and a battery plant. Memorandum to John Haines, Strategies and Air Standards Division, Office of Air Quality Planning and Standards, October 22, 1985.

Hunt, W.F., Jr. (1986) A comparison of the precision asociated with alternative sampling plans for one versus three years of information and monthly versus quarterly averaging times. Memorandum to John Haines, Strategies and Air Standards Division, Office of Air Quality Planning and Standards, January 30, 1986.

Hunter, J.; Urbanowicz, M.A.; Yule, W.; Lansdown, R. (1983) Automated testing of reaction time and its association with lead in children. Presented at: British Psychological Society; December; London, United Kingdom. Available for inspection at: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

Huntzicker, J.J.; Friedlander, S.K.; Davidson, C.I. (1975) Material balance for automobile-emitted lead in Los Angeles basin. Environ. Sci. Technol. 9: 448-457.

Hutchinson, T.C. (1980) Effects of acid leaching on cation loss from soils. In: Hutchinson, T.C.; Havas, M., eds. Effects of acid precipitation on terrestrial ecosystems: North Atlantic Treaty Organization conference on effects of acid precipitation on vegetation and soils; May 1978; Toronto, ON, Canada. New York, NY: Plenum Press; pp. 481-497.

ICRP [International Committee on Radiological Protection] (1975) Report of the Task Group on Reference Man: Report #23. Pergamon Press, New York.

Idaho Department of Health and Welfare (1977) Shoshone Lead Health Project Work Summary, January 1976. Division of Health, Boise, Idaho.

Impelman, D.; Lear, C.L.; Wilson, R.; Fox, D.A. (1982) Central effects of low level developmental lead exposure on optic nerve conduction and the recoverability of geniculocortical responses in hooded rats. Soc. Neurosci. Abstr. 8: 81.

Ingalls, M.N.; Garbe, R.J. (1982) Ambient pollutant concentrations from mobile sources in microscale situations. From: Passenger car meeting; June; Troy, MI. Warrendale, PA: Society of Automotive Engineers; SAE Paper No. 820287.

Inglis, J.A.; Henderson, D.A.; Emerson, B.T. (1978) The pathology and pathogenesis of chronic lead nephropathy occurring in Queensland. J. Pathol. 124: 65-76.

International Agency for Research on Cancer. (1980) Lead and lead compounds. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: some metals and metallic compounds; October 1979; Lyon, France. Geneva, Switzerland: World Health Organization/IARC; pp. 325-416. (IARC monographs on the carcinogenic risk of chemicals to humans: v. 23.)

Jackson, D.R.; Watson, A.P. (1977) Disruption of nutrient pools and transport of heavy metals in a forested watershed near a lead smelter. J. Environ. Qual. 6: 331-338.

Jacquet, P.; Gerber, G.B. (1979) Teratogenic effects of lead in the mouse. Biomedicine 30: 223-229.

Jacquet, P.; Leonard, A.; Gerber, G.B. (1976) Action of lead on early divisions of the mouse embryo. Toxicology 6: 129-132.

James, A.C. (1978) Lung deposition of sub-micron aerosols calculated as a function of age and breathing rate. In: National Radiological Protection Board annual research and development report. Harwell, United Kingdom: National Radiological Protection Board; pp. 71-75.

Jason, K.M.; Kellogg, C.R. (1981) Neonatal lead exposure: effects on development of behavior and striatal dopamine neurons. Pharmacol. Biochem. Behav. 15: 641-649.

Jelinek, C.F. (1982) Levels of lead in the United States food supply. J. Assoc. Off. Anal. Chem. 65: 942-946.

Jelinek, C.F. (1984) Comments on Air Quality Criteria for Lead, External Review Draft #2, Volume II, Chapter 7.

Jennett, J.C.; Wixson, B.J.; Bolter, E.; Lowsley, I.H.; Hemphill, D.D.; Tranter, W.H.; Gale, N.L.; Purushotaman, K. (1977) Transport and distribution around mines, and smelters. In: Lead in the environment: a report and analysis of research at Colorado State University, University of Illinois, and University of Missouri (W.R. Boggess, ed.); Washington, D.C.: National Science Foundation; NSF report no. NSF/RA - 770214: pp. 135-178.

Johnson, A.H.; Siccama, T.G.; Friedland, A.J. (1982) Spatial and temporal patterns of lead accumulation in the forest floor in the northeastern United States. J. Environ. Qual. 11: 577-580.

Johnson, B.L.; Burg, J.R.; Xintaras, C.; Handke, J.L. (1980) A neurobehavioral examination of workers from a primary nonferrous smelter. Neurotoxicology 1: 561-581.

Johnson, D.E.; Prevost, R.J.; Tillery, J.B.; Thomas, R.E. (1978) The distribution of cadmium and other metals in human tissue. Research Triangle Park, NC: U.S. Environmental Protection Agency; EPA report no. EPA-600/1-78-035. Available from: NTIS, Springfield, VA; PB 285200.

Johnson, J.R.; Myers, R.C. (1981) Alkaline earth metabolism: a model useful in calculating organ burdens, excretion rates and committed effective dose equivalent conversion factors. Radiat. Prot. Dosim. 1: 87-94.

Johnson, T.; Paul, R. (1986) Estimation of daily lead uptake in children and resulting end-of-month blood lead levels. PEI Associates, Inc., Durham, N.C., Prepared for Strategies and Air Standards Division, Office of Air Quality Planning and Standards, U.S. EPA, February 1986.

Kadowski, S.; Norman, A.W. (1984a) Dietary vitamin D is essential for normal insulin secretion from the perfused rat pancreas. J. Clin. Invest. 73: 759-766.

Kadowski, S.; Norman, A.W. (1984b) Pancreatic vitamin D-dependent calcium binding protein: biochemical properties and response to vitamin D. Arch. Biochem. Biophys. 233: 228-236.

Kang, H.K.; Infante, P.F.; Carra, J.S. (1980) Occupational lead exposure and cancer [Letter]. Science (Washington, D.C.) 207: 935-936.

Kehoe, R.A. (1961) The metabolism of lead in man in health and disease: the normal metabolism of lead. (The Harben lectures, 1960). J.R. Inst. Public Health Hyg. 24: 81-97.

Keller, C.A.; Doherty, R.A. (1980) Bone lead mobilization in lactating mice and lead transfer to suckling offspring. Toxicol. Appl. Pharmacol. 55: 220-228.

Khan, D.H.; Frankland, B. (1983) Effects of cadmium and lead on radish plants with particular reference to movement of metals through soil profile and plant. Plant and Soil 70: 335-345.

Khan, M.Y.; Buse, M.; Louria, D.B. (1977) Lead cardiomyopathy in mice. Arch. Pathol. Lab. Med. 101: 89-94.

Kimmel, C.A.; Grant, L.D.; Sloan, C.S.; Gladen, B.C. (1980) Chronic low-level lead toxicity in the rat. Toxicol. Appl. Pharmacol. 56: 28-41.

Kishi, R.; Ikeda, T.; Miyake, H.; Uchino, E.; Tsuzuki, T.; Inoue, K. (1983) Effects of low lead exposure on neurobehavioral function in the rat. Arch. Env. Health 38: 25-33.

Klauder, D.S.; Petering, H.G. (1977) Anemia of lead intoxication: a role for copper. J. Nutr. 107: 1779-1785.

Klein, A.W.; Koch, T.R. (1981) Lead accumulation in brain, blood, and liver after low dosing of neonatal rats. Arch. Toxicol. 47: 257-262.

Klein, A.W.; Koch, T.; Lapinsky, P.; Schein, J.; Moda, L. (1978) The effects of critical periods and low levels of lead exposure on prenatal rat brain morphology. Anat. Rec. 190: 447.

Kline, T.S. (1960) Myocardial changes in lead poisoning. Am. J. Dis. Child. 99: 48-54.

Kneip, T.J.; Mallon, R.P.; Harley, N.H. (1983) Biokinetic modelling for mammalian lead metabolism. Neurotox. 4: 189-192.

Koeppe, D.E. (1981) Lead: understanding the minimal toxicity of lead in plants. In: Lepp, N. W., ed. Effect of heavy metal pollution on plants. Vol. 1: Effects of trace metals on plant function. Barking, United Kingdom: Applied Science Publishers, Ltd.; pp. 55-76. (Mellanby, K., ed. Pollution monitoring series.)

Kon, E.I.; Caples, V. (1977) Nutrition survey of black families in Clairborne County of Southwest Mississippi: I. Food practices and dietary intake, 1973-1974. Dept. of Home Economics, Alcorn State Univ., Lorman, Miss.

Kopp, S.J.; Barany, M.; Erlanger, M.; Perry, E.F.; Perry, H.M., Jr.; Barany, M. (1980b) Cadmium and lead effects on myocardial function and metabolism. J. Environ. Pathol. Toxicol. 4: 205-227.

Kopp, S.J.; Glonek, T.; Erlanger, M.: Perry, E.F.; Perry, H.M., Jr. (1980a) The influence of chronic low-level cadmium and/or lead feeding on myocardial contractility related to phosphorylation of cardiac myofibrillar proteins. Toxicol. Appl. Pharmacol. 54: 48-56.

Kotok, D. (1972) Development of children with elevated blood levels: a controlled study. J. Pediatr. (St. Louis) 80: 57-61.

Kotok, D.; Kotok, R.; Heriot, T. (1977) Cognitive evaluation of children with elevated blood lead levels. Am. J. Dis. Child. 131: 791-793.

Kromhout, D.; Coulande, C.L. (1984) Trace metals and CHD risk indicators in 152 elderly men (the Zutphen study). Eur. Heart J. 5 (abstract suppl. 1): 101.

Lagerwerff, J.V.; Armiger, W.H.; Specht, A.W. (1973) Uptake of lead by alfalfa and corn from soil and air. Soil Sci. 115: 455-460.

Lamola, A-A.; Joselow, M.; Yamane, T. (1975) Zinc protoporphyrin (ZPP): a simple, sensitive, fluorometric screening test for lead poisoning. Clin. Chem. (Winston Salem, N.C.) 21: 93-97.

Lancranjan, I.; Popescu, H.I.; Gavanescu, O.; Klepsch, I.; Serbanescu, M. (1975) Reproductive ability of workmen occupationally exposed to lead. Arch. Environ. Health 30: 396-401.

Landrigan, P.M.; Baker, E.L. (1981) Exposure of children to heavy metals from smelters: epidemiology and toxic consequences. Environmental Research 25: 204-224.

Landrigan, P.M.; Baker, E.L., Jr.; Feldman, R.G.; Cox, D.H.; Eden, K.V.; Orenstein, W.A.; Mather, J.A.; Yankel, A.J.; von Lindern, I.H. (1976) Increased lead absorption with anemia and slowed nerve conduction in children near a lead smelter. J. Pediatr. (St. Louis) 89: 904-910.

Landrigan, P.J.; Gehlbach, S.H.; Rosenblum, B.F.; Shoults, J.M.; Candelaria, R.M.; Barthel, W.F.; Liddle, J.A.; Smrek, A.L.; Staehling, N.W.; Sanders, J.F. (1975) Epidemic lead absorption near an ore smelter: the role of particulate lead. N. Engl. J. Med. 292: 123-129.

Lane, S.D.; Martin, E.S.; Garrod, J.F. (1978) Lead toxicity effects on indole-3-ylacetic acid-induced cell elongation. Planta 144: 79-84.

Lau, W.M.; Wong, H.M. (1982) An ecological survey of lead contents in roadside dusts and soils in Hong Kong. Environ. Res. 28: 39-54.

Lauwerys, R.; Buchet, J-P.; Roels, H.A.; Materne, D. (1974) Relationship between urinary δ-aminolevulinic acid excretion and the inhibition of red cell δ-aminolevulinate dehydratase by lead. Clin. Toxicol. 7: 383-388.

Lawrence, D.A. (1981) Heavy metal modulation of lymphocyte activities: I. in vitro effects of heavy metals on primary humoral immune responses. Toxicol. Appl. Pharmacol. 57: 439-451.

Laxen, D.P.H.; Harrison, R.M. (1977) The highway as a source of water pollution: an appraisal with the heavy metal lead. Water Res. 11: 1-11.

Lepow, M.L.; Bruckman, L.; Gillette, M.; Markowitz, S.; Robino, R.; Kapish, J. (1975) Investigations into sources of lead in the environment of urban children. Environ. Res. 10: 415-426.

Lepow, M.L.; Bruckman, L., Rubino, R.A., Markowitz, S., Gillette, M.; Kapish, J. (1974) Role of airborne lead in increased body burden of lead in Hartford children. Env. Health Perspect. 7: 99-102.

Levander, O.A.; Welsh, S.O.; Morris, V.C. (1980) Erythrocyte deformability as affected by vitamin E deficiency and lead toxicity. Ann. N.Y. Acad. Sci. 355: 227-239.

Levin, E.D.; Bowman, R.E. (1983) The effect of pre- or postnatal lead exposure on Hamilton search task in monkeys. Neuro. Toxicol. Teratol. 5: 391-394.

Liang, C.N.; Tabatabai, M.A. (1978) Effects of trace elements on nitrification in soils. J. Environ. Qual. 7: 291-293.

Lilis, R. (1981) Long-term occupational lead exposure, chronic nephropathy, and renal cancer: a case report. Am. J. Med. 2: 293-297.

Lilis, R.; Fischbein, A.; Eisinger, J.; Blumberg, W.E.; Diamond, S.; Anderson, H.A.; Rom, W.; Rice, C.; Sarkozi, L.; Kon, S.; Selikoff, I.J. (1977) Prevalence of lead disease among secondary lead smelter workers and biological indicators of lead exposure. Environ. Res. 14: 255-285.

Lilis, R.; Gavrilescu, N.; Nestorescu, B.; Dumitriu, C.; Roventa, A. (1968) Nephropathy in chronic lead poisoning. Br. J. Ind. Med. 25: 196-202.

Lindberg, S.E.; Harriss, R.C. (1981) The role of atmospheric deposition in an eastern U.S. deciduous forest. Water Air Soil Pollut. 16: 13-31.

Lin-Fu, J.S. (1972) Undue absorption of lead among children - a new look at an old problem. N. Engl. J. Med. 286: 702-710.

Lioy, R.J.; Mallon, R.P.; Kneip, T.J. (1980) Long-term trends in total suspended particulates, vanadium, manganese, and lead at near street level and elevated sites in New York City. J. Air Pollut. Control Assoc. 30: 153-156.

Litman, D.A.; Correia, M.A. (1983) L-tryptophan: a common denominator of biochemical and neurological events of acute hepatic porphyrias? Science (Washington, D.C.) 222: 1031-1033.

Lucchi, L.; Memo, M.; Airaghi, M.L.; Spano, P.F.; Trabucchi, M. (1981) Chronic lead treatment induces in rat a specific and differential effect on dopamine receptors in different brain areas. Brain Res. 213: 397-404.

Madden, N.A., (1980). Environmental influrneces on mouthing in children with lead intoxication. J. Ped. Psych. 5: 207.

Mahaffey, K.R.; Annest, J.L. (1985). Association of blood lead level, hand-to-mouth activity and pica among young children. 69th Annual Meeting of the Federation of American Societies for Experimental Biology. Anaheim, CA; USA April 21-26, 1985. Fed. Proc. 44: 752.

Manatfey, K.R.; Annest, J.L.; Roberts, J.; Murphy, R.S. (1982) National estimates of blood lead levels: United States, 1976-1980: association with selected demographic and socio-economic factors. N. Engl. J. Med. 307: 573-579.

Mahaffey, K.R.; Michaelson, I.A. (1980) The interaction between lead and nutrition. In: Needleman, H.L., ed. Low level lead exposure: the clinical implications of current research. New York, NY: Raven Press; pp. 159-200.

Mahaffey, K.R.; Rosen, J.F.; Chesney, R.W.; Peeler, J.T.; Smith, C.M.; DeLuca, H.F. (1982) Association between age, blood lead concentration, and serum 1,25-dihydroxycholecalciferol levels in children. Am. J. Clin. Nutr. 35: 1327-1331.

Mahaffey-Six, K.; Goyer, R.A. (1970) Experimental enhancement of lead toxicity by low dietary calcium. J. Lab. Clin. Med. 76: 933-942.

Mahaffey-Six, K.; Goyer, R.A. (1972) The influence of iron deficiency on tissue content and toxicity of ingested lead in the rat. J. Lab. Clin. Med. 79: 128-136.

Maisin, J.R.; Jade, J.M.; Lambiet-Collier, M. (1975) Progress report on morphological studies of the toxic effects of lead on the reproductive organs and embryos. Economic Community and Europe; Contract no. 080-74-/; Env. B. Brussels, Belgium; ECE.

Maker, H.S.; Lehrer, G.M.; Silides, D.J. (1975) The effect of lead on mouse brain development. Environ. Res. 10: 76-91.

Mallon, R.P. (1983) A metabolic model of lead kinetics based upon measured organ burdens during chronic exposure experiments with infant and juvenile baboons. Doctoral Dissertation, New York University.

Manton, W.I. (1977) Sources of lead in blood: identification by stable isotopes. Arch. Environ. Health 32: 149-159.

Manton, W.I.; Cook, J.D. (1984) High accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid. Brit. J. Ind. Med. 41: 313-319.

Marcus, A.H. (1984) Testing alternative nonlinear kinetic models in compartmental analysis. In: Eisenfield, J.; Delisi, C., eds. Proceedings, second IMACS international symposium in biomedical systems modelling, Amsterdam, The Netherlands: Elsevier Science, New York, pp. 259-268.

Marcus, A.H. (1985) Multicompartment kinetic models for lead: part III. lead in blood plasma and erythrocytes. Environ. Res.: 36: 473-489.

Martin, M.H.; Coughtrey, P.J. (1981) Impact of metals on ecosystem function and productivity. In: Lepp, N.W., ed. Effect of heavy metal pollution on plants. Vol. 2: Metals in the environment. Barking, United Kingdom: Applied Science Publishers, Ltd.; pp. 119-158. (Mellanby, K., ed. Pollution monitoring series).

Martonen, T.B. (1983) Measurement of particle dose distribution in a model of human larynx and tracheobronchial tree. J. Aerosol Sci. 14: 11-22.

Maxwell, J.D.; Meyer, U.A. (1976) Effect of lead on hepatic δ-aminolavulinic acid synthetase activity in the rat: a model for drug sensitivity in intermittent acute porphyria. Eur. J. Clin. Invest. 6: 373-379.

McBride, W.G.; Black, B.P.; English, B.J. (1982) Blood lead levels and behaviour of 400 preschool children. Med. J. Aust. 2: 26-29.

McCauley, P.T.; Bull, R.J.; Lutkenhoff, S.D. (1979) Association of alterations in energy metabolism with lead-induced delays in rat cerebral cortical development. Neuropharmacology 18: 93-101.

McCauley, P.T.; Bull, R.J.; Tonti, A.P.; Lutkenhoff, S.D.; Meister, M.V.; Doerger, J.U.; Stober, J.A. (1982) The effect of prenatal and postnatal lead exposure on neonatal synaptogenesis in rat cerebal cortex. J. Toxicol. Environ. Health 10: 639-651.

McElroy, F.F. (1984). Letter to Leonard Bruckman, Director, Air Compliance, Department of Environmental Protection, State of Connecticut concerning Connecticut's request for an equivalent method determination for low-volume lead sampler, May 30, 1984.

McKeague, J.A.; Wolynetz, M.S. (1980) Background levels of minor elements in some Canadian soils. Geoderma 24: 299-307.

McMichael, A.J.; Johnson, H.M. (1982) Long-term mortality profile of heavily-exposed lead smelter workers. J. Occup. Med. 24: 375-378.

McNurney, J.M.; Larimore, R.W.; Wetzel, M.J. (1977) Distribution of lead in the sediments and fauna of a small midwestern stream. In: Drucker, H.; Wildung, R.E., eds. Biological implications of metals in the environment. Proceedings of the fifteenth annual Hanford life sciences symposium; September-October 1975; Richland, WA. Energy Research and Development Administration, Technical Information Center. Available from: NTIS, Springfield, VA; CONF-750929.

Melgaard, B.; Clausen, J.; Rastogi, S.C. (1976) Electromyographic changes in automechanics with increased heavy metal levels. Acta. Neurol. Scand. 54: 227-240.

Mellins, R.B.; Jenkins, C.D. (1955) Epidemiological and psychological study of lead poisoning in children. J. Am. Med. Assoc. 158: 15-20.

1982b; Schlipkoter and Winneke, 1980; Fox et al., 1977, 1982; with embryonic nutrition through competition with calcium, iron, and zinc McCauley et al., 1982; Barrett and Livesy, 1985)

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 (Mahaffey and Michaelson, 1980); and d) interference with embryonic energy 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 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, 1981,1984; McMichael and Johnson, 1982; Sheffet et al., 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 necessarily reflect findings from several recent experimental and occupational studies cited in the criteria document that continue to focus attention on lead acetate and other inorganic lead compounds as possible carcinogens. It appears, therefore, that there is some need for caution and further research on the carcinogenicity of lead compounds 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 studies showing alterations in vitamin D hormone metabolism that is secondary to interference

with heme synthesis, there have been few neuroendocrine studies in humans or animals at low levels of lead. A recent analysis of the NHANES II data (Angle et al., 1985) shows a significant negative correlation of stature with childhood blood lead. Sex, race, dietary protein and calories, blood lead and hematocrit accounted for 91% of the variance in height of 2695 children 6 months through 7 years. The correlation was not improved by the inclusion of the variables of income; urbanization; dietary carbohydrate, fat calcium, potassium, phosphorus, Vitamin A, Vitamin C, niacin, thiamine and riboflavin; serum albumin, copper iron and zinc. Although lead may be a surrogate for multiple environmental factors not defined by the NHANES data, the authors propose consideration of endocrine toxicity such as that mediated by inhibition of calcium activated receptors for TRH or of hypothalamic dopaminergic and α adrenergic receptors.

APPENDIX E. THE LONG-TERM ACCUMULATION OF LEAD IN SOIL IN RURAL AREAS

This appendix presents a simple linear model to predict the long-term accumulation of lead in soil in rural areas. This model was developed as a tool to assess the potential long-term impact of lead in rural terrestrial ecosystems based on the predicted increases in soil lead concentration. Dry deposition rates that are associated with various air lead levels are the bases for estimating the long-term increase in soil lead concentrations. The contribution of wet deposition is included to approximate total lead deposition. Model predictions are based on a fixed lead particle size distribution and dry deposition velocity that are representative of rural areas only. Model outputs apply to typical rural terrestrial ecosystems with low natural soil lead levels, but do not represent rural areas that are impacted by point source emissions of lead or possibly certain rural areas that may experience unusually high deposition rates of lead, e.g., rural mountain areas at high elevations. Model predictions do not apply to urban or roadway areas where soil lead concentrations may already exceed levels of concern.

1. Model Structure/Inputs

A simple linear equation is used to estimate total soil lead concentration:

$$\begin{array}{l}\text{Soil Lead Concentration} \\ (\mu g\ Pb/g\ soil)\end{array} = \begin{array}{l}\text{Initial Soil Lead Concentration} \\ (16\ \mu g\ Pb/g\ soil)\end{array} + \left[\begin{array}{l}\text{Dry deposition flux} \\ (\mu g\ Pb/m^2 \cdot day)\end{array} \times \right.$$

$$\left. (\text{Volume soil/surface area})^{-1}_{(m^2/cm^3)} \times \text{Soil density}^{-1}_{(cm^3/1.5\ g\ soil)} \times \frac{\text{Days}}{\text{Year}} \right] \times \text{Years}.$$

This equation is based on the following assumptions:

1) leaching of lead is negligible (CD, p. 8-13; Tyler, 1978); 2) a steady

state relationship exists between the resuspension and deposition of lead particles so that there is no net loss due to resuspension; 3) mechanisms that remove lead from vegetation before it reaches the soil are insignificant, e.g., no net loss due to grazing or harvesting; and 4) any lead taken up by plant roots or accumulated on or in leaves is recycled to the soil. Although these simplifying assumptions are reasonably appropriate for long-term predictions concerning large-scale natural ecosystems, they introduce uncertainty for model predictions.

Dry deposition flux ($\mu g\ Pb/m^2 \cdot day$) is a function of air lead concentration ($\mu g\ Pb/m^3$) x dry deposition velocity (cm/sec). A range of dry deposition velocities that are representative of lead particles are used to compute the dry deposition flux under alternative air lead levels. For one scenario, a particle size distribution weighted dry deposition velocity (V_D) is used to compute the dry deposition flux of lead. This V_D of 0.56 cm/sec is weighted by the mass of lead particles in each particle size range based on an average particle size distribution of lead in rural areas (Milford and Davidson, 1985), and predicted V_D from the Davidson et al. (1982) model (Figure E-1). The lead particle size distribution data are an average for 6 rural/remote sites for the time period 1973-1980. The particle size aerodynamic diameter of this average distribution ranged between 0.05-40 μm, with approximately 63% of the mass of lead particles in the submicron fraction. Each fraction of airborne lead mass in a size interval was assigned a dry deposition velocity based on the Davidson et al. model (Table E-1). In this way, a particle size distribution weighted V_D was computed. The Davidson et al.

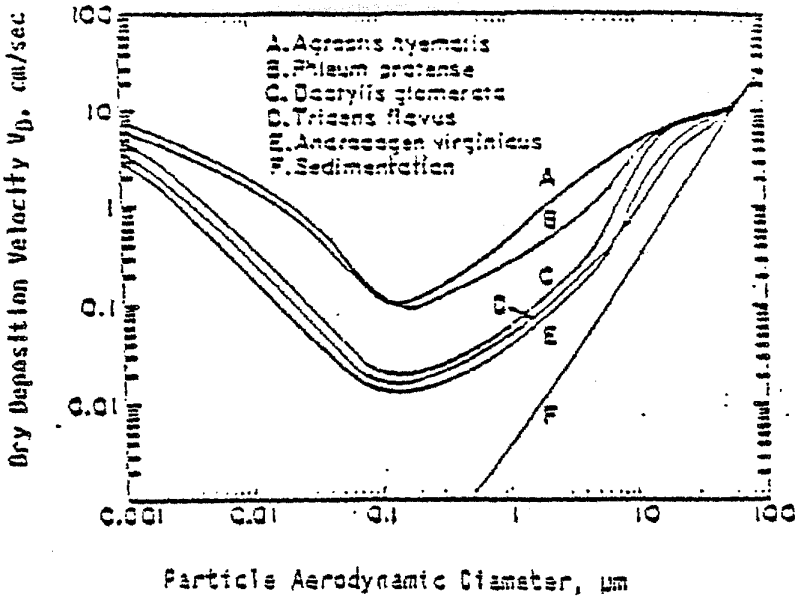

Figure E-1. Predicted particle dry deposition velocity for wild grass canopies. Wind profile and canopy characterization data for 5 wild grass canopies: surface roughness height 4-14 cm, wind speed 2.1-3.3 m/sec, friction velocity 32-64 cm/sec, maximum canopy height 30-100 cm.

Source: Davidson et al., 1982.

Table E-1. Estimation of Particle Size Distribution Weighted Dry Deposition Velocity

Particle size interval[a], aerodynamic diameter	$\Delta \log d_p$[b]	Fraction of airborne mass in size interval	Dry deposition velocity, V_g[c] cm/sec	Particle size distribution weighted V_g[d] cm/sec
0.25 - 0.1 μm	0.3	11%	0.11	
0.1 - 0.5 μm	0.73	25%	0.09	
0.5 - 1.2 μm	0.22	15%	0.17	
1.2 - 1.5 μm	0.2	8%	0.23	
1.5 - 4.2 μm	0.43	13%	0.515	
4.2 - 5.3 μm	0.14	5%	0.3	0.35
5.3 - 6.2 μm	0.52	0.3%	1.085	
6.2 - 7.3 μm	0.07	2%	1.25	
7.3 - 9.1 μm	0.09	2%	1.55	
9.1 - 10 μm	0.041	0.3%	1.9	
10 - 14.2 μm	0.152	2.5%	2.7	
14.2 - 40 μm	0.45	4%	5.25	

[a] Particle size data from Milford and Davidson (1985).
[b] $\Delta \log d_p = \log d_p$ max - $\log d_p$ min, where d_p max and min are, respectively, the maximum and minimum particle size (μm) aerodynamic diameter of the particle size interval.
[c] Davidson et al. (1982).
[d] Weighted by mass in each particle size range.
$V_g = (0.11)(0.13) + (0.09)(0.25) + (0.17)(0.15) + (0.23)(0.08) + (0.515)(0.13) + (0.3)(0.05) + (1.085)(0.008) + (1.25)(0.02) + (1.55)(0.02) + (1.9)(0.008) + (2.7)(0.026) + (5.25)(0.04) = 0.56$ cm/sec

dry deposition model predicts dry deposition velocity as a function of particle size, windspeed and surface characteristics of wild grass canopies. Because this model predicts V_D as a function of the effective depositional area, i.e., detailed measurements of vegetative structure and surface area are input into the model to approximate the canopy collection efficiency for particles, it is an appropriate model to estimate dry deposition flux in rural areas. Soil lead concentrations predicted for the weighted V_D of 0.56 cm/sec are presented in Table E-2. The V_D of 0.2 cm/sec that is used to compute the dry deposition flux of lead represents calculations of particle dry deposition velocity based on field data of lead deposition onto artificial surfaces (Davidson et al., 1985; Elias and Davidson, 1980; Davidson, 1977). Soil lead concentrations predicted for this V_D are presented in Table E-3.

For both dry deposition velocities, the model predicts soil lead concentrations for three scenarios of lead immobilization, i.e., within the upper 2-5 cm of an undisturbed soil profile (CD, p. 7-28), and for a cultivated soil profile (lead uniformly mixed to a plow depth of 18 cm; Ewing and Pearson, 1974). Soil lead concentrations are predicted for rural areas for the 100 year period following the introduction of lead additives to gasoline.

2. Model Results

Tables E-2 and E-3 describe soil lead concentrations (µg Pb/g soil) predicted for rural areas for the 100 year period following the introduction of lead additives to gasoline. These predictions are made for two dry deposition velocities (0.56 and 0.2 cm/sec), and for a range of air lead levels (0.05-1.5 µg Pb/m^3). The predicted total soil lead concentrations

TABLE E-2. ESTIMATION OF LONG-TERM ACCUMULATION OF LEAD IN SOIL IN RURAL AREAS BASED ON DRY DEPOSITION FLUX UNDER DIFFERENT AIR LEAD LEVELS

Dry Deposition Velocity, V_D[a] cm/sec	Air Lead Level µg Pb/m³	Dry Deposition Flux[b] µg Pb/m².day	Soil Lead Concentration[c] µg Pb/g soil 5 years	10 years	25 years	50 years	75 years	100 years
0.56 cm/sec	0.05[g]	25	20[d]	20[d]	25[d]	30[d]	40[d]	45[d]
			17[e]	17[e]	19[e]	22[e]	25[e]	28[e]
			16[f]	16[f]	17[f]	18[f]	19[f]	19[f]
	0.1[h]	50	20[d]	20[d]	30[d]	45[d]	60[d]	75[d]
			17[e]	18[e]	22[e]	29[e]	34[e]	40[e]
			16[f]	17[f]	18[f]	19[f]	20[f]	25[f]
	0.25	120	25[d]	30[d]	50[d]	90[d]	130[d]	160[d]
			20[e]	20[e]	30[e]	45[e]	60[e]	75[e]
			17[f]	13[f]	20[f]	25[f]	30[f]	30[f]
	0.5	240	30[d]	45[d]	90[d]	160[d]	240[d]	310[d]
			20[e]	30[e]	45[e]	75[e]	105[e]	135[e]
			18[f]	19[f]	25[f]	30[f]	40[f]	50[f]
	0.75	360	40[d]	60[d]	130[d]	240[d]	340[d]	450[d]
			25[e]	35[e]	60[e]	105[e]	150[e]	190[e]
			18[f]	20[f]	30[f]	40[f]	55[f]	65[f]
	1.0	480	45[d]	75[d]	160[d]	310[d]	450[d]	600[d]
			30[e]	40[e]	75[e]	135[e]	190[e]	250[e]
			20[f]	25[f]	30[f]	50[f]	65[f]	80[f]
	1.25	600	50[d]	90[d]	200[d]	380[d]	560[d]	750[d]
			30[e]	45[e]	90[e]	160[e]	235[e]	310[e]
			20[f]	25[f]	35[f]	55[f]	75[f]	95[f]
	1.5	730	60[d]	105[d]	240[d]	460[d]	680[d]	900[d]
			35[e]	50[e]	105[e]	195[e]	285[e]	370[e]
			20[f]	25[f]	40[f]	65[f]	90[f]	115[f]

[a]Particle size distribution weighted V_D (weighted by mass in each particle size range), based on average particle size distribution of lead in rural areas (Milford and Davidson, 1985) and predicted V_D from Davidson et al. (1982).

[b]Flux µg Pb/m².day = V_D cm/sec x air concentration µg Pb/m³.

[c]See text; years are the number of years following the introduction of lead additives to gasoline.

[d]Lead immobilized within upper 2 cm of undisturbed soil profile.

[e]Lead immobilized within upper 5 cm of undisturbed soil profile.

[f]Lead immobilized within upper 18 cm of cultivated soil profile.

[g]Represents lower bound of range of geometric mean quarterly lead concentrations at nonurban stations 1974-80 (CD, Table 7A-2).

[h]Represents upper bound of range of geometric mean quarterly lead concentrations at nonurban stations 1974-80 (CD, Table 7A-2).

TABLE E-3. ESTIMATION OF LONG-TERM ACCUMULATION OF LEAD IN SOIL IN RURAL AREAS BASED ON DRY DEPOSITION FLUX UNDER DIFFERENT AIR LEAD LEVELS

Dry Deposition Velocity, V_D[a] cm/sec	Air Lead Level μg Pb/m³	Dry Deposition Flux[b] μg Pb/m².day	Soil Lead Concentration[c] μg Pb/g soil					
			5 years	10 years	25 years	50 years	75 years	100 years
0.2 cm/sec	0.059	10	17[d] 16[e] 16[f]	17[d] 17[e] 16[f]	19[d] 17[e] 16[f]	22[d] 18[e] 17[f]	25[d] 20[e] 17[f]	28[d] 21[e] 17[f]
	0.1[h]	20	17[d] 17[e] 16[f]	18[d] 17[e] 16[f]	22[d] 18[e] 17[f]	28[d] 21[e] 17[f]	35[d] 23[e] 18[f]	40[d] 26[e] 19[f]
	0.25	45	20[d] 17[e] 16[f]	20[d] 18[e] 17[f]	30[d] 22[e] 18[f]	45[d] 27[e] 19[f]	60[d] 32[e] 21[f]	70[d] 38[e] 22[f]
	0.5	90	20[d] 18[e] 17[f]	25[d] 20[e] 17[f]	45[d] 25[e] 19[f]	70[d] 40[e] 22[f]	100[d] 50[e] 25[f]	125[d] 60[e] 28[f]
	0.75	130	24[d] 19[e] 17[f]	32[d] 22[e] 18[f]	55[d] 30[e] 20[f]	95[d] 50[e] 25[f]	135[d] 65[e] 30[f]	175[d] 80[e] 35[f]
	1.0	170	30[d] 20[e] 17[f]	40[d] 25[e] 18[f]	70[d] 35[e] 22[f]	120[d] 60[e] 30[f]	170[d] 80[e] 35[f]	225[d] 100[e] 40[f]
	1.25	220	30[d] 20[e] 18[f]	45[d] 30[e] 19[f]	85[d] 45[e] 23[f]	150[d] 70[e] 30[f]	220[d] 100[e] 40[f]	280[d] 125[e] 45[f]
	1.5	260	30[d] 20[e] 18[f]	50[d] 30[e] 20[f]	95[d] 50[e] 25[f]	175[d] 80[e] 35[f]	250[d] 110[e] 40[f]	330[d] 145[e] 50[f]

[a]Calculated dry deposition velocity from field studies that measured lead deposition onto artificial surfaces.

[b]Flux μg Pb/m².day = V_D cm/sec x air concentration μg Pb/m³.

[c]See text; years are the number of years following the introduction of lead additives to gasoline.

[d]Lead immobilized within upper 2 cm of undisturbed soil profile.

[e]Lead immobilized within upper 5 cm of undisturbed soil profile.

[f]Lead immobilized within upper 18 cm of cultivated soil profile.

[g]Represents lower bound of range of geometric mean quarterly lead concentrations at nonurban stations 1974-80 (CD, Table 7A-2).

[h]Represents upper bound of range of geometric mean quarterly lead concentrations at nonurban stations 1974-80 (CD, Table 7A-2).

in Tables E-2 and E-3 represent the contribution of dry deposition only. Although the relative importance of dry and wet deposition varies both spatially and temporally, on a global and long-term, e.g., annual as contrasted with daily basis, dry deposition has been estimated to account for approximately 50% of total lead deposition (CD, p. 6-27). This estimate is consistent with the limited data available of the relative contribution of wet and dry deposition of lead in rural areas (NAS, 1980; Lindberg and Harriss, 1981). For model predictions that are based solely on dry deposition flux, the estimated net increase in soil lead concentration above a natural soil lead level of 16 μg Pb/g soil is, therefore, doubled to approximate the contribution of wet deposition to the total atmospheric deposition of lead. A doubling of the estimate of dry deposition flux to account for total lead deposition requires the simplifying assumption that a steady state exists between the addition and removal of particulate lead from the atmosphere. It is also assumed that the atmospheric residence time of lead is long relative to the duration of rain events. These seem to be reasonable assumptions given that a dynamic model best represents reality and lead aerosols have atmospheric residence times of approximately 1-2 weeks (NAS, 1980; Nriagu, 1978; Shirahata et al., 1980).

Although the sources of lead in rural areas are not entirely certain, the historical accumulation of anthropogenic lead in soil in these areas, remote from point sources, is attributed primarily to the long-range transport of fine lead particles that originate from mobile sources. Fine lead particles (aerodynamic diameter < 2 μm) have relatively long atmospheric residence times and have the potential for long-range transport (CD, p. 5-10, 6-16). Point source emissions of lead tend to have a more

localized impact on air and soil lead concentrations with background levels typically reached within 5-10 km (Landrigan and Baker, 1981; Jennett et al., 1977; CD, p. 8-40; Battye et al., 1985). Given that rural areas may be impacted by local sources of lead emissions, these model predictions of the long-term accumulation of lead in soil best apply to rural areas not within 10 km of point sources.

Lead-alkyls were first added to gasoline in the 1920's (CD, p. 5-1). The plausibility of the estimates of the long-term accumulation of lead (Tables E-2 and E-3) is, therefore, evaluated by comparing current field measurements of soil lead concentrations in rural areas to model predictions at 50-75 years into the simulation, i.e., time period following the introduction of lead additives to gasoline. Current soil lead concentrations in rural areas are estimated to range from 5-50 µg Pb/g soil (NAS, 1980; CD, p. 7-31; Nriagu, 1978; Getz et al., 1977; Jackson and Watson, 1977; Palmer and Kucera, 1980).

At air lead levels that are most representative of rural areas in the U.S. (0.05-0.1 µg/m^3; CD, Table 7A-2, 7A-3), and with the immobilization of lead in the upper 5 cm of the soil profile, model predictions of the long-term accumulation of lead in rural areas (Tables E-2 and E-3) appear plausible as order of magnitude estimates. For example, under an air lead level of 0.05 µg/m^3 and with a dry deposition velocity of 0.56 cm/sec, the model predicts an increase in soil lead concentration (associated with dry deposition flux) from a background level of 16 µg Pb/g soil to 22-25 µg Pb/g soil at 50-75 years into the simulation (Table E-2). For the same scenario, under an air lead level of 0.1 µg/m^3 the model predicts a soil lead concentration of 28-34 µg Pb/g soil (Table E-2). For these two air

lead levels, a doubling of the dry deposition flux to account for the contribution of wet deposition gives an estimated soil lead concentration of 28-34 and 40-52 μg Pb/g soil. Similarly, model predictions based on a lower bound dry deposition velocity of 0.2 cm/sec (Table E-3) are plausible order of magnitude estimates of soil lead concentrations in rural areas.

As an alternative to doubling the estimate of the dry deposition flux to account for total lead deposition, empirical data of lead concentration in precipitation and precipitation rates in rural areas are used to calculate wet deposition rates of lead. These estimates are then added to the model's predicted dry deposition rates to approximate total lead deposition. Although concentrations of lead in precipitation are highly variable making it difficult to assign a representative concentration value (Galloway et al., 1982; CD, p. 6-25), wet deposition flux is estimated based on a median concentration of lead in precipitation of 8 μg Pb/l for rural areas in the U.S. (Galloway et al., 1980; Galloway et al., 1982). For a lead concentration of 8 μg/l and precipitation rates of 20-140 cm/year that represent the range observed in different geographic regions of the U.S. (Climatic Atlas of the U.S., 1968), the wet deposition rate of lead is 4 and 31 $\mu g/m^2 \cdot day$, respectively. Estimated total soil lead concentrations that are associated with the sum of these average wet deposition rates and the dry deposition rates predicted by the model appear plausible, and the soil lead concentrations predicted by either method are comparable as order of magnitude estimates. For example, for dry deposition velocities of 0.2 and 0.56 cm/sec, air lead levels of 0.05 and 0.1 $\mu g/m^3$, and with the immobilization of lead in the upper 2-5 cm, predicted soil lead concentrations at 50-75

years following the introduction of lead additives to gasoline range from 20-90 μg Pb/g soil (Table E-4).

Although concentrations of lead in precipitation are highly variable, these calculations that are based on a median concentration of lead in precipitation and a range of precipitation rates give some indication of the appropriateness of doubling the dry deposition flux to account for total lead deposition. As expected, the average wet deposition rates suggest that a doubling of the dry deposition flux predicted by the model to account for the total deposition of lead overestimates the contribution of wet deposition in the more arid rural areas of the U.S. In rural areas that experience relatively high annual precipitation rates, a doubling of the dry deposition flux based on a V_D of 0.56 cm/sec is a reasonable approximation to total lead deposition. A doubling of this estimate, however, would tend to overestimate total deposition in areas with moderate precipitation rates. A doubling of the dry deposition flux that is associated with a V_D of 0.2 cm/sec likely underestimates the contribution of wet deposition in areas with moderate to high annual precipitation rates.

Although the model estimates under the above scenarios appear plausible, it should be noted that the plausibility check was based on model predictions for air lead levels representative of rural areas between 1974-1980, i.e., 0.05-0.1 $\mu g/m^3$. In the absence of reliable data of air lead levels in rural areas from 1920 through the mid 1960's, it is difficult to evaluate the predictive power of the model with respect to the historical accumulation of lead in soil. Air lead levels in rural areas can, however, be estimated based on past emission data. Because anthropogenic lead in rural areas is

TABLE E-4. ESTIMATED SOIL LEAD CONCENTRATION IN RURAL AREAS BASED ON MODEL PREDICTED DRY DEPOSITION FLUX FOR AIR LEAD LEVELS REPRESENTATIVE OF RURAL AREAS AND ESTIMATED AVERAGE WET DEPOSITION FLUX

Dry Deposition Velocity, V_D cm/sec	Air Lead Level μg Pb/m³	Dry Deposition Flux[c] μg Pb/m².day	Wet Deposition Flux μg Pb/m².day	Total Lead Deposition[f] μg Pb/m².day	Soil Lead Concentration[g] μg Pb/g soil 50 years	75 years
0.56 cm/sec[a]	0.05	25	4[d]	29	35[h] 25[i] 20[j]	40[h] 30[i] 20[j]
		25	31[e]	56	50[h] 30[i] 20[j]	70[h] 40[i] 20[j]
	0.1	50	4[d]	54	50[h] 30[i] 20[j]	65[h] 35[i] 20[j]
		50	31[e]	81	65[h] 35[i] 20[j]	90[h] 45[i] 25[j]
0.2 cm/sec[b]	0.05	10	4[d]	14	25[h] 19[i] 17[j]	29[h] 21[i] 17[j]
		10	31[e]	41	40[h] 25[i] 20[j]	55[h] 30[i] 20[j]
	0.1	20	4[d]	24	30[h] 20[i] 20[j]	40[h] 25[i] 20[j]
		20	31[e]	51	50[h] 30[i] 20[j]	65[h] 35[i] 20[j]

[a]Particle size distribution weighted V_D (weighted by mass in each particle size range), based on average particle size distribution of lead in rural areas (Milford and Davidson, 1985) and predicted V_D from Davidson et al. (1982).

[b]Calculated dry deposition velocity from field studies that measured lead deposition onto artificial surfaces.

[c]Dry deposition flux μg Pb/m^2·day = V_D cm/sec x air Pb concentration μg Pb/m^3.

[d]Wet deposition flux μg Pb/m^2·day = 8 μg Pb/l x 20 cm/year precipitation.

[e]Wet deposition flux μg Pb/m^2·day = 8 μg Pb/l x 140 cm/year precipitation.

[f]Total lead deposition μg Pb/m^2·day = Dry deposition flux + wet deposition flux.

[g]Years are the number of years following the introduction of lead additives to gasoline.

[h]Lead immobilized within upper 2 cm of undisturbed soil profile.

[i]Lead immobilized within upper 5 cm of undisturbed soil profile.

[j]Lead immobilized within upper 18 cm of cultivated soil profile.

attributed to mobile source emissions, historical data of lead consumption in gasoline (U.S. Bureau of Mines Minerals Yearbook, 1929-1983) can be used to estimate past air lead levels. This was done by comparing data of yearly lead consumption in gasoline (Table E-5) to the level of consumption during 1974-1980.

Based on the data of lead consumption in gasoline (Table E-5), air lead levels in rural areas during the late 1920's through the early 1960's are estimated to have been less than or approximately equal to air lead concentrations that are representative of rural areas between 1974-80. Air lead levels during 1966-73 may have averaged 30% higher than concentrations in 1974-80. Deposition rates that would be expected during these time periods are directly proportional to air lead concentration. As a result, model predictions of soil lead concentration that are based on deposition fluxes associated with 1974-80 rural air lead concentrations may overpredict deposition flux for the time period since the introduction of lead additives to gasoline through the early 1960's, but may underpredict deposition flux for the 8 year period between 1966-73. The magnitude of this underprediction appears small, however, as indicated by the dry deposition flux associated with a 30% increase in air lead concentration (above the upper bound level of 0.1 $\mu g/m^3$), and dry deposition velocities of 0.56 and 0.2 cm/sec, i.e., 63 and 22 $\mu g/m^2 \cdot day$, respectively. This small increase in dry deposition flux (from 50 to 63 $\mu g/m^2 \cdot day$ and from 20 to 22 $\mu g/m^2 \cdot day$; Tables E-2 and E-3) over a relatively short period of time would not significantly change soil lead concentrations predicted by the model. The net effect of using a constant air lead level (0.05-0.1 $\mu g/m^3$) as representative

TABLE E-5. ANNUAL CONSUMPTION OF LEAD IN GASOLINE ADDITIVIES IN THE UNITED STATES FROM 1929-1983

Metric Tons

Year	Consumption	Year	Consumption	Year	Consumption
1929	16,329	1948	76,030	1966	223,964
1930	9,979	1949	85,859	1967	224,228
1931	5,443	1950	103,279	1968	237,588
1932	3,175	1951	116,488	1969	245,962
1933	4,536	1952	133,104	1970	252,654
1934	6,622	1953	147,365	1971	239,713
1935	9,072	1954	145,544	1972	252,504
1936	10,070	1955	149,805	1973	248,939
1937	10,886	1956	174,169	1974	227,250
1938	5,443	1957	160,572	1975	189,242
1939	8,074	1957	144,615	1976	217,504
1940	9,979	1959	145,167	1977	211,291
1941	43,841	1960	148,620	1978	161,778
1942	45,497	1961	154,041	1979	169,593
1943	59,257	1962	153,246	1980	116,031
1944	75,357	1963	174,914	1981	101,030
1945	68,846	1964	202,724	1982	108,167
1946	43,513	1965	204,300	1983	80,846
1947	71,014				

SOURCE: U.S. Bureau of Mines Mineral Yearbook, 1929-1983.

of rural areas most likely is to overpredict soil lead concentration given the relatively long time period during which rural air lead levels are estimated to have been less than or equal to 1974-80 levels.

The alternative method to estimate total lead deposition relies on dry deposition flux predicted by the model and average wet deposition rates of lead. The concentration of 8 µg Pb/l precipitation represents a median value of lead concentration in precipitation for the time period 1975-1980. Applying the same rationale stated above, it is likely that soil lead concentrations predicted for an average wet deposition flux of lead (associated with a concentration of 8 µg Pb/l) are overestimates, given the relatively long time period during which lead concentrations in precipitation are estimated to have been less than or equal to concentrations measured during 1975-1980.

Empirical data of soil samples collected from cultivated fields in Illinois show an increase in soil lead concentration from 13 µg Pb/g soil in the 1920's to 26 µg Pb/g soil in the late 1960's (Ewing and Pearson, 1974). Model predictions of soil lead concentration for cultivated soil (Tables E-2 and E-3) underestimate soil lead concentration using these field data for empirical validation. Under air lead levels most representative of rural areas and with dry deposition velocities of 0.2 and 0.56 cm/sec, based on a doubling of the estimated dry deposition flux, the model predicts an increase in soil lead concentration from a natural background level of 16 µg Pb/g soil to 18-22 µg Pb/g soil for the time period 1920-1970, i.e., 50 years into the simulation. Alternatively, soil lead concentration can be estimated based on the sum of the dry deposition flux predicted by the model and the estimated average wet deposition flux for rural areas. For this same scenario, this summation yields a similar soil lead concen-

tration of 17-20 µg Pb/g soil (Table E-4). Either method results in an underprediction of soil lead concentration compared to empirical data collected in Illinois. The low levels predicted are, in part, due to the dilution effect of uniformly distributing the lead concentration through an 18 cm soil depth. It is possible that the higher soil lead concentrations measured in Illinois may represent the continual addition of fertilizers containing lead to these agricultural fields.

For the model scenario associated with maximum soil lead concentration (V_D 0.56 cm/sec, lead immobilization within the upper 2 cm of an undisturbed soil profile) and for the range of air lead concentration that is most representative of rural areas (0.05-0.1 µg/m^3), an increase in soil lead concentration from a natural background level of 16 µg Pb/g soil in 1920 to 75-135 µg Pb/g soil is predicted for rural areas for the 100 year period following the introduction of lead additives to gasoline (Table E-2). These levels are well below total soil lead concentrations that are associated with adverse effects in plants and soil microbes, i.e., 1000 µg Pb/g soil and 750-1000 µg Pb/g soil, respectively. Although soil lead concentrations predicted by the model for rural areas are not anticipated to approach levels associated with adverse effects in terrestrial biota, there is much uncertainty in assessing potential environmental impact in terms of total soil lead concentration. This is due to the varying capacity of different soil types to immobilize lead and the lack of a clear quantitative relationship between total soil lead concentration and biologically available lead.

With the recently revised phasedown schedule for lead in gasoline, it is estimated that by 1990 the annual average air lead level for neighborhood

scale monitoring sites, due only to mobile source impacts, will be 0.02 $\mu g/m^3$ (Battye et al., 1985). Although impacts for remote and rural monitoring sites were not projected, air lead levels in rural areas should be no higher than 0.02 $\mu g/m^3$ and will likely be much lower. Assuming a similar particle size distribution of lead in rural areas in the future, at such low air lead levels the anticipated rate of increase in soil lead concentration in most rural areas, based on this linear model and dry deposition velocities of 0.2 and 0.56 cm/sec, is quite small and it appears unlikely that total soil lead concentrations will reach levels of concern within the next several decades. Rural areas that have already experienced significant increases in soil lead concentration or have elevated natural soil lead concentration may be approaching levels of concern. These model predictions may not apply to rural areas at high elevations that appear to be more rapidly approaching soil lead concentrations of concern (Johnson et al., 1982). The more rapid accumulation of lead might be explained by increased precipitation due to orographic effects, and by the nature of the soil in certain high elevation forests. It appears that there may be an effect in high elevation forests that requires further research.

3. Model Uncertainties

These model predictions must be considered, at best, as crude estimates of the long-term accumulation of lead in soil. Predicted soil lead concentrations are dependent on both the dry deposition model selected and the particle size distribution data that determine the dry deposition velocity and the resulting deposition flux. As a result, predicted soil lead concentrations are highly uncertain due to the complex interaction of parameters that influence particle deposition and that are not entirely well-defined, the high degree of uncertainty associated with dry deposition velocities,

the questionable accuracy of particle size distribution data, and the reliance on model assumptions and predictions that are difficult to validate. The dry deposition velocity curves of Figure E-1, for example, have not been validated experimentally. The range of dry deposition velocities predicted by models are comparable with dry deposition velocities that are calculated from field measurements of deposition onto surrogate and natural surfaces. Either method of estimating dry deposition velocity, however, gives highly variable results with dry deposition velocities varying by several orders of magnitude. This reflects the actual variations and also the uncertainties associated with these estimates (Davidson et al., 1982; Slinn, 1982; Sehmel, 1980).

Much uncertainty is associated with calculating or predicting particle dry deposition velocity which is a function of many variables. The weighted V_D (0.56 cm/sec) that is derived from the Davidson et al. model is considered here to be an upper-bound that may overpredict the dry deposition flux and accumulation of lead in soil due to the relatively greater surface roughness heights (4-14 cm) and plant geometry that increase collection efficiency and result in higher deposition velocities for grass canopies compared to bare soil. This weighted V_D may possibly underpredict dry deposition flux for forest canopies that are characterized by higher deposition velocities compared to grasslands (CD, p. 6-28). To the extent that a V_D of 0.56 cm/sec is an upper-bound, a doubling of the estimate of dry deposition flux to account for the contribution of wet deposition may compound this overestimation, especially in areas with low to moderate annual precipitation rates. In addition, the Davidson et al. model predictions are specific for meteorological

Thus, while any individual child's IQ score may fluctuate over time, the implications of a 5 point average deficit among children are serious (see Figure D-2).

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 and other neurobehavioral deficits appear to be associated with lead exposures of U.S. children resulting in dentine lead values that exceed 20-30 ppm and likely average 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) (see Figure D-2).

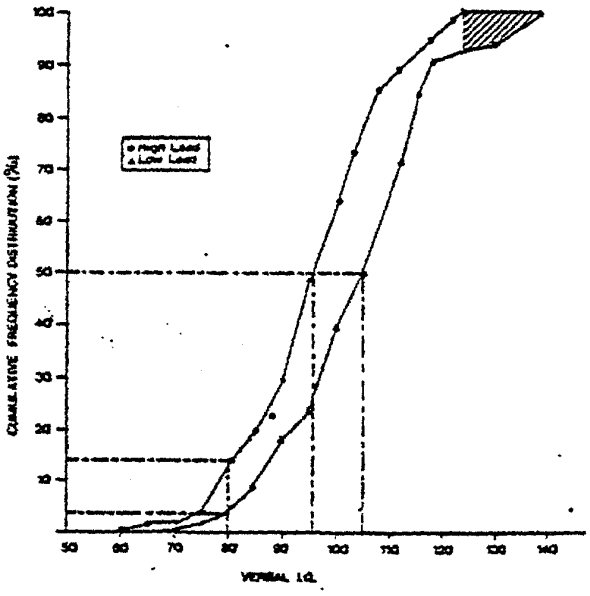

Figure D-2. Cumulative Frequency Distribution of Verbal IQ Scores in Subjects with Low or High Levels of Lead (Source: Needleman et al., 1982).

Bellinger et al. (1984) followed up on the academic performance of a subset of the children initially evaluated by Needleman et al. (1979) and

found that only grade retention was clearly associated with past dentine lead levels; other outcomes (e.g., remedial instruction, classroom behavior) tended to be in the predicted direction of effect but generally at p values between 0.5 and 0.15.

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).

Initial assessment of 104 lower SES children, aged 10 months to 6.5 years showed an inverse linear relationship of PbB and IQ across concentrations from 6 to 59 µg/dl after controlling for SES, quality of the care-giving environment, maternal IQ, and other social factors (Schroeder et al., 1985). In addition, a dissociation of maternal and child IQ was found ($r = 0.058$; the expected normal mother-child IQ correlation is about 0.50) in children below 30 months of age with PbB levels above 30 µg/dl, consistent with other studies (Perino and Ernhart, 1974; Bellinger and Needleman, 1983). Five years later, the PbB levels of the 50 children retested had dropped to below 30 µg/dl and the correlation between maternal and child IQ returned to a nearly normal value ($r = 0.45$). Furthermore, the effect of either contemporary or initial PbB levels on 5-year follow-up IQ scores was not significant after covariates were accounted for in the regression model (Schroeder et al., 1985).

A replication of the above study using 75 low SES children between 2 and 3 years of age showed the same continuous linear decrease in IQ with increasing PbB across a wide range (6-47 µg/dl) with 78% of subjects having PbB levels below 30 µg/dl (Schroeder and Hawk, 1986). The effect was almost equally as strong regardless of whether contemporary, past maximum, or mean PbB levels were used in the analysis. The potentially confounding factor of SES was effectively controlled by selecting a very homogeneous group of children.

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). [The study by Silva et al.(1986) on 11-year old New Zealand children with a mean PbB of 11 µg/dl found no effects of lead on IQ but significant associations between PbB and various behavioral measures. These results on older children are difficult to relate to the other studies cited here on young children]. 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 or those of manual working class fathers 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. The findings by Schroeder et al. (1985) and Schroeder and Hawk (1986) of significant dose-response relationships down to very low PbB levels after controlling for social factors may be attributable to the uniformly low SES of the children studied. Although SES was not a significant covariate in Schroeder and Hawk (1986), quality of the home environment (which may be linked to IQ) was a significant predictor of lead exposure, consistent with other work (Milar et al., 1980; Dietrich et al., 1985). This close relationship between SES, home environment, and lead exposure suggests that SES may not be the sole determinant of increasesd risk for cognitive impairment. Further research is needed to investigate the possibility that any 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 indicate that a wide range of lead levels may be 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; see discussion below).

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. [Psychometric evaluation revealed a significant lead-related IQ decrement at the time of initial testing (Schroeder et al., 1985); no relation between blood lead and hyperactive behavior was noted in these children (Milar et al., 1981).] Neurophysiological evidence suggests that slow surface-positive potentials in very young children may reflect

axodendritic inhibitory processes (Otto and Reiter, 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 (Benignus et al., 1981). Increased synchrony and relative amplitude of the EEG at these PbB levels 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). The clinical nor the functional significance of this measure has yet to be established, however.

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, slow-wave voltage varied as a function of current PbB level during active conditioning, but not during the passive conditioning test used in earlier studies (Otto et al., 1985). Measurements of pattern-reversal visual-evoked potential (PREP) revealed increased amplitude and decreased latency of certain components as a linear function of original PbB level, which is contrary to predictions but consistent with results of Winneke et al. (1984). Significant associations were also found between PbB levels and increased latencies in brainstem auditory evoked potentials (BAEP), indicative of auditory nerve conduction slowing (Otto et al., 1985).

Results of a replication study in an independent group of children 3-7 years old indicate that contrary to earlier findings (Otto et al., 1981,1982),

slow-wave voltage did not vary with PbB level. Although age differences between the two groups studied (1-6 versus 3-7 years) and their different exposure routes may account for these inconsistencies, earlier findings must be interpreted cautiously in the absence of further study. [Psychometric evaluation of these children revealed a continuous linear decrease in IQ with increasing PbB level across the range of 6-47 µg/dl (Schroeder and Hawk, 1986).] Only one PREP amplitude measure varied systematically with PbB levels and this was in the opposite direction of earlier findings. In contrast to the 5-year follow-up study in which a simple linear relationship was observed, several BAEP latency measures showed a curvilinear relationship to maximal PbB levels in the replication such that latencies decreased as PbB levels rose from 6 to 25 µg/dl, but increased at higher PbB levels (Otto, 1985; Robinson et al., 1985). In addition, latency of central transmission time in the auditory pathway increased directly with PbB as did hearing threshold, a reflection of peripheral auditory function. The latter finding is inconsistent with earlier findings (Otto et al., 1985), although it warrants concern in view of other reports suggesting impaired auditory processing (along with performance deficiencies) in lead-exposed school-age children (Perino and Ernhart, 1974; Needleman et al., 1979).

Given that the clinical and functional significance of many of the electrophysiological measures used are presently considered experimental and given the inconsistent correlations between PbB and the various measures, the current electrophysiological evidence concerning lead exposure and brain function in children is too fragmentary to draw any firm conclusions. Nevertheless, the criteria document concludes that these findings suggest the possibility 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. 12-157).

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 Appen-

dix 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 and monkeys 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, social behavior) (Klein et al., 1978; Bushnell and Bowman, 1979; Crofton 1977; et al., 1980; Grant et al., 1980; Overmann et al., 1981; Winneke et al., 1977;

APPENDIX D. HEALTH EFFECTS OF LEAD

This appendix discusses and evaluates the information reviewed in detail in Chapter 11 of the criteria document 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

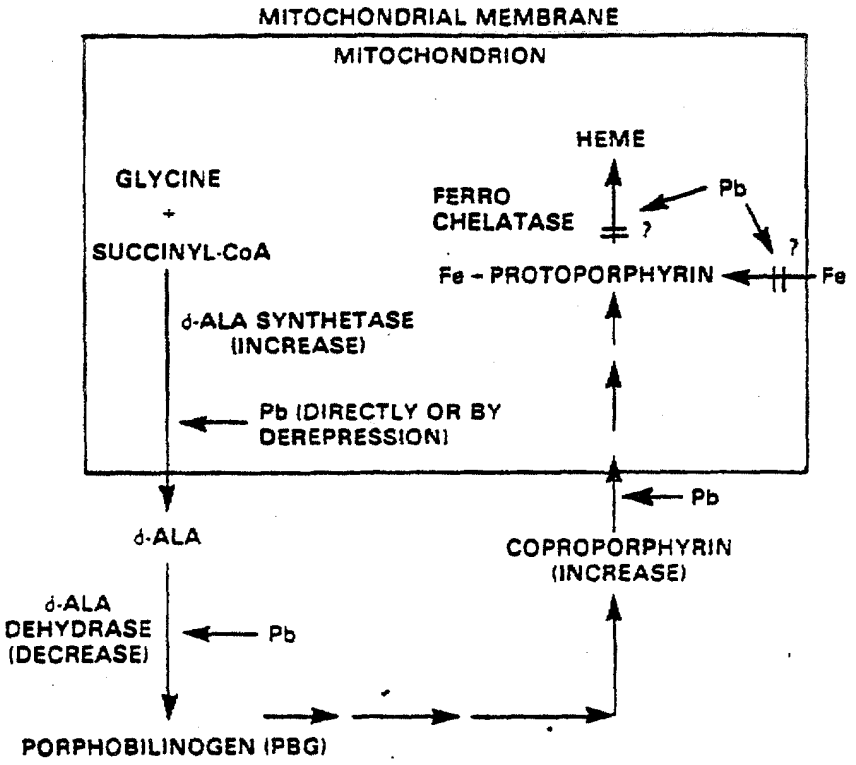

Figure D-1. Lead effects on heme biosynthesis, from CD; Figure 6-1.

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 (Mahaffey et al., 1982). 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 (i.e., 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 in children by which lead-induced reductions in 1,25-$(OH)_2$ D interfered with intestinal lead absorption. Short-term experimental studies with rats (Smith et al., 1981), however, indicate that: (i) dietary intake of vitamin D does not affect blood lead concentration; (ii) lead ingestion totally blocked calcium transport thereby enhancing lead absorption; and (iii) reduced 1,25-$(OH)_2$ D levels do not protect target organs (e.g., kidney) by sequestering lead in bone. Furthermore, experimental data (Smith et al., 1981; Edelstein et al., 1984) confirm the inhibitory effects of lead on the conversion of 25 to 1,25-$(OH)_2$ D in the kidney. (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 stage I rickets; these changes are therefore not meaningful indicators of the signifiance of reduced 1,25-$(OH)_2$ D in children (Rosen and Chesney, 1983). The fact that the mineralization of bone matrix is impaired in vitamin D deficiency rickets but not in lead-induced 1,25-$(OH)_2$ D deficiency is also not relevant since vitamin D deficient children may have normal or even elevated 1,25-$(OH)_2$ D levels.

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, particularly when exposure occurs during early development. Mechanisms that explain the neurological effects of lead include (but are not limited to) direct alteration of sodium and calcium metabolism, inhibition of certain neuronal enzymes (Na, K-ATPase and adenyl cyclase), and a decrease in mitochondrial oxidative phosphorylation (Silbergeld et al., 1982). Other evidence suggests that some aspects of lead neurotoxicity may be mediated through its inhibition of heme synthesis by the following mechanisms:

(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-aminobutyric 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 treatment of rats with a combination of phenobarbital and DDEP, to induce depletion of the hepatic free "heme" pool, resulted in inhibition of the hepatic heme-requiring enzyme system, tryptophan pyrrolase, and 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). The conduction velocity of electrically stimulated nerves in the arm or leg provides a readily accessible indication of neurophysiological function in sensory as well as motor nerves. Small reductions in nerve conduction velocities (NCVs) have been observed in some apparently asymptomatic workers with PbB levels as low as 30-50 µg/dl (Seppalainen et al., 1975, 1979, 1983; Araki and Honma, 1976; Melgaard et al., 1976; Bordo et al., 1982; Johnson et al., 1980; Seppalainen and Hernberg, 1980, 1982; Singer et al., 1983; Triebig and Nottbohm, 1983; Rosen et al., 1983). It is difficult to draw conclusions from these observations without further prospective studies and in light of contrasting, negative findings (Spivey et al., 1980; Triebig et al., 1984), as well as a lack of consistency in the nerves examined and in the significance of the results. Neverhtheless, the preponderence of results have been positive, and of the various nerves examined, the most consistently decreased NCVs appear to involve the median motor nerve in the arm. Although lead-induced impairment of nerve conduction may be reversible, at least in part by a reduction in PbB levels through chelation therapy (Feldman et al., 1977; Araki et al., 1980), it is not clear whether such effects reflect mild, fully reversible impacts of lead (Buchtal and Behse, 1981) or are early warning signals of progressively more serious neuropathy in otherwise undiagnosed lead intoxication (Feldman et al., 1977; Seppalainen and Hernberg, 1980).

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 (CNS) 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. Although effects in adults are not the focus in this paper, the lead-induced CNS effects reported in non-overtly lead intoxicated adults are important to note. Disturbances in oculomotor function, reaction time, visual-motor performance, hand dexterity, IQ scores, memory, learning ability, mood, nervousness, and "coping" have been observed in lead workers with PbB levels of 50-80 µg/dl, and in some cases, at time-weighted average levels as low as 27-52 µg/dl (Baloh et al., 1979; Spivey et al., 1980; Arnvig et al., 1980; Grandjean et al., 1978; Haenninen et al., 1978; Hogstedt et al., 1983; Mantere et al., 1982; Baker et al., 1983; Valciukas et al, 1978). 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 from that which may exist for humans; b) significant species differences exist for absorption, retention, and internal compartmentalization of lead; and c) with some exceptions, the measurements of animal neurotoxicity are not comparable to those possible in studies of children (Silbergeld and Goldberg, 1980; Winneke et al., 1982b). Although in vitro or animal results should not be quantitatively applied to lead-induced effects in humans,the continuum of lead neurotoxic effects starting with biochemical changes at the lowest observed dose levels provides an important foundation in assessing the more overt effects reviewed in this section.

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 elements 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; Averill and Needleman, 1980; 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 (See CD, Tables 12-4 and 12-5).

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 = 15 µg/dl) during the first two years of life may have a small impact on early and mental development (Bellinger et al., 1985; Dietrich et al., 1985). 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 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 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 exposures 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 12-4). 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; 1977; 1985; Gittleman and Eskenazi, 1983) and mentally retarded children (Youroukas et al., 1978), while other studies have not (Rummo, 1974; Milar et al., 1981). Because of methodological limitations, conclusions from these studies are also limited.

In an experimental intrevention study designed to avoid some of these problems, 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.

Several methodological problems have been noted in this study as well (Needleman and Bellinger, 1984; Rutter, 1983). 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). A follow-up of the children studied by Needleman et al. (1979) suggests that other measures of classroom performance may show long-term effects of early lead exposure more effectively than IQ measures (Bellinger et al., 1984). Silva et al. (1986) found similar results on 11-year old children. 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; Gillberg et al., 1982; 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) (e.g., Winneke et al., 1977, 1982b; Cory-Slechta and Thompson, 1979; Gross-Selbeck and Gross-Selbeck, 1981; Bushnell and Levin, 1983; Cory-Slechta et al., 1983, 1985; Alfano and Petit, 1985). 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). Another series of studies on monkeys using conditioning tasks demonstrated consistently impaired learning ability, even in some cases where the peak PbB levels reached only 15 µg/dl and steady state levels were only 11 µg/dl (Rice, 1985). 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; Rice and Willes, 1979; Schlipkoter and Winneke, 1980; Rice, 1985; Alfano and Petit, 1985). 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).

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).

Several of the studies for which data are 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 would not be expected today with normally controlled emissions; d) 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); e) The relatively high soil and dust lead levels in relation to concurrent air lead concentration measured near the Bartlesville smelter by Hartwell et al. (1983) was probably due to a drastic reduction of total suspended particulate emissions, from 1600 tons/year to 15 tons/year, just prior to the onset of the study.

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 -- those with high paint lead levels were excluded) 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 soil/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 (1979) and DOE (1983) 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 260 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 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

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	5-30	20-100	5-30	20-100
0.1	20-90	50-300	40-100	40-200
0.2	40-150	80-450	70-200	70-400
0.3	70-250	125-600	100-250	250-600
0.4	100-350	200-700	200-300	300-650
0.5	150-500	350-800	250-400	350-700
0.6	200-650	450-1000	300-500	400-750
0.7	250-800	550-1150	350-600	500-800
0.8	300-950	650-1300	450-700	600-900
1.0	500-1150	750-1450	525-875	800-1150
1.25	600-1250	850-1600	625-1000	1000-1400
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 dusts (both indoors and outdoors) and in the top layers of soil.

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 measured at 0.8 $\mu g/m^3$ by Roels et al., and 337 ppm 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 concentrations. 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 because outdoor soil 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. It is estimated that a young child typically sleeps about 12 hours a day (Pope, 1986c), leaving approximately 12 waking hours in which he or she is capable of ingesting dirt. The time weighted concentration of lead in dust and soil that a child is exposed to is thus computed by: [(outdoor soil/dust lead concentration x time spent outdoors) + (indoor dust lead concentration x time spent indoors)] ÷ 12 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. Lepow et al., (1974) measured a mean of 10 µg of dirt on the hands of 22 young children which would be ingested with each episode of hand to mouth activity. 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 transferred from a child's hands to a typical "sticky sweet", and estimated that a daily intake of 2-20 sweets would lead to a dirt intake of 10-1000 mg. These authors estimated that a child puts its hand into its mouth ten times per day which would result in the ingestion of 100 mg (0.1 g) of dust and soil per day. An average estimate of 100 mg of dirt ingested daily by young children has been used in several documents (Drill et al., 1979; NAS, 1980; CD, Table 7-23) and will be used here as well to represent a probable value for a "typical" child.

It should be noted that this value probably underestimates the dirt ingestion rate for many children in certain circumstances. For example, among young children hospitalized for asymptomatic lead poisoning and exposed to three play environments which differed in their stimulus complexity (e.g., number and type of toys, availability of playmate), significantly more mouthing behavior occurred in the impoverished play setting (Madden et al., 1980). In particular, children with pica who display patterns of repetitive hand-to-mouth activity or deliberately 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 substances. Pica occurs to some degree in a substantial percentage of young children. Data from NHANES II indicate that the percent of children with a history of pica is significantly higher for those 6 months through

3 years old (11.0%) than for those 4 through 5 years old (3.2%) and for children living in households with annual family incomes < $10,000 (11.9%) than for those in households with incomes > $10,000 (6.0%) (Mahaffey and Annest, 1985). Estimates for pica prevalence rates, based on more limited samples, range as high as approximately 10 to 30% in children 1 to 6 years old to 35-50% in those 1 to 3 years old (Millican et al., 1962; Barltrop, 1966). Children exhibiting pica for paint are of major concern because of the high levels of lead in some paints, with older painted surfaces containing lead in concentrations greater than 1 percent (10,000 ppm). [The allowable lead content of paint was set in 1978 by the Consumer Product Safety Commission at 0.06 percent lead (600 ppm)]. Pica for paint is believed to occur in episodes, possibly 2 to 3 times per week (NAS, 1972). It has been estimated that a child can consume somewhat greater than 1 gram within a 24 to 36 hour period, with cases reported of up to 20 grams within the same time period (Sachs, 1975) and that children with pica for paint may consume 1 to 3 grams per week (NAS, 1972). Estimates of daily lead uptake under alternative air lead levels are presented in Table 5-1 only for children without pica. In order to calculate the contribution of lead in paint to the total lead exposure of children with pica, the above range of 1 to 3 grams of paint chips consumed per week (i.e., approximately 140 to 430 mg/day) could be used. As discussed in Section VII, future reductions in airborne lead emissions are not likely to significantly alter pica exposure to lead over the next few years and other regulatory alternatives to protect these children must be considered.

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 (CD, 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.

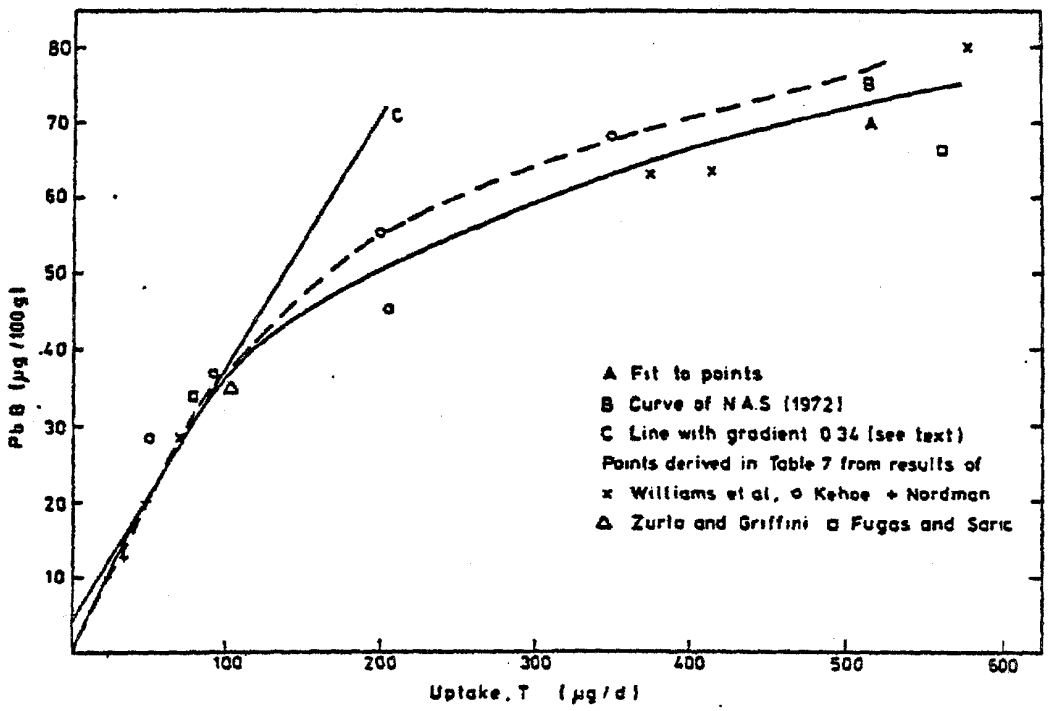

Figure C-1. Relationship between daily lead uptake and blood lead in adult men. From Chamberlain and Heard (1931).

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

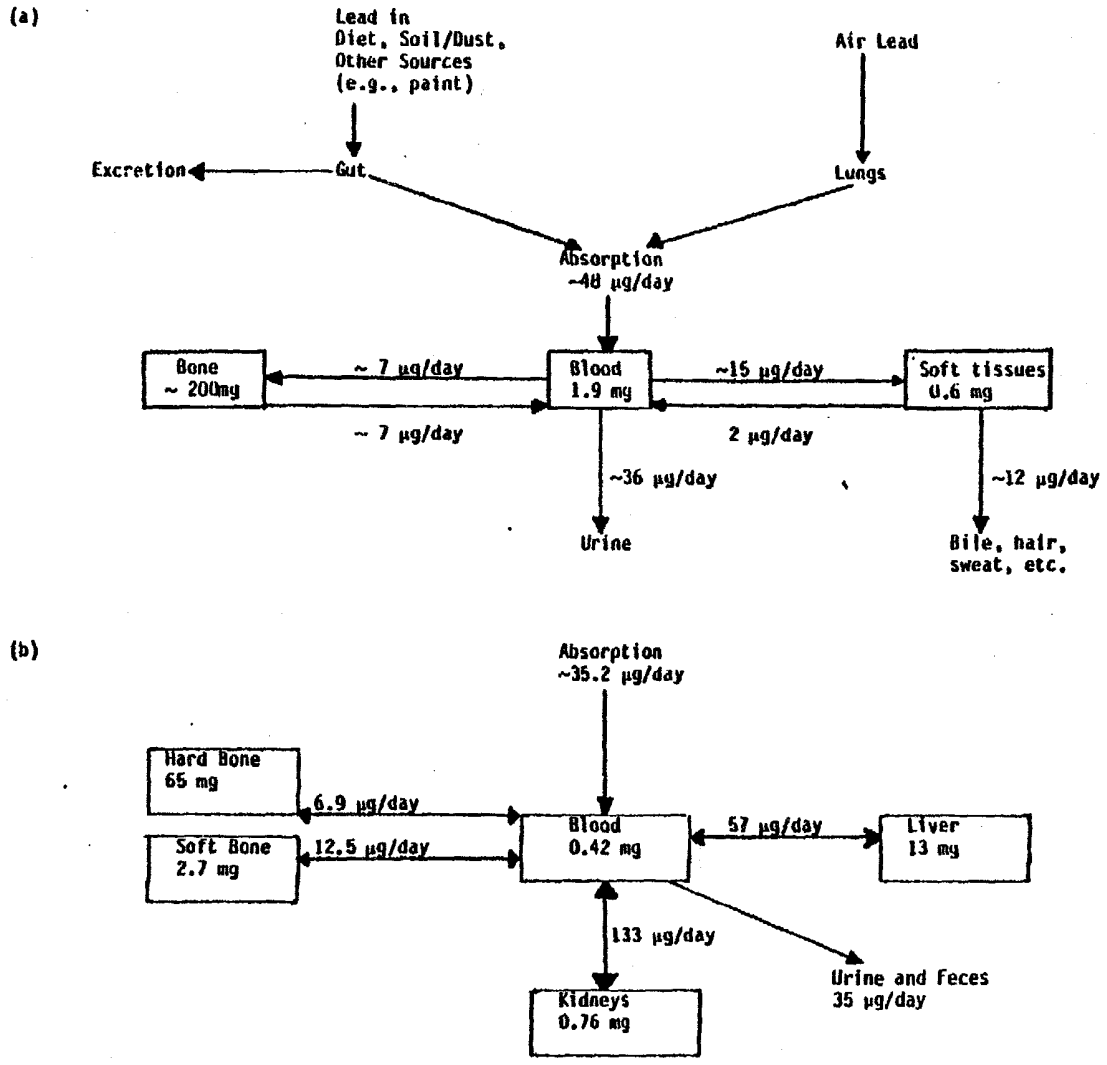

Figure C-2. Schematic models of lead metabolism in adult men described by (a) Rabinowitz et al., 1976 and (b) Bernard, 1977. The amounts of lead in each compartment, exchanging daily between compartments, and excreted daily are shown for steady state conditions of continuous exposure to inhaled and ingested 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 ages, 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) to estimate children's PbB levels 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 (µg/dl) 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 Tables C-3, C-4, and C-5.

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	0.62	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.

remedies specific to lead-based paint, as well as sustained funding, political support from the public and health and housing authorities, and financial incentives for "deleading" and maintaining old housing in good condition by property owners (Farfel, 1985). Research on effective lead hazard abatement measures (in 1981 HUD's prevention research was terminated), including their cost-effectiveness, as well as continued screening programs and large-scale, population-based surveys are needed to support these efforts.

Several studies have shown that in addition to environmental factors, sociodemographic factors are associated with increased lead exposure (Stark et al., 1982; Urban, 1976; Gilsinn, 1972; O'Hara, 1982). These include income, marital status of parents, disturbed mother-child relationships, frequent moves, education of parents, inadequate parental supervision and large family size. Although some or all of these variables may be confounded by lead exposure, it is necessary to advance educational programs on lead toxicity and sources of lead in homes, and sustain social-welfare programs as well as regulating environmental sources of lead.

In addition to abatement of lead paint hazards, further efforts and source-specific control measures are also required for other high intensity exposure situations involving heavily-contaminated soils due to historical accumulations of deposited lead from smelters, roadways, and other sources, as well as homes with unusually high tap water concentrations due to the combination of soft, acidic (corrosive) water and lead plumbing. It is clear that Federal agencies regulating various sources of lead (EPA, FDA, HUD, HHS) need to better integrate their activities and address total lead exposure from multiple sources.

D. Summary of Staff Conclusions and Recommendations on the Primary Standard

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

1) Based on available information, a monthly average appears to be the most appropriate health target;

2) The standard itself could be expressed as either a monthly average or as an appropriately adjusted quarterly average that would assure that the monthly average health target is achieved during periods and in areas of maximum concentration;

3) The standard, either as a monthly or quarterly average should be expressed in a statistical form;

4) Sampling frequency using the high volume sampler could vary depending on the averaging period and form of the standard, and the site type;

5) The use of "low-volume" samplers in lieu of the high-volume sampler as a modification to the Federal Reference Method for lead may be appropriate, but site-specific testing would be needed;

6) 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;

7) 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 and behavioral functions. Conversely, it is felt that the risks of adverse effects are minimal for an individual child at a PbB level below 15 µg/dl. In order to avoid potentially significant risks among young children and to protect as many children as possible who can be protected by a lead NAAQS with an adequate margin of safety, the staff concludes that the maximum acceptable individual PbB level should be chosen from the range between 15 and 20 µg/dl;

8) 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

blood lead/air lead slope approach, and the disaggregate epidemiological approach presented in the criteria document. Conclusions discussed below pertain to estimates derived from applying a geometric standard deviation (GSD) for the child population of 1.42 to calculate blood lead distributions around mean PbB levels predicted by the models. In addition, these calculations pertain to children not excessively exposed to lead in paint or with a high degree of pica:

a) At constant air lead concentrations at and above 1.0 $\mu g/m^3$, 99.5% of young children would not be protected from reaching PbB levels of 20 µg/dl, unless only children living away from lead point sources are considered in the integrated uptake/biokinetic model, or lower bound estimates only are considered in the aggregate model;

b) If 20 µg/dl is chosen as the maximum acceptable PbB for an individual child and assuming a goal of 99.5% protection for the population, the highest air lead concentration that should be permitted under a revised lead NAAQS is 0.75 $\mu g/m^3$, according to the integrated uptake/biokinetic model and the lower to middle estimates of the aggregate model. If only the upper bound estimates of the aggregate model, or the criteria document disaggregate model is considered, an average air lead level between 0.25 and 0.5 $\mu g/m^3$ would be required to protect 99.5% of young children from PbB levels of 20 µg/dl;

c) If 15 µg/dl is chosen as the maximum acceptable PbB for an individual child, an average air lead concentration of 0.5 $\mu g/m^3$ would provide protection for 99.5% of young children according to the integrated uptake/biokinetic model. According to the other models, an average air lead level below 0.5 $\mu g/m^3$ (0.25 $\mu g/m^3$ and possibly lower) would be required to prevent PbB levels above 15 µg/dl, depending on which assumptions are relied upon.

In order to model children with excessive exposures to non-air sources of lead, it would be necessary to account for a high degree of pica (i.e., repeated ingestion of non-food items) and/or to account for the impact of flaking and peeling lead-based paint, commonly found in homes built before 1960, or severely contaminated soils/dusts due to historical accumulations of point source emissions.

Because of the large stock in the U.S. of old, occupied housing containing lead pigment paints which have deteriorated and will in the future continue to deteriorate, it seems likely that exposure to lead in old housing, in combination with poverty, sub-optimal nutrition, and parental stresses and limitations will constitute the major issue in childhood lead toxicity during the coming decades. It is important to recognize that any lead NAAQS would not suffice in reducing health risks posed to children from lead-based paints and further coordinated, preventive measures by appropriate governmental activities to eliminate the hazards associated with lead-based paint (e.g., removal of severely contaminated soil, sealing or repainting surfaces) are needed.

In addition to abatement of lead paint hazards, further efforts and source-specific control measures are also required for other high intensity exposure situations involving heavily-contaminated soils due to historical accumulations of deposited lead from smelters, roadways, and other sources, as well as homes with unusually high tap water concentrations due to the combination of soft, acidic (corrosive) water and lead plumbing. It is clear that Federal agencies regulating various sources of lead (EPA, FDA, HUD, and HHS) need to better integrate their activities and address total lead exposure from multiple sources.

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 its effects; and 3) an evaluation of the quantitative relationships between levels of lead in the natural habitat and biologically available lead. A staff recommendation, which recognizes the major uncertainties in the available data, is also presented that if it is judged that retention of a secondary standard is appropriate consideration should be given to making it equivalent to the primary standard in all respects.

A. 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.

1. 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.

2. 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.

a. Flora

i) 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 the foliar uptake of lead deposited on vegetative surfaces may be of greater importance than previously thought.

ii) 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.

iii) 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).

iv) 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.

b. 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).

i) 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, p. 8-22, 8-23), a broader data base, encompassing various taxonomic groups, is required for environmental impact prediction. Environmental impact prediction of the effect of lead on soil microbes based on the findings of 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

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	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

microbes in terrestrial ecosystem processes (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.

ii) 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:

a) 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

b) the lack of quantitative information concerning the effect of other environmental factors that influence the decomposition rate, e.g., temperature and moisture conditions (Smith, 1981).

c. Fauna

i) Exposure

The principal pathway of exposure for fauna is through dietary intake (CD, p. 8-26). Animals 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).

ii) 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, that may result in 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 whether 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).

3. Long-term Impact of Lead in Terrestrial Ecosystems

The persistence and continued accumulation of anthropogenic sources of lead in the soil reservoir raise concern about the long-term environmental impact of this pollutant in terrestrial ecosystems. With a net increase in soil lead concentration over the long-term, even under relatively low deposition rates, it is anticipated that at some unknown future time concentrations that exceed a soil's capacity to bind lead may be reached. In some geographical areas this binding capacity may already be exceeded.

Model predictions of the long-term accumulation of lead in soil in rural areas suggest that it is unlikely that soil lead concentrations will reach levels of concern in the immediate future in most rural areas (Appendix E). This is indicated by the small rate of increase in soil lead concentration predicted for air lead levels that are representative of rural areas. Model predictions apply to typical rural terrestrial ecosystems with low natural soil lead levels, but do not represent rural areas that are impacted by point source emissions of lead or possibly rural/remote areas that are impacted by unusually high deposition rates, e.g., high elevation forests (Johnson et al., 1982). Although model predictions give some indication of the potential long-term impact of

lead in rural terrestrial ecosystems, predictions are highly uncertain given the many assumptions and limitations of the model. The structure and results of the model, in addition to its many uncertainties, are discussed in Appendix E.

B. Aquatic Ecosystems

1. 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).

2. 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

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 135 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	Hardness 42-48 mg/l as $CaCO_3$, pH 6.8-8	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.

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 has 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).

The U.S. EPA Office of Water Regulations and Standards has published new ambient water quality criteria for lead to protect aquatic life. These criteria concentrations are expressed as a function of water hardness and indicate the need to consider the influence of this chemical water quality parameter on the bioavailability and toxicity of lead. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the 4-day average criteria concentrations of lead for freshwater systems are 1.3, 3.2, and 7.7 µg/l, respectively, and the one-hour average concentrations are 34, 83, and 200 µg/l (50 FR 30791).

C. 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 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. This concern is primarily directed to urban and point source areas that may already be approaching or have exceeded their soil capacity to bind lead. Rural or remote areas that may experience unusually high deposition rates (e.g., high elevation forests) are areas of special concern for the continued accumulation of lead.

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. The limited data base of the ecosystem effects of lead and the lack of a clear quantitative relationship between total soil lead concentration and biologically available lead prevent the identification of an appropriate deposition target. This results from the inability to identify the effects on terrestrial biota that would be associated with incremental additions of lead to total soil lead concentration for different soil types. If the data were available to develop such a target, its implementation would be constrained by the lack of reliable methods for measuring deposition. The model discussed above and in Appendix E that predicts the long-term accumulation of lead in rural areas relies on current methods to measure dry deposition. The questionable reliability of dry deposition measurements and the resulting highly variable calculations of dry deposition velocity are identified as sources of uncertainty in these model predictions.

In summary, the available data clearly indicate that the potential ecosystem effects are of real concern. The data are limited, however, and do not permit any definitive finding as to the level of a secondary standard in either the form of an ambient concentration or as a deposition rate. A key question in determining the need for a separate secondary standard is whether the levels considered for the primary lead NAAQS discussed in Section VII would provide adequate welfare protection. While this question cannot be answered definitively, the levels considered for the primary standard would reduce current ambient lead loading. These reductions, particularly when coupled with reductions achieved by the continued phase-down of lead in gasoline (gasoline combustion through the early 1980's has accounted for 85-90% of total airborne lead emissions), would likely mitigate or delay 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.

Although the available data are quite limited and do not provide a clear basis for specifying the level and form of a secondary standard, they do suggest that the levels considered for the primary standard, coupled with the ambient lead reductions associated with the continued phasedown of lead in gasoline, should minimize the incremental risk of lead-induced ecosystem effects in the short-term. Therefore, until a stronger data base is developed that more accurately assesses the

In summary, the available data clearly indicate that the potential ecosystem effects are of real concern. The data are limited, however, and do not permit any definitive finding as to the level of a secondary standard in either the form of an ambient concentration or as a deposition rate. A key question in determining the need for a separate secondary standard is whether the levels considered for the primary lead NAAQS discussed in Section VII would provide adequate welfare protection. While this question cannot be answered definitively, the levels considered for the primary standard would reduce current ambient lead loading. These reductions, particularly when coupled with reductions achieved by the continued phase-down of lead in gasoline (gasoline combustion through the early 1980's has accounted for 85-90% of total airborne lead emissions), would likely mitigate or delay 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.

Although the available data are quite limited and do not provide a clear basis for specifying the level and form of a secondary standard, they do suggest that the levels considered for the primary standard, coupled with the ambient lead reductions associated with the continued phasedown of lead in gasoline, should minimize the incremental risk of lead-induced ecosystem effects in the short-term. Therefore, until a stronger data base is developed that more accurately assesses the

environmental impact of lead, it is largely a matter of judgment as to whether a separate secondary standard should be retained. If it is judged that retention of the secondary standard is appropriate, the staff recommends that consideration be given to making it 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 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 industrial areas (MMAD = 0.53 μm) 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 inhaled 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 Osborn, 1984) where absorption into the bloodstream appears to be rapid and nearly complete, regardless of the chemical form of the inhaled lead particles (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) are estimated to deposit in the nasopharyngeal 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 $\sim$ 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 nasopharyngeal and tracheobronchial regions, yielding an estimate of 16-32% for total respiratory absorption of inhaled lead particles among

adults in various U.S. atmospheres. For present purposes, this range will be rounded off to 15-30%.

Given that lead particles larger than 1 μm which are prevalent near lead smelters (within 2-5 km) and other stationary sources (Landrigan et al., 1975; Dorn et al., 1976; Davidson and Osborn, 1984) are likely to deposit in the respiratory tract with increasing efficiency as particle size increases up to about 8 μm (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 industrial 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 more efficient (i.e., 20-40%) around point sources compared to the general case representing typical urban, rural, and urban industrial areas (15-30%).

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, lung clearance mechanisms,

and body compartment weight must be applied to make projections from adult data.

Mathematical predictions of particle deposition in tracheobronchial airways of children have been developed based on morphological measurements on airway casts of people aged 11 days to 21 years (Phalen et al., 1985). Airflow rates for different physical activity states and different particle sizes (0.05, 0.5 and 5.0 μm) were used for modeling purposes. The computed particle deposition efficiencies indicate that under most circumstances smaller (younger) people will have greater tracheobronchial deposition efficiencies than larger (older) people. For example, Phalen et al. (1985) predicted that in 2 year old children at light exertion levels (20 L/min) about 50% of 5.0 μm particles deposit in the tracheobronchial region as compared to about 40% in 18 year olds. For 0.5 μm particles, 2 year old children at light activity levels are estimated to have 5% tracheobroncial deposition in contrast to about 2% in 18 year olds.

In general, the age-related differences in tracheobronchial deposition efficiencies estimated by Phalen et al. (1985) are not large except for 5.0 μm particles at light activity levels and it will be assumed that these patterns hold for alveolar and nasopharyngeal deposition as well. Therefore, the previously derived range for total respiratory absorption rates in adults living in typical urban/rural atmospheres (15-30%) will be applied to young children in those areas. Near point sources, there is in general a greater fraction of large particles in the ambient air that appear to deposit with greater efficiency in young children. Based on the model of Phalen et al. for 5.0 μm particles, it is estimated that these larger particles deposit in 2 year old children 25% more efficiently than in adults. Furthermore, it appears that lead particles greater than 1 μm

comprise between 50-70% of the total airborne lead mass near point sources (Landrigan et al., 1975; Dorn et al., 1976). By incorporating these factors, the range of respiratory deposition rates of airborne lead particles estimated for adults living near point sources (20-40%) is adjusted upwards to 35 to 60% for 2 year old children.

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, young children 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. 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 (Báloh, 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

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 airborne particles are more prevalent 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). Phalen et al. (1985) determined average ventilation rates for males and females from birth through age 18 from graphical fits of published tabulated data (Altman and Dittmer, 1971, 1972). For example, a two-year old at "low activity" is estimated to have a minute ventilation rate of 2.75 liters/minute, which corresponds to an average daily rate of approximately 4 m^3/day while a three-year old is estimated to have a daily

rate of 4.3 m^3/day. Other estimates that appear in the literature are 4.7 m^3/day (ICRP, 1975) and 4 to 6 m^3/day (Nutrition Foundation, 1982) for active one-year olds, and 4.7 m^3/day for a three-year old (Nutrition Foundation, 1982). These values combined with those determined by Phalen et al. are used to construct a range for the average daily ventilation rate for a typical 2 year old child of 4 to 5 m^3/day.

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 15 to 30% is calculated for young children living in typical urban/rural areas, while a rate of 35 to 60% 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: Given the wide spatial and temporal distribution of atmospheric lead to different populations via the food pathway, it is difficult to reliably estimate current and future contributions of lead to the diet under alternative air lead levels. Estimates of current (1982-1984) mean dietary lead intake are, however, provided in the criteria document (CD, Table 7-25). Based on FDA data on the lead content of various foods and beverages both before and after processing, packaging, and preparation, and on food consumption

patterns (Beloian and McDowell, 1981; Jelinek, 1982; National Food Processors Association, 1982, Pennington, 1983; Wolnik et al., 1983; U.S. FDA, 1984), the CD estimates that, on the average, 25.1 µg of dietary lead are ingested daily by a 2-year old child through food, water and beverage consumption. The direct atmospheric deposition of lead accounts for 10.3 µg of this daily intake. The remaining 14.8 µg/day is attributed to natural lead (0.7 µg/day), indirect atmospheric lead, i.e., lead previously incorporated into soil (1.7 µg/day), lead solder (11.2 µg/day), and undetermined sources (1.2 µg/day). 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. 7-51).

The 11.2 µg/day of dietary lead intake attributed to lead in solder includes that contained in food, beverages and water. Based on the percentage of lead in water that is solder lead (CD, Table 7-23) and on the average water consumption in a 2 year old (CD, Table 7-22), it is estimated that water distribution systems (solder lead) currently contribute an average of 1.2 µg/day to the typical dietary intake of lead. In order to estimate the future contribution of the water distribution system to dietary lead intake, the impact of a revised lead drinking water standard that is expected to be promulgated in the near future must be projected. The U.S. EPA Office of Drinking Water currently anticipates that this standard will be revised to a level of approximately 20 µg Pb/l, which represents a 60% reduction in the lead content of drinking water relative to the current standard of 50 µg Pb/l (W. Coniglio, personal communication, November 14, 1985). Assuming that there will be a 5 year period before the impact of this standard is observed (W. Coniglio, personal communication, November 14, 1985), it is estimated that the dietary intake of lead from water will be 0.48 µg/day in

1990. This projection assumes that the revised drinking water standard, which applies to a lead concentration at the tap, is attainable, although water treatment will be required in many areas nationwide to achieve the level of the new standard (P. Lassovszky, personal communication, November 14, 1985).

The remaining 10 µg/day of the current dietary intake of lead attributed to solder is associated with food and beverage consumption. Because the U.S. FDA, in conjunction with the National Food Processors Association, is actively pursuing programs to further reduce lead in foods, it is estimated that lead in adult canned foods should eventually decline by 70% from pre-1978 levels as a result of the efforts of the two major U.S. can manufacturers (CD, p. 7-48). With the combined efforts of the leading and smaller can manufacturers, the removal of 90% of solder lead from the diet is expected over the next decade (CD, p. 7-51). Based on this projection and the 50% reduction in the usage of lead soldered cans that has already occurred between 1979-1983 (Jelinek, 1984), it is estimated that the contribution of solder lead to the dietary intake of food lead in a 2 year old child will decline to 3.3 µg/day in 1990.

The remaining source of lead in the diet that requires a projection to account for future trends is direct atmospheric lead. In estimating the direct atmospheric lead contribution to dietary lead intake, it appears reasonable to make several assumptions that do not account for spatial and temporal variations in the contamination of foods by atmospheric sources of lead. 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 the surface deposition of lead and its uptake into foliage and crops is a significant source of animal and human exposure to atmospheric lead throughout the country (CD, Table 7-18).

The average lead contribution to a 2-year old's diet from direct atmospheric deposition is estimated in the criteria document to be 10.3 µg/day and is derived from data on the lead content of foods consumed in the U.S. during 1982-84 (CD, Table 7-25). A portion of the food consumed during this period represents crops that were grown and animals that were raised prior to 1982. The annual average lead concentration in non-urban areas in the late 1970's was as high as 0.2 $\mu g/m^3$ (CD, Table 7A-3). Most crops are grown, and most animals are raised in rural areas where atmospheric lead has been primarily attributed to mobile source emissions of lead. The recent EPA revisions to the gasoline lead phasedown schedule (EPA, 1985b) that lower the allowable lead content from 1.10 grams per gallon of leaded gasoline (gplg) to 0.10 gplg, effective January 1, 1986, are expected to reduce dietary lead consumption in relation to reduced atmospheric lead deposition nationwide. It is necessary, therefore, to estimate the impact of the recent revisions to the lead-in-gasoline phasedown schedule so that future trends in dietary lead consumption can be estimated.

By 1990, the average annual lead concentration due only to mobile source impacts for neighborhood scale monitoring sites is estimated under the revised phasedown program to be approximately 0.02 $\mu g/m^3$ (Battye et al., 1985). Mobile source impacts for remote or rural areas were not projected. Based on the projections for neighborhood scale monitors, it is clear that independent of the level of the lead NAAQS, the average air lead levels in areas away from

point sources (where food is generally grown and raised) will be below current rural air lead levels. Battye (1985d) has made year-specific estimates of the future mobile source contribution to ambient lead concentration in urban areas. Although these estimates were made for urban areas, the same relative reduction in the mobile source contribution is expected in rural areas. Based on this relative reduction, the dietary lead intake due to direct atmospheric lead was estimated to be 0.36 µg/day in 1990. This estimate is rounded off to 0.4 µg/day and represents the direct atmospheric lead contribution to calculate exposures under each of the air lead levels presented in Table 5-1.

The total average dietary lead intake under alternative air lead levels can then be calculated by adding the atmospheric contribution to the estimated lead intake from solder, natural soil lead, indirect atmospheric lead, 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-based painted and brick houses and buildings, and distance from lead 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 are limited in that samples were collected 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 point sources 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.

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)
			"Post-control"[a] (1973-1976) measurements in Omaha neighborhoods:
0.22	80	215	suburban
0.04	91	162	
0.32	591	280	mixed (battery plant in residential neighborhood)
0.46	260	470	commercial (Angle and McIntire, 1979; Angle, 1985)
1.6 - 2.0	1,200	11,000	Hartford (Lepow et al., 1975)
			Distance range (km) from zinc or copper smelters in:
0.13	35	241	(3.5 - 24.0)
0.20	243	409	(1.3 - 3.7) Bartlesville, OK;
0.30	829	386	(0.8 - 4.3)
0.31	821	441	(0.8 - 1.5)
0.14	75	235	(10.0 - 26.0)
0.18	115	164	(3.5 - 21.0) Anaconda, MT;
0.09	294	210	(2.0 - 11.0)
0.26	424	398	(2.0 - 3.5)
0.09	58	75	(3.4 - 68.0)
0.11	65	60	(1.0 - 6.4) Ajo, AZ;
0.19	77	65	(0.5 - 2.3)
0.26	95	116	(0.5 - 1.3)
0.36	532	263	(11.0 - 26.0)
0.56	117	201	(5.4 - 14.5) Palmerton, PA
0.13	326	198	(3.3 - 9.9)
0.28	331	438	(0.3 - 2.8)
			(Hartwell et al., 1983)
0.30	114	-	"Post-control"[a] measurements (1976)
0.45	112	-	in rural area, Brussels, and near
0.8	466	-	lead smelter, Belgium (Roels et
3.67	2,560	-	al., 1980)

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

Average Air Lead ($\mu g/m^3$)	Average Outdoor Soil/ Dust Lead ($\mu g/g$)	Average Indoor Dust Lead ($\mu g/g$)	Location/Reference
0.41	690 (street dust) 240 (soil)	1,239	Near Arnheim secondary lead smelter, Holland (Brunkreef et al., 1981; Diemel et al., 1981)
0.82	924	713	Near Toronto secondary lead smelters and in city (Roberts et al., 1974)
3.01	2,416	1,550	
1.3	427	1,479	Near El Paso primary lead smelter "Post-control"[a]
2.7[b]	948[c]	8,623[c]	"Pre-control" (Morse et al., 1979)
0.5	337	1,800	Near Silver Valley, Idaho, primary lead smelter; Pre-control[a] (Yankel et al., 1977; Idaho Dept. Health and Welfare, 1977)
0.5	700	3,900	
0.7	2,300	3,400	
3.0	1,400	3,300	
6.6	1,250	2,400	
14.2	3,300	10,300	
16.8	7,470	11,700	

[a]"Post-control" refers to the period of time following the application or increase in emission controls at the lead point source(s) involved in the particular study. Conversely, "pre-control" refers to the period of time before the application or increase in emission controls.

[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

level under alternative lead NAAQS. For comparative purposes, the calculations of blood lead distributions under various air lead levels using the three models presented below will use the GSD of 1.42 as well as values of 1.34 and 1.39 that are derived for homogeneous sub-populations of children.

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). For example, correcting the GSDs for homogeneous subpopulations of children (1.34 - 1.39) 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 the distribution of children's PbB levels around a 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.

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 if different protection "goals" are chosen, e.g., 99.9 or 99.0%. Given a population mean PbB level the relationship between different percentiles in the corresponding blood lead distribution is illustrated in Figure 7-6. The population mean PbB levels used in this example are the lower bound estimates from the integrated lead uptake/biokinetic model for children living near lead point sources under specified constant air lead levels. The GSD used to calculate the different percentiles is 1.42. It is clear that for a given population mean PbB as one moves higher in the lognormal blood lead distribution, a progressively greater change in predicted blood lead levels is observed. For example, at an average air lead of 0.75 µg/m^3, the integrated uptake/biokinetic model predicts a population mean of approximately 8.2 µg/dl. Given that population mean and assuming a GSD of 1.42, 99.0% of the population would be below 18.5 µg/dl, 99.5% would be below 20.2 µg/dl, and 99.9% would be below 24.2 µg/dl. So, if a protection target of 99.9% is chosen, and given a maximum acceptable PbB level of 20 µg/dl, inadequate protection would be provided at this air lead level. If a protection target of 99.0 or 99.5% is chosen, then acceptable protection would be assumed. It is important to recognize how sensitive the decision on a lead NAAQS is to the choice of an appropriate protection target.

Table 7-9 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 (1.34 - 1.39) and for the entire mix of children excluding those with PbB levels above 40 µg/dl (1.42). (Mean PbB levels necessary

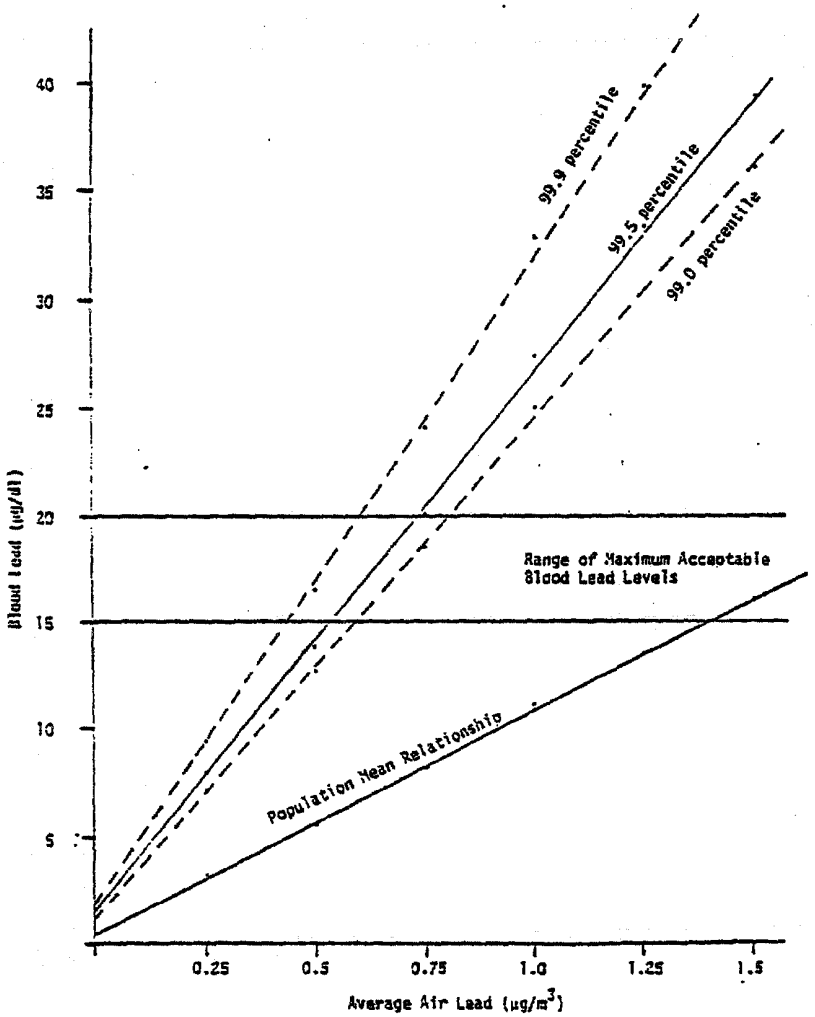

Figure 7-6 . Distribution of children's blood lead levels as a function of population mean blood lead level under different air lead concentrations. Illustrative population mean blood lead levels are lower bound estimates of integrated uptake/biokinetic model for 2-year old children living near a lead point source. Percentiles in blood lead distribution for each population mean blood lead are calculated assuming lognormality and a GSD of 1.42. (Lines drawn through the datapoints were fitted by eye and not through regression techniques.) Range of maximum acceptable blood lead levels was derived by staff based on health effects information in criteria document (see Section 7.C.1).

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 7-9. 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, 1.42)

	Maximum Acceptable Individual Blood Lead Level (µg/dl)			
GSD	25	20	15	10
1.42	10.1	8.1	6.1	4.1
1.39	10.7	8.6	6.4	4.3
1.34	11.8	9.4	7.1	4.7

a) Integrated Lead Uptake/Biokinetic Model

Table 7-10 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).

Table 7-10. AVERAGE BLOOD LEAD LEVELS FOR CHILDREN UNDER CONSTANT 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	5.9 - 11.0	2.4 - 4.4
	Pt. Source	7.9 - 19.6	3.2 - 7.9
0.50	General	10.4 - 17.2	4.2 - 7.0
	Pt. Source	14.1 - 26.8	5.6 - 10.8
0.75	General	14.9 - 25.6	6.0 - 10.3
	Pt. Source	20.3 - 34.4	8.2 - 13.9
1.0	General	19.1 - 34.4	7.7 - 13.9
	Pt. Source	27.6 - 42.9	11.1 - 17.4
1.25	General	22.2 - 38.1	9.0 - 15.4
	Pt. Source	33.5 - 49.7	13.5 - 20.1
1.5	General	25.9 - 43.0	10.4 - 17.4
	Pt. Source	39.4 - 57.5	16.0 - 23.2

[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 bounds 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.

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 these ranges in particular may represent "worst case" population mean uptake and PbB estimates for each air lead concentration. 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 children in different locations within the population. 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 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, assuming lognormality with a geometric mean and GSD, it is possible to calculate for any mean PbB, the individual PbB exceeded by a specified percentage of the population. This calculation is illustrated below for the other two modeling approaches and the results are later summarized in Table 7-14.

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 (i.e., disaggregate) 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. 11-105).

To account 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 measured lead concentrations in dust from a wide range of locations and conditions, the integrated uptake model discussed in the previous section implicitly includes average contributions to total exposure from lead-based paint, but excludes from the analysis high level exposures associated with deteriorated lead-based painted housing. In addition, based on recent FDA data the criteria document directly provides estimates of the dietary contribution of non-air sources of lead 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 in the number 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 13.9 µg/dl (Annest et al., 1982). After three adjustments are made to the NHANES II data, a true "non-air" PbB of 6.6 µg/dl is estimated for children that are living in the U.S. by the time a revised lead NAAQS can be expected to be implemented (i.e., 1990). 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 mobile sources and more localized impacts from point sources 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 approximately 11.4% of the blood lead in adult men living in the countryside within 25 km of Turin 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 estimated average of 11.4% for rural Turin men is

multiplied by two, yielding an estimate of 23% for PbB related to gasoline lead and industrial sources in rural U.S. children. Thus, the remaining 77% 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 has decreased from 90% in 1979 to 50% in 1983 and as the switchover continues, lead in canned foods for children should decrease by as much as 70% of pre-1978 levels (CD, p. 7-48; Jelinek, 1984). Since lead from solder and other metals is estimated to account for approximately 24% of a typical child's background lead exposure (CD, Table 7-25), it is estimated that the average child's total PbB levels will decline by (0.24 x 0.7) or 17%.

3) The staff estimates that ongoing efforts to reduce occupational exposures (and thereby reduce children's indirect exposures) and to prevent childhood lead poisoning, and the gradual reduction of lead exposure to lead-based paint in old homes will have resulted in a 25% reduction in the average PbB level in U.S. children from the 1976-1980 time period by 1990.

Based on these three considerations, the NHANES II mean value of 13.9 µg/dl for rural children sampled between 1976 and 1980 is adjusted in the following calculation:

13.9 µg/dl x (0.77) x (0.83) x (0.75) = 6.6 µg/dl

This estimate represents the mean PbB levels that would be expected in 1990 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 distribution systems, those living in deteriorated or recently resurfaced lead-painted housing who inadvertently ingest paint dust through normal mouthing activities, children of parents who work in lead-related industries and are exposed to lead dust that is subsequently carried home on clothing, or children living near lead smelters and other point sources where historical accumulations of lead 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 accumulations of 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 (between 15-20 µg/dl) to protect against effects discussed in Sections VII.C.1 and Appendix D with an adequate margin of safety;

2) calculating a target geometric mean PbB level for U.S. children based on placing a specified percentage below the maximum acceptable PbB: for purposes of the present discussion the goal is assumed to be 99.5% (Table 7-9);

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 $\mu g/m^3$) discussed in Section V.B.

Tables 7-11, a-c present the alternative air lead levels derived from these calculations assuming a goal of protecting 99.5% of the population and GSDs of 1.42, 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

Table 7-11. 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.

a) GSD for Population Assumed to be 1.42

	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	-	-	0.4	-	0.9	0.4	1.4	0.9
5	-	-	0.3	-	0.7	0.3	1.1	0.7
6	-	-	0.3	-	0.6	0.3	1.0	0.6

b) 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

c) 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

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 1.42, a non-air blood contribution of 4.4 μg/dl, and a blood lead/air lead slope of 4, an air lead level of 0.9 $\mu g/m^3$ would be adequate. At this time, the staff does not attempt to judge which of the values in the ranges presented are most valid for 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 given a maximum acceptable PbB no higher than 20 μg/dl for an individual child, all of the air lead alternatives predicted as necessary for adequate protection (99.5%) by the aggregate epidemiological model are below the current standard level of 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 fully protect 99.5% of 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 7-14 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 7-12 (CD, Table 13-6) presents estimates for the direct and indirect contributions of air lead to children's (intended to represent 2-year olds) 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/biokinetic model estimated the range of contributions that both atmospheric and non-atmospheric sources of 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 epidemiological studies relating blood lead and lead in the environment.

It is of interest to note that after adjusting the estimated PbB in Table 7-12 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 7-12 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 blood lead distribution

TABLE 7-12. 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.

characteristics of the population, the individual PbB at a specified standard deviation. Table 7-9 for example, indicates that given a geometric mean PbB level between 8.1 and 9.4 µg/dl, 99.5% of the population of individual children 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 7-12), would prevent 99.5% of the population from exceeding a PbB of either 18.1, 19.9 or 21.0 µg/dl (for GSD's of 1.34, 1.39, and 1.42, respectively). Table 7-13 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 7-12. These results are presented in Table 7-14 for comparison with those of the other two modeling approaches.

Table 7-13. 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 (µg/dl)	Maximum Individual PbB (µg/dl)		
		GSD		
		1.34	1.39	1.42
0	4.42	9.4	10.3	10.9
0.25	6.49	13.8	15.1	16.0
0.50	8.51	18.1	19.9	21.0
0.75	10.62	22.5	24.8	26.2
1.0	12.69	26.9	29.6	31.3
1.25	14.76	31.3	34.4	36.4
1.50	16.82	35.7	39.2	41.5

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

Table 7-14a presents the various estimates of PbB levels for children (both means and individual maxima for 99.5% of the population) under different

Table 7-14a. SUMMARY OF ESTIMATED BLOOD LEAD LEVELS UNDER DIFFERENT AIR LEAD LEVELS USING THREE MODELLING APPROACHES[a]

Model		Air Lead Level (μg/m³; monthly or quarterly average) 0.25	0.5	0.75*	1.0	1.25	1.5
Integrated Uptake/ Biokinetic[b]	Urban/ Rural:	5.9 (2.4)	10.4 (4.2)	14.8 (6.0)	19.0 (7.7)	22.2 (9.0)	25.7 (10.4)
	Point Source:	7.9 (3.2)	13.8 (5.6)	20.2 (8.2)	27.4 (11.1)	33.3 (13.5)	39.5 (16.0)
Aggregate Model[c]		13.3-20.0 (5.4-8.1)	15.8-23.7 (6.4-9.6)	18.3-27.4 (7.4-11.1)	20.7-31.1 (8.4-12.6)	23.2-34.8 (9.4-14.1)	25.7-38.5 (10.4-15.6)
Criteria Document Disaggregate Model[d]		16.0 (6.49)	21.0 (8.51)	26.2 (10.62)	31.3 (12.69)	36.4 (14.76)	41.5 (16.82)

[a]PbB levels are given in μg/dl and represent the estimated levels (using GSD of 1.42) that 99.5% of children will not exceed for a given air lead level. Estimated population mean PbB levels are given in parentheses. Calculations do not include those children with a high degree of pica or excessive exposures to paint lead and/or severely contaminated soil and dusts.

[b]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 GSD of 1.42 used to convert population mean PbB levels in parentheses 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 μg/m³); non-air PbB contribution (4.4-6.6 μg/dl); GSD of 1.42 used to convert population mean PbB levels in parentheses into 99.5% maximum individual levels.

[d]PbB levels (presented in CD to represent 2 year old children) reflect GSD of 1.42 used to convert population mean PbB levels in parentheses into 99.5% maximum individual levels.

average (monthly or quarterly) air lead levels based on the three modeling approaches discussed in this section and using a population GSD value of 1.42. As discussed previously, the staff concludes that a GSD of 1.42 derived from NHANES II data is the most appropriate value to use in predicting how the distribution of blood lead levels among U.S. children would be affected by incremental changes in air lead levels. For comparative purposes, Table 7-14b presents the same estimates using the three modeling approaches assuming that the GSD is between 1.34 and 1.39, the range calculated from NHANES II for homogeneous subpopulations of U.S. children.

It must be emphasized that for present purposes, each of the air lead levels are considered constant. As discussed in the criteria document (Chapter 6) and in Section IV, airborne lead concentrations are highest near sources of lead emissions and decrease rapidly by dispersion or deposition. As a result, sharp downward gradients in air lead levels are seen with increased distances from the immediate vicinities of highways and stationary lead sources (Roberts et al., 1974; EPA, 1984b). In reality, in an area that is in attainment with a standard, air lead levels at some points close to the source or directly downwind may be at the standard level, but the remaining locations will have concentrations below the standard. Consequently, assuming constant air lead quality at the level of a specified lead NAAQS in all locations would tend to over-predict the impacts expected for a wide area. Therefore these results from the models should be interpreted as conservative in the context of projections for large populations of children in point source (and non-point source) "areas". Analyses will be presented in a separate report to better represent actual exposures surrounding lead point sources in the future under alternative lead NAAQS.

It should also be noted that the three exposure modeling approaches presented in Section V all employ data on indoor and outdoor dust and soil

Table 7-14b. 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:	5.1-5.6 (2.4)	8.9-9.8 (4.2)	12.8-14.0 (6.0)	16.4-18.0 (7.7)	19.1-21.0 (9.0)	22.1-24.3 (10.4)
	Point Source:	6.8-7.5 (3.2)	11.9-13.1 (5.6)	17.4-19.2 (8.2)	23.6-25.9 (11.1)	28.7-31.5 (13.5)	34.0-37.3 (16.0)
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 (GSD values between 1.34 - 1.39)) that 99.5% of children will not exceed for a given air lead level. Estimated population mean PbB levels are given in parentheses. Calculations do not include those children with a high degree of pica or excessive exposures to paint lead and/or severely contaminated soil and dusts.

[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 in parentheses 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 values (1.34 - 1.39) used to convert population mean PbB levels in parentheses into 99.5% maximum individual levels.

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

lead concentrations measured in various locations where children were exposed. As best that can be determined from the studies, these data do not include measurements from in and around homes where peeling paint, holes in the walls, or other unsound conditions were reported. [Those data from homes with identified lead paint hazards are excluded from analysis; see Appendix B.] To the extent that the studies appeared to have sampled populations and dwellings representative of the study areas, a heterogeneous mix of homes are likely included and it is reasonable to assume that the data do include older homes with lead-based paint (but no overt hazards) and therefore may be suitable to represent average or "typical" lead exposures excluding those due to excessively high paint lead levels. In addition, where applicable, available information was used on the average rate of dirt ingestion through inadvertent hand-to-mouth activity in children. No attempt is made here to distinguish exposures to lead in children with a high degree of pica (i.e., abnormal tendency to repeatedly ingest non-food items) or who are excessively exposed to lead in paint from deteriorating housing conditions. Such children cannot be effectively protected from the hazards of lead in their environment by a lead NAAQS. Further discussion on this issue is provided at the end of this section.

The ranges of PbB estimates under each air lead level reflect the differences among the available modeling approaches. For each air lead level and each GSD, the protection predicted for young children not excessively exposed to non-air sources of lead (e.g., paint lead) by the three models can be compared. For example, based on the criteria document's disaggregate model, at an average air lead level of 1.5 $\mu g/m^3$ and a GSD of 1.42, 99.5% of exposed children (2 year olds) would have PbB levels below 41.5 µg/dl. The integrated uptake/biokinetic model predicts that the

corresponding 99.5% cutoff would be 39.5 µg/dl among 2-year old children living near lead point source and 25.7 µg/dl among those in generalized urban/rural (i.e., non-point source) areas. (As discussed previously, all PbB estimates presented in this section for the integrated uptake/biokinetic model are those from the lower end of the calculated range since the assumption of constant air lead levels used in this model would tend to over-predict exposures.) The range of PbB levels calculated using the aggregate model at 1.5 µg/m^3 encompasses that predicted by the other two models at this air lead concentration. Relatively comparable results are also found among the three models at air lead levels of 1.0 and 1.25 µg/m^3. It is clear that each model estimates that, given the range of PbB levels of concern (15-20 µg/dl), 99.5% of young children would not be adequately protected at an air lead level above 1.0 µg/m^3. In fact, given a maximum acceptable PbB level for an individual child of 20 µg/dl, and a GSD of 1.42, the models predict that 99.5% of children would not be adequately protected at an average air lead level of 1.0 µg/m^3, unless the least conservative parameter values of the aggregate model are accepted (i.e., blood/air lead slope (β) of 4, non-air background PbB of 4.4 µg/dl), or only children living away from lead point sources in the uptake/biokinetic model are considered.

At 0.75 µg/m^3, however, 99.5% of 2-year old children not excessively exposed to paint lead would have PbB levels below 20.2 µg/dl according to the integrated uptake/biokinetic model (including point source areas) as well as the aggregate model, using low and mid-range parameter values [β of 4 or 5, non-air background PbB of 4.4; a β of 5 and non-air PbB of 4.4 at an air lead level of 0.75 µg/m^3 yields a mean PbB of 8.2 µg/dl, identical to that predicted by the integrated uptake model for point source areas and which would be associated with a 99.5 percentile PbB of 20.2 µg/dl.] Given that

20 µg/dl is the upper bound for a maximum acceptable PbB level for an individual child, the staff recommends based on this analysis that the upper bound of the range of air lead levels that should be permitted under a revised lead NAAQS should be no higher than 0.75 µg/m^3. It must be noted that even at this air lead level, the criteria document's disaggregate model and the upper bound parameter values of the aggregate model do not predict adequate protection (99.5%) against individual blood lead levels of 20 µg/dl.

At the lower air lead levels analyzed (0.25 and 0.5 µg/m^3), the integrated uptake/biokinetic model predicts greater protection (i.e., lower PbB levels) than the other two models, especially at 0.25 µg/m^3. This divergence may be related to the wider array of data sources employed in the integrated model. Specifically, the daily lead uptake estimates which determine the PbB estimates in the integrated uptake/biokinetic model are calculated at each air lead level in part from dust and soil lead concentrations that were measured concurrently with air lead, even at low levels, at various locations. The epidemiological studies that were used in the aggregate and disaggregate models to derive relationships between air lead and blood lead and soil/dust lead and blood lead, on the other hand, were generally conducted during times and in areas where atmospheric air lead levels were relatively high compared to levels that would be predicted under a 0.25 or 0.5 µg/m^3 lead NAAQS. As a result, relationships from these epidemiological models to predict PbB levels under low air lead levels are for the most part, extrapolations from higher pollution conditions. The dust and soil lead concentrations estimated at low air lead levels and thus the PbB levels predicted in the integrated uptake/biokinetic model are more directly derived from actual measurements closer to the scenario modeled and may therefore be more reliable than the PbB levels estimated by the aggregate or disaggregate models at these lower air lead levels.

At 0.5 $\mu g/m^3$ and with a GSD of 1.42, the integrated uptake/biokinetic model estimates that 99.5% of 2-year old children living near point sources and not excessively exposed to paint lead would have PbB levels below 15 µg/dl, which is the lower bound PbB level of concern. In contrast, the other two models predict that a smaller fraction of children would be below 15 µg/dl at 0.5 $\mu g/m^3$, but that 99.5% could be expected to have PbB levels below approximately 20 µg/dl, the upper bound PbB level of concern, under certain assumptions. For example, calculations using the aggregate model at 0.5 $\mu g/m^3$ and a β of 5 and non-air background PbB of 4.4 yields a mean PbB of 6.9 µg/dl, which corresponds to a 99.5 percentile of 17.0 µg/dl given a GSD of 1.42. The disaggregate model estimates that at 0.5 $\mu g/m^3$, 99.5% of 2-year old children would have PbB levels below 21 µg/dl, given a GSD of 1.42. Only at air lead levels below 0.5 $\mu g/m^3$ (e.g., 0.25 $\mu g/m^3$) do all three models predict adequate protection (99.5%) from 20 µg/dl regardless of the assumptions employed. Even at 0.25 $\mu g/m^3$, however, inadequate protection from PbB levels of 15 µg/dl among young children is predicted by the middle to upper bound estimates in the aggregate model and by the disaggregate model, given a GSD of 1.42. In fact, given the mean non-air background PbB estimate used as an upper bound in the aggregate model (6.6 µg/dl), no air lead level considered would be calculated as providing adequate protection from PbB levels of 15 µg/dl among 99.5% of the population if the upper bound of the aggregate model is relied upon.

e) Staff Conclusions

With regard to Table 7-14a and 7-14b, the following conclusions can be made, all of which pertain to children not excessively exposed to lead in paint or with a high degree of pica:

1. At air lead concentrations at and above 1.0 $\mu g/m^3$, 99.5% of young children would not be protected from reaching PbB levels of 20 µg/dl,

unless only children living away from lead point sources are considered in the integrated uptake/biokinetic model, or lower bound estimates only are considered in the aggregate model.

2. If 20 µg/dl is chosen as the maximum acceptable PbB for an individual child and 99.5% chosen as the protection target for the population, the highest air lead concentration that should be permitted under a revised lead NAAQS is 0.75 $\mu g/m^3$, according to the integrated uptake/biokinetic model and the lower to middle estimates of the aggregate model. If only the upper bound estimates of the aggregate model, or the criteria document disaggregate model is considered, an average air lead level between 0.25 and 0.5 $\mu g/m^3$ would be required to protect 99.5% of young children from PbB levels of 20 µg/dl.

3. If 15 µg/dl is chosen as the maximum acceptable PbB for an individual child, an average air lead concentration of 0.5 $\mu g/m^3$ would provide protection for 99.5% of young children according to the integrated uptake/biokinetic model. According to the other models, an average air lead level below 0.5 $\mu g/m^3$ (0.25 $\mu g/m^3$ and possibly lower) would be required to prevent PbB levels above 15 µg/dl, depending on which assumptions are relied upon.

4. The above conclusions pertain to estimates derived from applying a GSD of 1.42 to calculate blood lead distributions around mean PbB levels predicted by the models. The staff concluded previously that this GSD appears to be the most appropriate GSD in determining a lead NAAQS that would protect the entire mix of U.S. children. If it is determined, however, that a GSD in the range of 1.34 to 1.39 is more appropriate, the results presented in Table 7-14b could be used to compare the relative protection provided under different air lead levels according to the three exposure models.

5. The above calculations all were presented in the context of keeping a constant fraction (99.5%) of the sensitive population below

some critical PbB level. By estimating different parts of the tail end of the PbB distribution that corresponds to a given mean PbB, it is possible to predict the impacts of different air lead levels if different protection "goals" (e.g., 99.0 or 99.9%) are chosen. For example, given a mean PbB of 8.2 µg/dl (predicted by the integrated uptake/biokinetic model for children living near a lead point source under an average air lead level of 0.75 $\mu g/m^3$) and a GSD of 1.42, the 99.9 percentile would be 24.2 µg/dl, compared to the 99.5 percentile of 20.2 µg/dl. The 99.0 percentile given a mean PbB of 8.2 µg/dl is 18.5 µg/dl. It is clear that the percentage of children in the tail end of the PbB distribution is sensitive to small changes in the mean, and conversely, if a different protection goal besides 99.5% is chosen, a significantly different air lead level would be required to achieve that target.

6. Finally, it must be emphasized that the potential health risks posed to children with very high levels of exposure to lead contaminated dusts, soil, and paint are not accounted for in these analyses. Average blood lead estimates are calculated for the population of "typical" children and subsequently, blood lead levels of individuals are presented who are in the upper end of the "normal" distribution. In order to model children with excessive exposures to non-air sources of lead, it would be necessary, for example, to: a) assume a higher daily ingestion rate of dirt than 100 mg so as to account for a high degree of pica (i.e., repeated ingestion of non-food items); and/or b) assume a significantly higher concentration of lead in indoor dust and outdoor soil and dust in order to account for the impact of flaking and peeling lead-based paint commonly found in homes built before 1960, or severely contaminated soils/dusts due to historical accumulations of point source emissions.

Because of the large stock in the U.S. of old, occupied housing containing lead pigment paints which have deteriorated and will in the future continue to deteriorate, it seems likely that exposure to lead in old housing, in combination with poverty, sub-optimal nutrition, and parental stresses and limitations will constitute the major issue in childhood lead toxicity during the coming decades (Chisholm 1984; Mahaffey, 1980). It is important to recognize that any lead NAAQS would not suffice in reducing health risks posed to children from lead-based paints and further coordinated, preventive measures by appropriate governmental activities to eliminate the hazards associated with lead-based paint (e.g., removal of severely contaminated soil, sealing or repainting surfaces) are needed.

Regulatory action directed at the large reservoir of existing lead in dust and paint in and about the older homes of urban children has had only limited impact because it pertains only to federally-assisted housing and the dwellings of children identified as lead-poisoned (Farfel, 1985; see Section IV.F). Together, these categories of housing constitute a small proportion of all housing. Only a few cities and states have enacted legislation requiring prophylatic removal of lead-based paint from dwellings, and the few abatement programs have had little impact due to a lack of commitment and capability for inspections and enforcement (Farfel, 1985). Although screening programs have been generally effective in the management of affected children at highest risk for symptomatic lead poisoning (CDC, 1985), primary rather than secondary preventive measures are required to address the vast majority of affected children with undue lead absorption who are at moderate risk.

The elimination of lead hazards from all housing (not just the houses of identified, affected children) will require strong housing codes and legal

In summary, the staff's assessment of the available information on the averaging period, form, and sampling frequency suggests the following:

1) Based on available information, a monthly average appears to be the most appropriate health target;

2) The standard itself could be expressed as either a monthly average or as an appropriately adjusted quarterly average that would assure the monthly average health target is achieved during periods and in areas of maximum concentration;

3) The standard, either as a monthly or quarterly average should be expressed in a statistical form. Of those examined, the expected highest 3 months (quarters) approach appears most appropriate;

4) Sampling frequency using the high volume sampler could vary depending on the averaging period and form of the standard, and the site type, from one-in-three days to everyday sampling (assuming a precision of $\pm$ 10%); and

5) The use of "low-volume" samplers in lieu of the high-volume sampler as a modification to the Federal Reference Method for lead may be appropriate, but site-specific testing would be needed.

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 7-5 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 individuals may

Table 7-5. 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.

not experience the stated effect until distinctly higher PbB levels are reached (CD, p. 13-32), or conversely may 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 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, which represents an extreme manifestation of reduced hemoglobin synthesis and 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 7-6. 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

Table 7-6. 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., 197 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	0.05-2.0% lead in diet	Reyners et al., 1979; Windebank et al., 1980; Stephens and Gerber, 1981
Delayed synaptogenesis and neuronal development in young, rat brain	0.1 - 2.0% 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; Bull et al., 1983
Delayed development of exploratory and locomotor activity; persistent learning and behavior deficits in animals exposed in utero or since birth	>0.001% lead in diet	Brown,1975; Overmann,1977;Overmann et a 1981; Hastings et al., 1979; Bull et al 1979,1983; McCauley et al., 1979, 1982; Bushnell and Bowman,1979; Rice and Hill 1979;Jason and Kellogg,1981; Petit et a 1983; Bushnell & Bowman,1983;Cory-Slech et al.,1983,1985; Rice,1984,1985
Possible small deficits in early mental development in infants	mean <15 μg/dl PbB	Dietrich et al., 1985; Bellinger et al., 1985
Electrophysiological		
Altered electrical activity of isolated neurons (in vitro)	>1 μM lead solution ≥0.5% 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	0.1% lead in diet	Bushnell et al., 1977; Fox et al., 1977 1979, 1982; Winneke, 1980; Cooper et al 1980; Impelman et al., 1982
Subtle, alterations of brain electrical activity (EEG patterns), auditory function in young children; inconsistent findings on slow-wave potential, visual and auditory evoked potential	No apparent threshold down to 25 μg/dl PbB and possibly below	Otto et al.,1981,1982,1985;Otto, 1985; Robinson et al., 1985; Benignus et al., 1981; Burchfiel et al., 1980; Winneke et al., 1984
Depressed conduction velocities in sensory and motor nerves of adults and children	>30-50 μg/dl PbB	Seppalainen et al., 1975,1979,1983; 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.,198 Feldman et al., 1977; Rosen et al., 198
Conflicting results at similar exposure levels		Spivey et al., 1980; Triebig et al., 19

Table 7-6. 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 neuropsychiatric disorders (hyperactivity, mental retardation) in children	Effect level not adequately defined	Baloh et al.,1975; Gittleman & Eskenazi, 1983; David et al.,1977, 1983, 1985; Beattie et al., 1975; Moore et al., 1980; Youroukos et al., 1978
Attention (reaction time) deficits and distractability in young children	>30-50 µg/dl PbB and possibly as low as 15-30 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		
1-4 point deficits in IQ scores on verbal performance, visual-motor perception, short-term memory, general intelligence among young children	>30-50 µg/dl PbB; [possibly below 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; Schroeder et al., 1985 [Harvey et al., 1983, 1984; Winneke et al., 1983; Schroeder and Hawk, 1986]
1-2 point, non-statistically significant IQ differences due to lead at lower exposure levels	15-30 µg/dl PbB	Smith et al., 1983; Harvey et al., 1983, 1984; Yule et al., 1983; Yule and Landsdown 1983, Winneke et al., 1984
Overt Toxicity		
Peripheral nerve damage among chronically exposed adults and children	>40 µg/dl	Lilis et al., 1977; Spivey et al., 1979; Haenninen et al., 1979; Zimmerman-Iansella 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 Bradley and Baumgartner, 1958; Cumings, 1959; Rummo et al., 1979

estimates of PbB levels at which such effects occur in humans, cannot be made, 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). 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 have proved to be difficult, however, and have 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.

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).

Figure D-2 in Appendix D illustrates how an apparently small shift (4 points) in IQ in the mean of a normal distribution may result in important differences in the tails of the distribution.

A recent study and follow-up of U.S. children from families of low socioeconomic status appear to confirm previous conclusions that PbB levels above 30 µg/dl may be associated with IQ decrements (Schroeder et al., 1985). An initial assessment at 1-6 years of age showed a significant effect of blood lead in the range 6-59 µg/dl on IQ after controlling for social covariates, such as SES, home environment, and maternal IQ. Five years later, when all PbB levels dropped below 30 µg/dl, lead effects on IQ were no longer significant. Furthermore, the correlation between maternal and child IQ, which had been suppressed initially in children with PbB levels above 30 µg/dl, returned to expected levels when decreases in PbB levels occurred, while concomitant variables remained stable over the 5-year period.

In European 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). The criteria document concluded from these studies that "the possibility of small neuropsychologic deficits being associated with lead exposure in apparently asymptomatic children at the exposure levels studied (i.e., 15-30 µg/dl) cannot be completely ruled out, given the overall pattern of results obtained with the cross-sectional study designs employed by Winneke and the British investigators. Small, 1-2 point differences in IQ seen in some of their studies between control and lead exposure groups might in fact be due to lead effects masked by much larger effects of socioeconomic factors, home environment, or parental IQ" (CD, p. 12-98).

In replicating their previous study, Schroeder and Hawk (1986) found a highly significant linear decrease in IQ with increasing blood lead level across the range of 6 to 47 µg/dl in low SES black children, 1-6 years of

age. This confirmatory finding is particularly compelling because the potentially confounding factor of socioeconomic status was effectively controlled by selecting a very homogeneous group of children, and the results indicate that IQ effects may be detected without evident threshold even at these low PbB levels, at least in this population of children. The recent study by Silva (1986) reported no significant effects on IQ among higher SES children in New Zealand, whose mean PbB level at age 11 years was 11 µg/dl. Although various behavioral measures were significantly related to PbB, these findings on older children are difficult to relate to the other childhood studies cited here.

[Results of encoding experts' probability judgments on lead-induced IQ decrements are summarized in Section 7.C.2. In general, the results indicate that according to most of the experts encoded, risks of small but measurable IQ deficits exist at PbB levels as low as 15 or 25 µg/dl. Some experts felt there were risks of small IQ decrements at a PbB level of 5 µg/dl.]

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. One study followed the academic performance of a subset of the children initially evaluated by Needleman et al. (1979) and found that grade retention was clearly associated with past dentine lead levels, while the relationship between other outcomes and past dentine levels were either marginally - (e.g., IQ scores, classroom behavior) or statistically non-significant (e.g., teacher ratings) (Bellinger et al., 1984).

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, 1985). 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), but inconsistent or unexpected findings across studies require clarification. (Winneke et al., 1984; Otto, 1985; Robinson et al., 1985).

The effects on hearing or nerve conduction in the auditory pathway that have been related to lead exposure in children may be indicative of subtle, but potentially important neurological impairment. Slowed nerve conduction in the auditory pathway (i.e., increased latencies of brainstem auditory evoked potentials [BAEP]) were directly related to increased PbB levels in children (6-12 years old across the range of 6 to 59 µg/dl) (Otto et al., 1985). Attempts to replicate these findings in an independent group of children 3 to 7 years old found that the latency of one BAEP wave, as well as hearing threshold, increased linearly with the maximal PbB levels found in the children's medical records, from 6 to 56 µg/dl (Otto, 1985; Robinson et al., 1985). Latencies of three other BAEP waves, however, exhibited a curvilinear relationship to lead exposure history, suggesting a possible biphasic effect of lead on nerve conduction velocity in the auditory pathway with facilitation at PbB levels below 25 µg/dl and slowing at PbB levels above 25 µg/dl (Otto, 1985; Robinson et al., 1985). In contrast, Otto et al. (1985) observed a linear relationship between PbB levels and BAEP across the entire range of exposure. Also, in contrast to their earlier

findings a significant increase was found in hearing threshold with increasing lead exposure history, suggesting that lead exposure may impair hearing and the peripheral segment of the auditory pathway (Otto, 1985; Robinson et al., 1985). Given that a hearing loss occurring in early childhood that remains undetected may result in speech and learning impairments as the child develops, the implications of this finding as well as the findings of altered nerve conduction in the auditory pathway should be pursued as part of understanding lead's putative role in subtle performance deficiencies among pre-school and school-age children. The preliminary nature of these auditory function results must be emphasized, however, and until comprehensive longitudinal, audiometric, electrophysiological, and speech measurements in children are done, it will be difficult to resolve this issue.

In summary, 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, however, indicates that lead is associated with neurological impairment in some children with PbB levels between 30 and 50 µg/dl and that effects on certain behavioral and electrophysiological measures which may have some small, but potentially important and persistent effects on neurological function, support a continuous dose-effect gradient down to exposure levels as low as 15-30 µg/dl PbB, or perhaps, somewhat lower (CD, p. 12-37).

The impacts of lead on heme synthesis and related systems are summarized in Table 7-7. 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

Table 7-7. 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 blood 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 neurotransmission	Meredith et al., 1978; O'Flaherty et al., 1980; Nicoll, 1976; Brennan and Cantrill, 1979; Silbergeld et al., 1980, 1982
≈40	Reduction in hemoglobin levels	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. Question mark signifies that the effect has been observed *in vitro* or *in vivo* in animal models and extrapolating dosages to children is not warranted.

functional consequences 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;

(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 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). The PbB threshold for elevated EP in children is approximately 15 µg/dl in children with significant elevations greater than one and two

standard deviations above normal EP mean levels occurring in 50% of children studied at PbB levels of between 25-30 and 35 µg/dl, respectively (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 considered to be 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 for an individual child, allowing some margin of safety relative to levels associated with inhibition of hemoglobin synthesis or neuropsychological deficits. This PbB level was equivalent to the Centers 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 biotransformation 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).

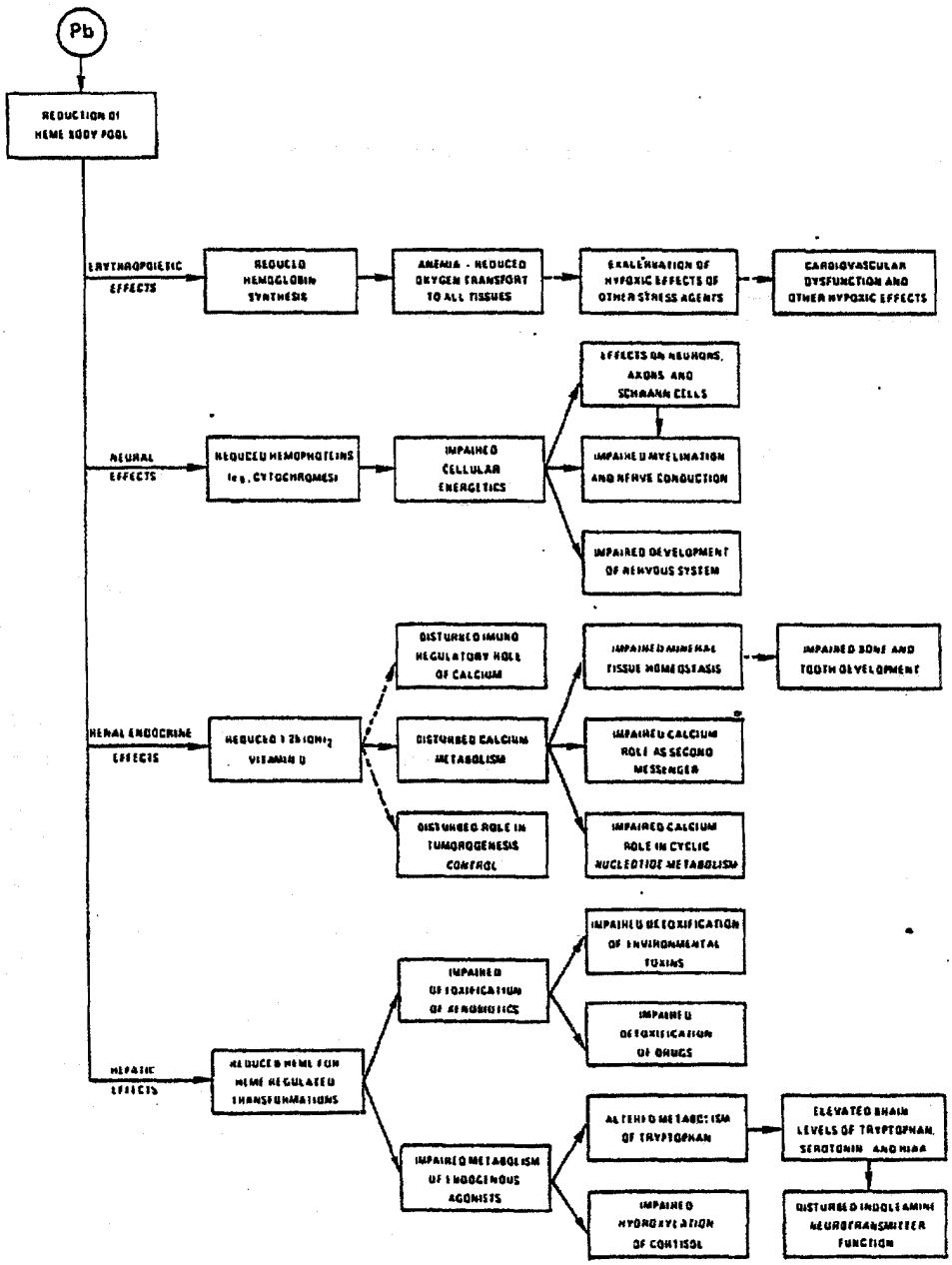

Figure 7-1. Multi-organ impact of reductions of heme body pool by lead. Impairment of heme synthesis by lead results in disruption of wide variety of important physiological processes in many organs and tissues. Particularly well documented are erythropoietic, neural, renal-endocrine, and hepatic effects 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).

Of the functional consequences associated with heme reductions and lead's interaction with those processes, perhaps the best quantitative data are 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 affect 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 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 are comparable to 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 based on available literature. [Section 7-C.2 summarizes results of the encoding of experts for their probability judgments with respect to lead-induced hemoglobin reductions. These results according to several experts suggest risks of hemoglobin deficits at a lower PbB level than is generally accepted as being associated with anemia, i.e., 40 µg/dl). Although anemia is a serious clinical manifestation, the inhibition of heme synthesis at lower blood lead levels has much wider implications for a multitude of organs and systems, as described above, especially in the developing 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 7-8 presents the staff's 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 7-5.

Based on the above discussion, the staff concludes that: 1) multi-organ effects resulting from impairments in heme synthesis and vitamin D metabolism are likely between 25-30 µg/dl, and potentially significant effects on these processes may be possible at the lower PbB levels indicated, but the evidence and risks are difficult to determine at present; 2) the risks associated with altered brainwave activity and possibly reduced auditory function at PbB levels < 30 µg/dl are also difficult to determine with available information; 3) similarly, there is incomplete information on the medical significance of elevations in EP that are first detected above 15 µg/dl, and the dose-response relationship between lead and hemoglobin decrements; and 4) 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 between lead, IQ, and disturbances in sensory/attention processes at levels between 30 and 50 µg/dl and possibly lower. It is expected that more conclusive information will result from ongoing research.

Table 7-3. 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 (1-4 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 (1-4 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, auditory function[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, auditory function[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, auditory function[10] Reduced ALA-D activity[11]	Small risk of multi-organ impairments resulting from heme and vitamin D impairment. Some risk of 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]	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; Schroeder et al., 1985; Schroeder and Hawk, 1986

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

[4]Seppalainen et al., 1979, 1983; Seppalainen and Hernberg 1980, 1982; Feldman et al., 1977

[5]Otto et al., 1981, 1982, 1985; Otto, 1985; Robinson et al., 1985; 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; Schroeder et al., 1985; Schroeder and Hawk, 1986

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

[9]Harvey et al., 1983, 1984; Yule et al., 1984; Hunter et al., 1983; Winneke et al., 1983, 1984; Schroeder and Hawk, 1986

[10]Otto et al., 1982, 1985; Otto, 1985; Robinson et al., 1985; Winneke et al., 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

The staff believes that the collective impact of all of these changes along with other lead-induced effects at low PbB levels should be considered sufficiently important to warrant avoidance. In evaluating the above health effects information in the context of deciding on an appropriate maximum acceptable PbB level, it is important to note that as part of its lead poisoning screening program, the CDC have revised its 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 between 30 and 50 µg/dl 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 on the level of risk that is tolerable in that context.

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. Conversely, it is felt that the risks of adverse effects are minimal for an individual child at a PbB level below 15 µg/dl. In order to avoid potentially significant risks among young children and to protect as many children as possible who can be protected by a lead NAAQS with an adequate margin of safety, the staff concludes that the maximum acceptable individual PbB level should be chosen from the range between 15 and 20 µg/dl.

2. Summary of Probability Encoding on Lead-Induced Health Effects

The scientific information describing dose-response relationships for lead, as with most environmental pollutants, is generally limited and incomplete. There is a large variation in people's susceptibility to air pollution-induced health effects, and scientific evidence is rarely conclusive in establishing a causal relationship for health effects resulting from pollutant exposure, especially if these effects involve a latency period or other contributing factors. Given the precautionary nature of the Clean Air Act and the need to protect public health with an adequate margin of safety, it is important to characterize, as explicitly as possible, the range and implications of uncertainties in the data base as part of the ambient standard review. One way to address uncertainties in the scientific

knowledge about a particular health effect is to obtain probability distributions based on expert judgments. Obtaining, or encoding these judgments involves interviewing experts to assess their judgments concerning the probability that a certain fraction of the sensitive population would suffer a particular adverse health effect at a given exposure level. Probability judgments can be used to describe an individual's assessment of the likelihood of an event based on the current state of information, which includes both his or her judgments or interpretations of existing studies and theories and the quantitative data available. Because different experts will have different judgments, it is also important not to merge these judgments into a single average, but rather to present to the decision makers the range of risks based on the range of judgments, and thereby also identify the range and form of disagreement among experts.

Probability distributions representing the judgments of experts on two health effects were formally assessed directly using the technique of probability encoding. Detailed results of the encoded judgments and their application to compute health risks in children living near representative lead point sources are provided in Wallsten and Whitfield (1986). The report also describes the methods used in eliciting the judgments. The methodology employed to calculate population exposures associated with different air lead scenarios used in the health risk assessment is summarized elsewhere (Johnson and Paul, 1986). It is important to note that the population exposure results are preliminary and are undergoing further evaluation.

Of the numerous health effects of lead, reductions in hemoglobin levels and IQ decrements were chosen for probability encoding. It must be emphasized that although there is considerable uncertainty regarding

the dose-response functions for these two effects, particularly at low lead levels, these endpoints are not the most sensitive indicators of lead toxicity, nor are they necessarily the most critical in terms of public health. Because this exercise was EPA's first application of formal risk assessment procedures in reviewing a NAAQS, it was important to select health endpoints: a) that could be readily quantifiable in common measurement units (in contrast to classroom behavior, for example); b) that could be readily understood in terms of their medical significance (in contrast to changes in ALA or nerve conduction velocity, for example); and c) for which exist a sufficient number of qualified experts who span the range of respected opinion and interpretation (unlike for example, lead-induced changes in vitamin D metabolism for which few experts can be identified).

Since only a finite number of PbB levels can be presented for encoding, it is necessary to interpolate between levels in order to use the judgments in risk assessments. Such interpolations were made by fitting suitable probability distributions to the encoded values for both hemoglobin and IQ effects (see Wallsten and Whitfield, 1986, for a detailed description). The present discussion utilizes the functions fit to each individual's probabilistic judgments to present a summary of the quantitative results for both hemoglobin and IQ. The functions provide an accurate representation of the underlying encoded values, both because goodness of fit was excellent and because each expert endorsed the output of the respective functions as representing his or her judgments.

2. Encoding Judgments on Lead-Induced Hemoglobin Decrements

Of five experts selected, probability judgments of four were encoded with respect to the frequency of lead-induced hemoglobin levels below

either 9.5 or 11.0 grams per deciliter (g/dl) in homogeneously exposed populations of young children. The fifth expert (Expert B) felt uncomfortable with the notion of judgmental probability encoding and declined to have his judgments encoded. The experts were given the option of considering separately the population of children in the age groups 0-3 and 4-6 years, because of the age-related differences in iron deficiency.

It is generally agreed that for children a hemoglobin level of about 12 g/dl is normal and about 9 g/dl is anemic. Thus, of the two levels specified, a hemoglobin concentration of 9.5 g/dl would be much more likely to be considered as an adverse health effect. Although both hemoglobin levels are sufficiently low to warrant concern, there would likely be extensive debate over whether a hemoglobin level of 11 g/dl would necessitate preventative measures in terms of a lead air quality standard. In the interests of brevity and of focusing in on the more critical effects, results are summarized here only for the judgments regarding 0-3 year olds (the more sensitive age group), and for the dose-response function for hemoglobin levels less than or equal to 9.5 g/dl (See Figure 7-2). [Expert C, believes that a single dose-response function applies to children in the 0-6 year age range; with his concurrence, his judgments were reproduced in both the 0-3 and 4-6 year age groups.]

The following discussion regarding Figure 7-2 is extracted directly from Wallsten and Whitfield (1986):

> The graphs are analogous to the usual dose-response functions found in the literature, except, of course, they are based on probabilistic judgments rather than on direct data. The dark, central curve in each panel shows the median judged dose-response curve for each expert. In other words, for a given panel, according to that expert, at each blood lead level there is a 0.50 probability that the true response rate is above the indicated value and a 0.50 probability that the true response rate is below it.

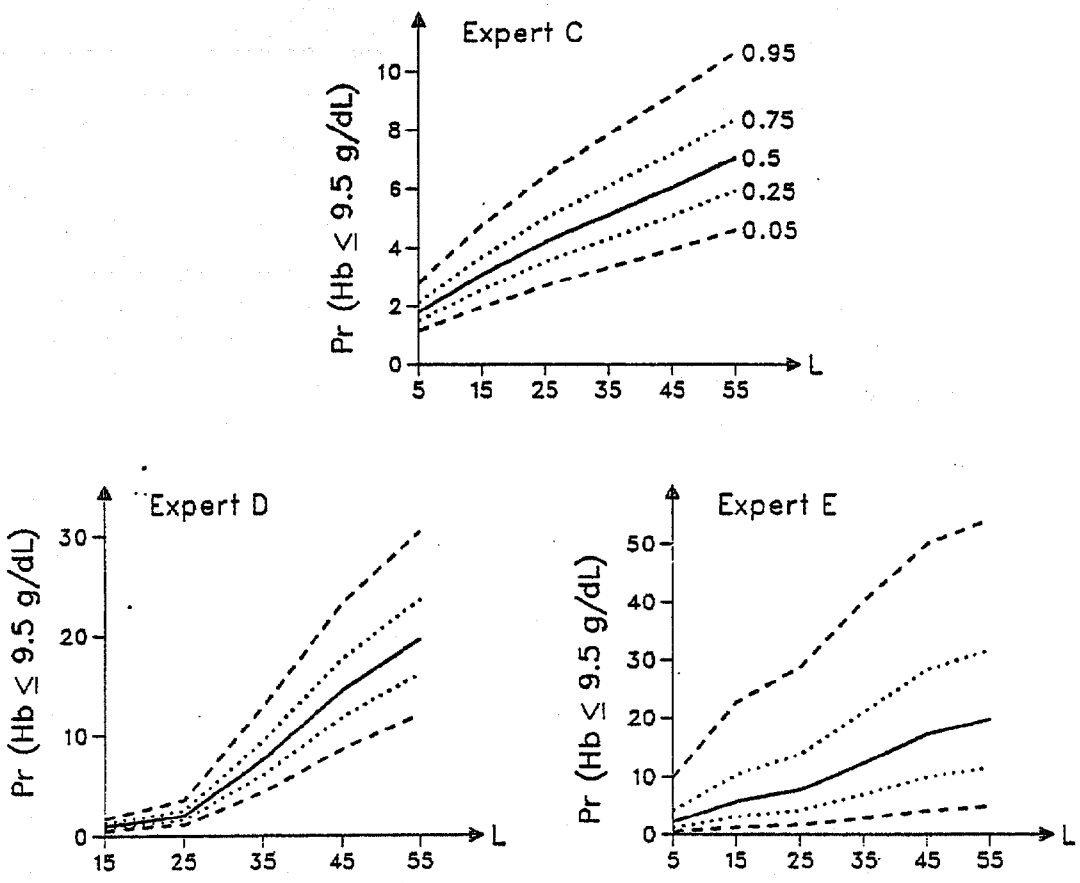

Figure 7-2. Probabilistic judgments of Experts C, D, and E regarding the dose-response function for hemoglobin levels ≤ 9.5 g/dl in children ages 0-3 years (from Wallsten and Whitfield).

The two lighter lines on either side of the median curve contain the central 50% credible interval. Thus, according to the expert in a particular panel, at each blood lead level there is a 0.25 probability that the true response rate is below the lower light curve, a 0.50 probability that it is between the two light curves, and a 0.25 probability that it is above the upper one. In a similar manner, the dashed curve contains the 90% credible interval.

The more tightly packed are a family of functions in a panel, the less uncertainty does an expert indicate in his judgments. Thus, Figure 7-2 gives a rather complete representation of each expert's probabilistic judgments.

Figure 7-3 is less complete, but provides a convenient means of comparing judgments across experts. The axes are the same as in Figure 7-2. The vertical bars at each lead level represent each expert's central 90% credible interval for response rate, and the symbol within each bar indicates the median judgment at that lead level.

It must be borne in mind that these judgments are with respect to lead-induced response rates over and above any base response rate due to iron deficiency and other factors. Thus, levels of uncertainty, as well as differences or similarities of opinion reflected here, are focused solely on the effects of lead on hemoglobin.

Note first that expert A did not feel that there was a measurable lead-induced hemoglobin effect at PbB levels below 45-55 µg/dl, and therefore judgments at 9.5 g/dl are not shown for him; indeed, his median judgment for the percentage of children age 0-3 years with hemoglobin levels below 11 g/dl at PbB = 45 µg/dl is 3%, and this rises to a most likely rate of 17% at PbB = 75 µg/dl.

There is overlap in the judgments of experts C, D, and E, although not to the degree as for their judgments regarding hemoglobin levels below 11.0 g/dl which are not displayed here. For example, these experts judged with a probability of 0.9 that the following fraction of children 0-3 years old which would have hemoglobin levels below 9.5 g/dl with PbB of 35 µg/dl were within the following ranges: 3-8% (Expert C); 4-13% (Expert D); 3-41% (Expert E). At a PbB of 25 µg/dl, the corresponding

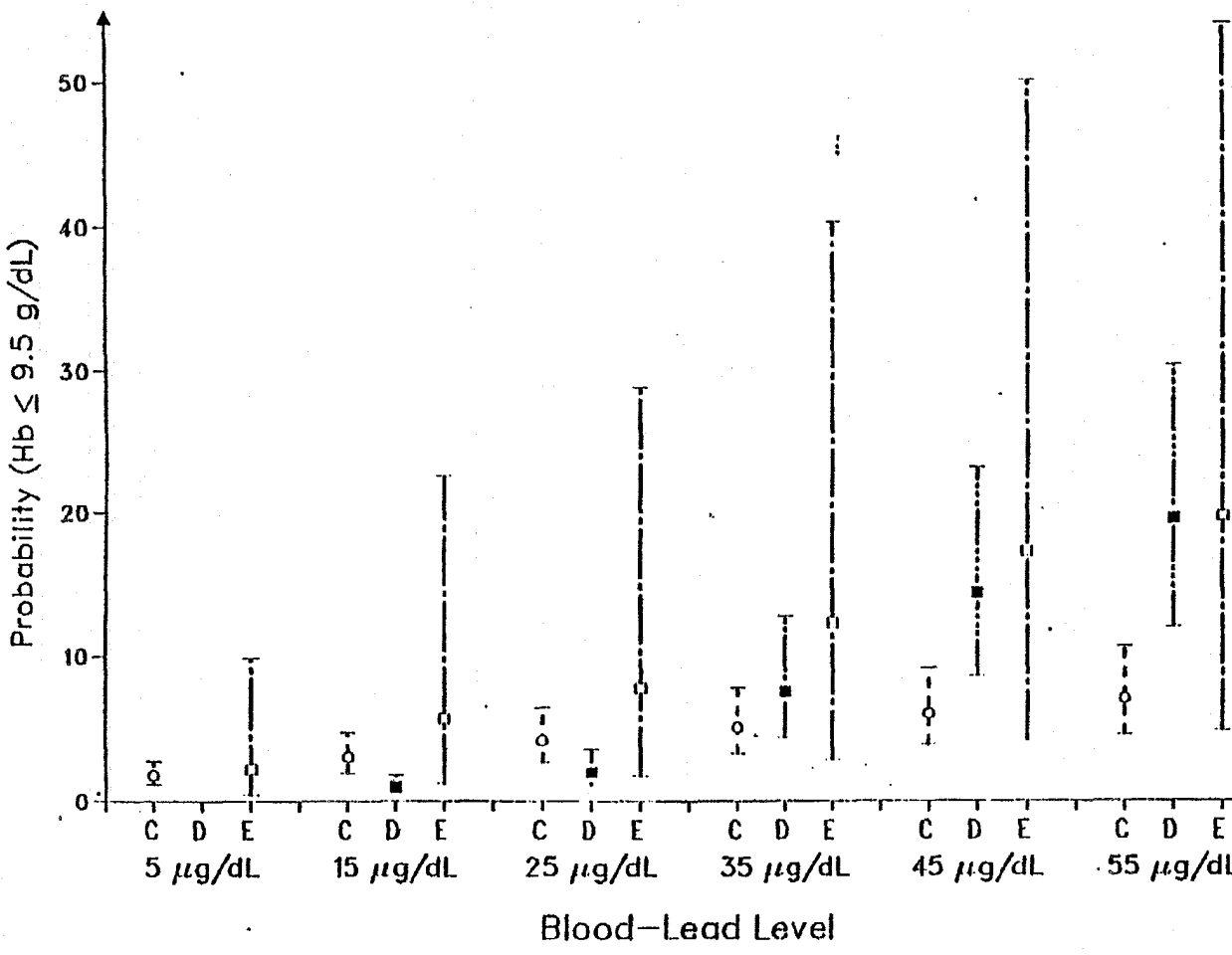

Figure 7-3. Comparison of judgments of Experts C, D, and E regarding the probability of hemoglo
in children ages 0-3 years at different blood-lead levels. The vertical bars at ea
represent each expert's 90% credible interval for response rate and the symbols ind
judgment at that blood-lead level (from Wallsten and Whitfield).

range of the fraction of children affected with a probability of 0.9 are: 3-6% (Expert C); 1-4% (Expert D); 2-29% (Expert E). For a PbB of 15 µg/dl, these 0.9 credible intervals are: 2-5% (Expert C); 1-2% (Expert D); 1-23% (Expert E). For a PbB of 5 µg/dl, the following range of fractions of children 0-3 years would have hemoglobin levels below 9.5 g/dl with 0.9 probability: 1-3% (Expert C); 0 (Expert D); 0-10% (Expert E).

Considering the median judgments (i.e., the response rate for which there is a 0.5 probability that the actual rate is either above or below the indicated value), C and E agree in estimating the most likely response rate at 5 µg/dl to be 2%, while D is most certain that the response rate is 0. Expert C's median response rate judgment increases relatively slowly with increased PbB, while that of expert D increases relatively quickly. As a result, at PbB = 55 µg/dl, D and E agree that the most likely response rate is 20%, while C considers it to be 7%.

Of these 3 experts, expert E expresses considerable uncertainty in his judgment about the dose-response function, while experts C and D express much less. Note also that the judgment of expert D suggests a slight threshold between PbB levels 25 and 35 µg/dl, but that the judgments of the other two do not suggest a threshold for hemoglobin levels below 9.5 g/dl in 0-3 year olds.

The corresponding judgments for lead-induced hemoglobin levels at or below 11.0 g/dl, and for children 4-6 years old, are not displayed here. Expert A judged that blood lead below 45 µg/dl would not cause hemoglobin levels to drop as low as 11.0 g/dl. As with 9.5 g/dl, the judgments of experts C, D, and E for 11.0 g/dl tend to overlap, but the degree of similarity displayed is greater than at the low hemoglobin level.

None of these 3 experts' judgments suggest a threshold above which blood lead would result in a hemoglobin level below 11.0 g/dl. According

to their median judgments, the best estimate of response rate for 0-3 year olds, hemoglobin $\leq$ 11.0 g/dl, is between 4% and 9% at PbB = 5 µg/dl, rising to between 26% and 33% at PbB = 55 µg/dl. The judgments for children 4-6 years of age followed the same patterns as for children 0-3 years, with all the experts judging smaller probabilities of effects in the older group. Detailed results can be found in Wallsten and Whitfield (1986).

b) Encoding Judgments About Lead-Induced IQ Decrements

It should be noted again that IQ was chosen not because it is the only, nor necessarily the best, measure of cognitive ability, nor is it being considered as a surrogate for other suspected lead-related central nervous system and behavioral effects that have been explored (e.g., brain wave activity, sensory motor, perceptual and attentional deficits, negative classroom behaviors). Rather, IQ decrement emerged as most appropriate to consider because of its acknowledged functional significance, its easy specification, and the amount of data (albeit controversial) on its relationship to lead exposure.

The probability judgments of six experts were encoded with respect to the outcomes of a hypothetical, ideal experiment in which a very large number of subjects were randomly assigned at conception to various exposure groups and were exposed to (or sheltered from) lead until their seventh birthdays. Although each child's lead uptake would not be constant due to changes with age, physiology and behavior, the hypothetical experimental conditions were specified such that at their third birthdays, all children in each group have the same measured PbB level. Environmental lead levels necessary to yield a given PbB level at age 3 in a particular child were specified as remaining constant through the seventh birthday, at which time the WISC-R IQ test was administered. The very large numbers of

subjects per group eliminated any concern about sampling error, and the random assignment of subjects to conditions eliminated any concern about complex analyses of covariance. Each group was assumed to differ only in terms of exposure to lead.

Probabilistic judgments were encoded regarding: (a) the mean IQ decrement for each exposure group (5, 15, 25, 35, 45, and 55 µg/dl on their 3rd birthday) relative to a lead-free control group; (b) the mean IQ of the control group; and (c) the within-group IQ standard deviation. Judgments about control group mean IQ values and within-group standard deviations were necessary to derive probabilistic estimates about the lead-induced increase in percent of children at each lead level whose IQ scores are below a specified IQ value of interest. Detailed results, including the encoded judgments, mathematical functions fit to those judgments, goodness of fit measures, and derived subjective probabilities about dose-response functions, are given in Wallsten and Whitfield (1986). For brevity, summaries of results for IQ decrements only are presented here.

The experts were given the option of considering possible interactive effects of socio-economic status and lead on IQ (based on findings from several studies discussed in the CD and this staff paper) by considering low SES children living in households with incomes in the lowest 15 percentile separate from the remainder of the population. All the experts, except F, believe that at the doses under consideration, lead interacts with variables that contribute to SES level. Therefore, all except Expert F provided separate judgments for the two SES levels.

Figure 7-4 summarizes the judgments of all six experts regarding mean IQ decrements for the low SES group. The following discussion regarding the figure is extracted directly from Wallsten and Whitfield (1986).

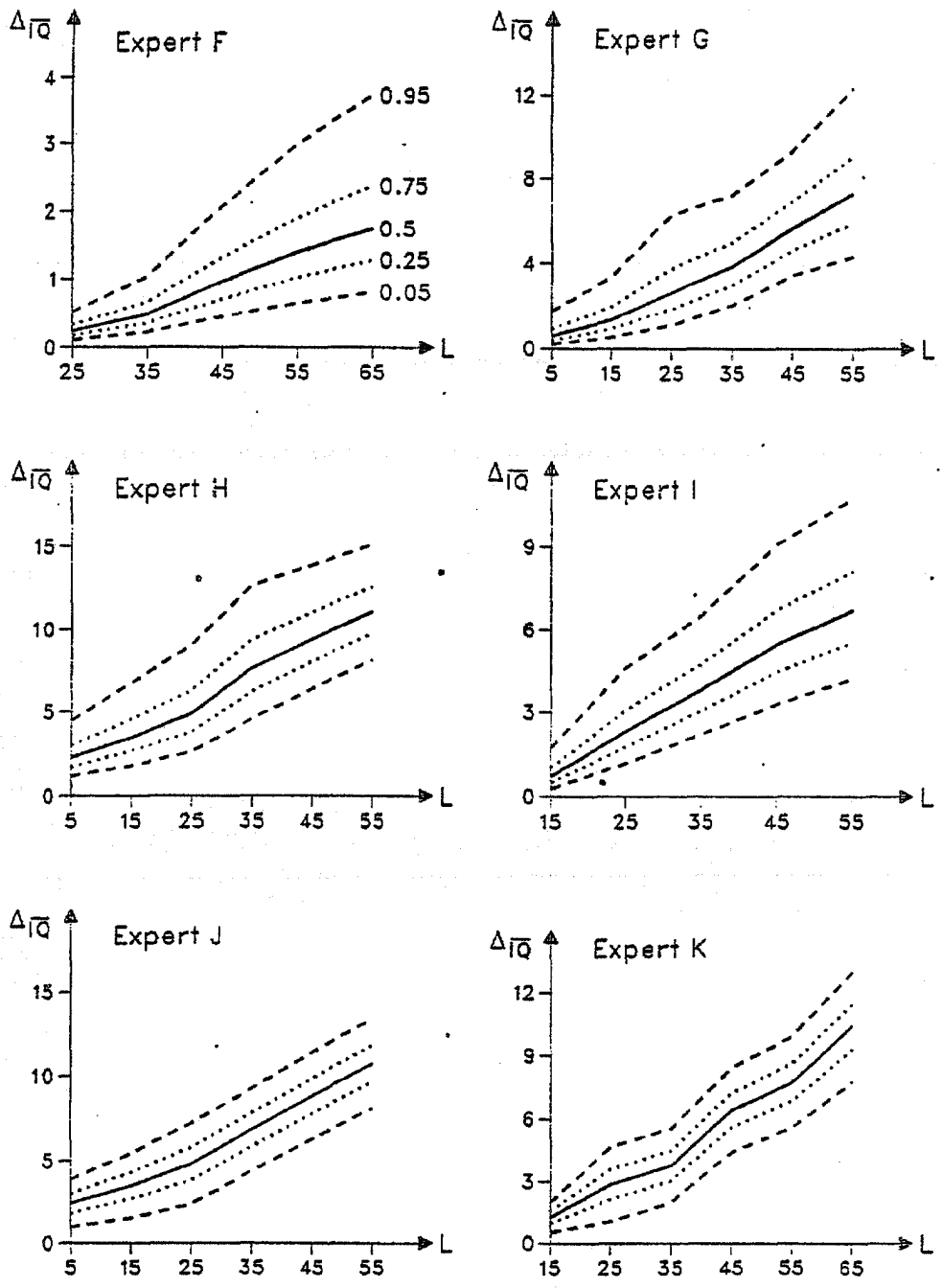

Figure 7-4. Probabilistic judgments of experts regarding mean IQ decrements for low SES group. Blood lead is on the abscessa and mean IQ decrement (mean control group IQ minus mean exposed group IQ) is on the ordinate of each panel (from Wallsten and Whitfield; 1986).

Each person's judgments are shown in a separate panel. Blood lead is on the abscissa and mean IQ decrement (mean control group IQ minus mean exposed group IQ) is on the ordinate.

The dark, central curve in each panel shows the median judged IQ decrement for each lead level. In other words, for a given panel, according to that expert there is a 0.50 probability that the actual mean IQ decrement would be greater than the indicated value, and a 0.50 probability that it would be less. The successively lighter pairs of curves that bracket the median curve represent central 50%, 90%, and 95% credible intervals.

Figure 7-5 allows a comparison of judgments across the experts. The axes are the same as in Figure 7-4 . The vertical bars at each lead level represent each expert's central 90% credible interval, and the symbols are his or her median judgments.

Expert F consistently judged the IQ effects of lead to be less than did the other experts, and evidenced considerably less uncertainty about the magnitude of these effects than did the others. F was certain that there is no IQ effect of lead up to at least 15 µg/dl. At 25 µg/dl, the median judged IQ decrement is about a 0.5 point, and this increases to a median judged IQ decrement of just under 2 points at 65 µg/dl. According to F, at 25 µg/dl, the IQ decrement exceeds approximately 1 point with probability 0.05, while at 65 µg/dl, it exceeds 5 points with the same probability.

There are overriding similarities in the judgments of the other experts, although there are also small, consistent differences among them. Thus, only G, H, and J give any credibility to there being IQ effects as low as 5 µg/dl, while I does so at 15 µg/dl, and K does at 25 µg/dl. The judgments of H and J are consistently very close, as are those of G, I, and K, which as a group are somewhat lower than those of and H and J. Considering the five sets of judgments, the median judged IQ decrement at 5 µg/dl ranges from 0 to 2.5 points. The median judged IQ decrement at 55 µg/dl is from about 7 to 11 points. According to the judgments of G, H, and J, with probability 0.05, the IQ decrement exceeds 3 to 5.5 points at 5 µg/dl, while according to all 5 experts, it exceeds 11 to 17 points at 55 µg/dl with the same probability.

Considering intermediate PbB levels, Expert F judged a probability of 0.5 that the mean IQ decrement at a PbB level of 35 µg/dl in low SES children would be 0.5 points. Corresponding median judged IQ decrements at 35 µg/dl for the other experts are: 1.5 (Expert G); 8.4 (Expert H); 3.6 (Expert I); 7.0 (Expert J); 4.0 (Expert K). The median judged IQ decrements at 25 µg/dl for low SES children are: 0.25 (Expert F); 2.7 (Expert G); 4.9 (Expert H); 2.3 (Expert I); 4.8 (Expert J); 2.9 (Expert K). At a PbB level of 15 µg/dl, the median judged IQ decrements

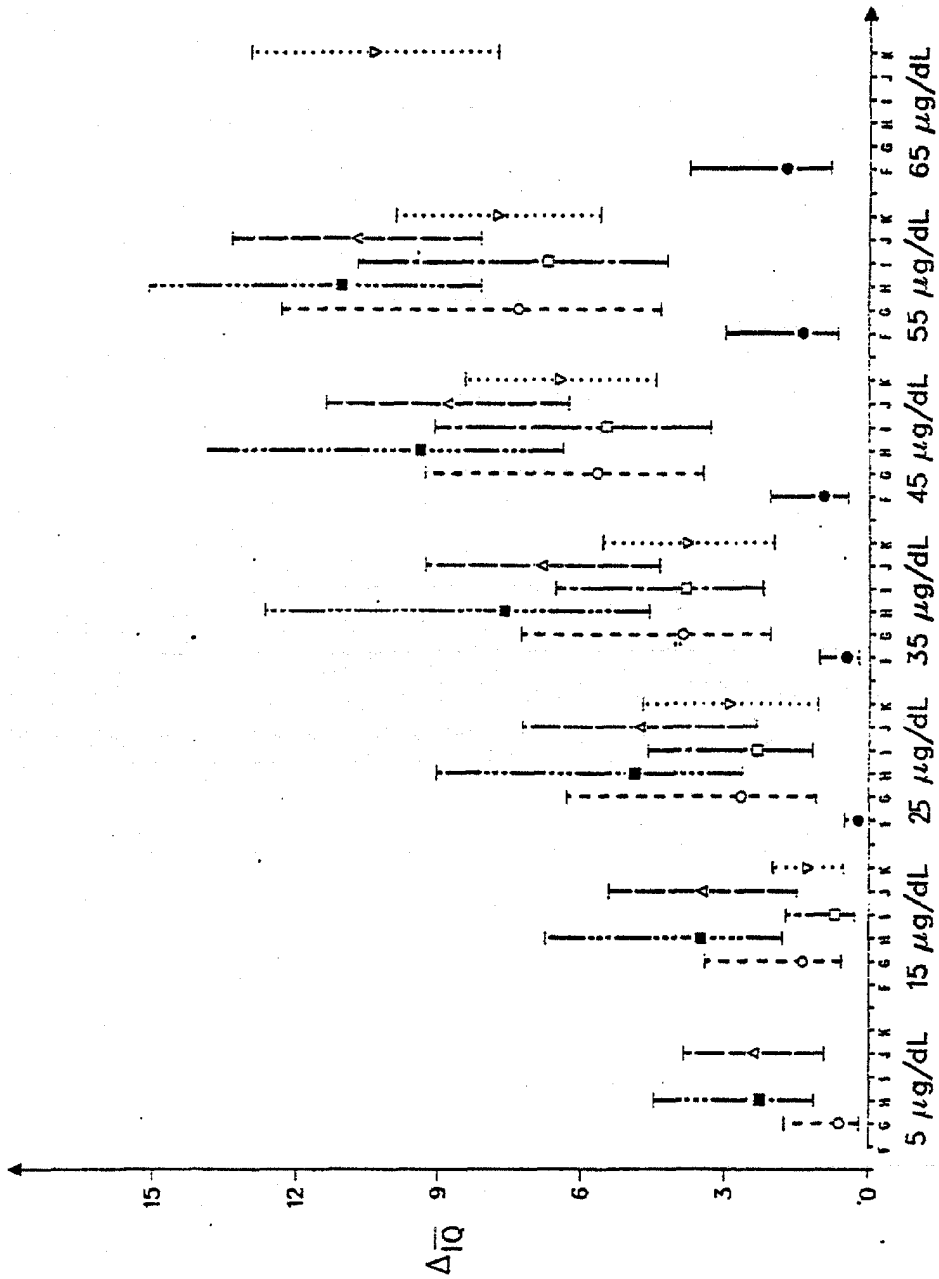

Figure 7-5. Comparison of judgments across experts regarding mean IQ decrements for low SES group. The vertical bar at each, blood-lead level represents each expert's central 90% credible interval, and the symbols indicate the median judgment at that blood-lead level (from Wallsten and Whitfield, 1986).

TEH 041357

for low SES children are according to these experts: 0 (Expert F); 1.4 (Expert G); 3.5 (Expert H); 0.7 (Expert I); 3.5 (Expert J); 1.3 (Expert K).

As with hemoglobin, credible intervals were calculated for each expert's judgments. For example, the 0.9 credible interval is a set of mean IQ decrement values such that there is a 0.9 probability of the true value falling within it. The 0.9 credible intervals concerning mean IQ decrements for the low SES children for different PbB levels are as follows:

45 µg/dl: 0.45-2.07 (Expert F); 3.5-9.3 (Expert G); 6.4-13.9 (Expert H); 3.3-9.1 (Expert I); 6.3-11.4 (Expert J); 4.4-8.4 (Expert K).

35 µg/dl: 0.23-1.05 (Expert F); 2.1-7.3 (Expert G); 4.6-12.7 (Expert H); 2.2-6.5 (Expert I); 4.4-9.3 (Expert J); 2-5.5 (Expert K).

25 µg/dl: 0.11-0.52 (Expert F); 1.1-6.3 (Expert G); 2.6-9.0 (Expert H); 1.2-4.6 (Expert I); 2.3-7.2 (Expert J); 1.1-4.7 (Expert K).

15 µg/dl: 0 (Expert F); 0.6-3.5 (Expert G); 1.8-6.7 (Expert H); 0.3-1.7 (Expert I); 1.5-5.4 (Expert J); 0.5-1.8 (Expert K).

5 µg/dl: 0 (Expert F); 0.2-1.8 (Expert G); 1.2-4.5 (Expert H); 0 (Expert I); 0.9-3.9 (Expert J); 0 (Expert K).

Judgments about mean IQ decrement for the high SES group are not displayed here, although all the experts, except F, felt that the risks of lead effects on IQ would be smaller in the high SES children. Also, as with the low SES population, F consistently judged the IQ effect to be less than did the other experts. From 25 µg/dl on, the judgments of the others overlap, with, as before, those of H and J being very similar and somewhat greater than those of G, K, and I, which themselves are similar. Only H gave any credibility to the existence of an IQ effect at 5 µg/dl, G, I, and J did so at 15 µg/dl, and F and K concur at 25 µg/dl (Wallsten and Whitfield, 1986).

Considering all the experts simultaneously, the median judged IQ decrement at 15 µg/dl in the high SES group ranges from 0 to 2.4 points; at 55 µg/dl, it ranges from 1.4 to 7.9 points. According to G, H, I, and J, with probability 0.05 it exceeds 1 to 7 points at 15 µg/dl, while according to all the experts it exceeds 4 to 11.5 points at 55 µg/dl with probability 0.05.

c) Discussion

Considering the scientific debate that has prevailed about the IQ effects of lead, the degree of consensus reflected in the present results is notable. This is particularly so, since the experts were selected so as to span the credible range of opinion. As occurred with the hemoglobin results, encoding subjective probabilities from the scientific experts about specific, well-defined scientific outcomes eliminated or minimized disagreements about definitions, policy, and other matters. The remaining differences, evidenced in the preceding results, are mainly due to differing interpretations of, and extrapolations from, the scientific evidence.

As discussed previously, the health endpoints that were assessed using probability encoding should not be considered the individual effects most crucial to a determination of the appropriate maximum acceptable PbB level. Judgments of some of the experts suggest that effects on IQ and hemoglobin could occur at and below 15 µg/dl. It should be noted, however, that in general the judgments tend to support that the range of 15-20 µg/dl, discussed previously, is appropriate for a decision on the maximum acceptable individual PbB level. In fact, several of the experts assigned fairly high probabilities that potentially important hemoglobin and IQ decrements could occur in children with PbB levels starting at 25 µg/dl.

3. 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 under specified 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 7-14) for consideration in the possible use of one, two, or all three approaches (with any necessary modifications using improved data) in assessing the protection provided 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 of children are protected from exceeding a maximum acceptable PbB level. In determining such a distribution, it is important to recognize that there is significant behavioral and biological variability within any population, and it is those individuals with the potentially 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.

As noted for other metals in tissues of human populations, the distribution of PbB levels for any relatively homogeneous population closely follows a lognormal distribution (CD, Section 11.3.4). A lognormal distribution is completely specified by its geometric mean and geometric standard deviation. It is possible, therefore, to use a geometric standard deviation of a population's blood lead distribution 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. 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). 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 homogeneous subgroups of young children with comparable race, sex, age, income, and place of residence (i.e., degree of urbanization) (CD, p. 11-29 to 11-30).

The distribution of PbB levels in U.S. children is a broad one because there is a distribution of exposures those children face, a distribution of behavior patterns that affect the uptake of that exposure, and a distribution of biological absorption and excretion rates. The GSDs for separate homogeneous populations identified in the NHANES II survey may not therefore be appropriate to use in targeting a protection level for a certain percentage of the non-homogeneous population of U.S. children (Schwartz, 1985b). 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). Furthermore, in calculating a GSD that would be used to predict the effect of changes in exposure under alternative lead NAAQS on the percent of children exceeding some cutoff PbB level, the appropriate GSD removes a portion of the total variation in blood lead due to differences in air lead exposure without removing the variance due to other factors such as baseline exposure and biological differences (CD, p. 11-7) so that the distribution of PbB levels at an air lead zero can be estimated. With regard to the above GSDs cited in the CD, by adjusting the PbB distribution for demographic variables, much of the variance in baseline exposure, behavior patterns, or biological factors, and not solely the variation due to air lead levels may be removed. For example, NHANES II blacks have consistently higher PbB levels regardless of income, residence location, parent's educational level, or dietary consumption, and this difference should remain as a real factor that contributes to the GSD (Schwartz, 1985c). Similarly, location is another factor that represents more than just differences in air lead exposure given that food lead levels, baseline soil and dust lead levels, water lead levels, and other factors can vary from city to city. In fact, regression analyses of NHANES II data indicate that there is a variation in mean PbB levels among cities, and that correcting for demographic proxies (e.g., income, race, degree of urbanization) for air lead exposure leaves a residual variation in site means due to variations in non-air exposure (Schwartz, 1985c).

In regression analyses, Schwartz (1985c) attempted to directly remove the variance in NHANES II PbB levels due to air lead exposure by adjusting every individual's PbB level to what it would be at zero air lead, while

allowing for variations in background non-air lead exposure. The estimated GSD from this analysis, 1.428, is shown to be higher than those calculated for the homogeneous sub-groups primarily because of the natural variation in baseline exposure among sites with similar demographic characteristics, rather than the variation in demographic characteristics between sites.

Schwartz (1985d) reapplied the same techniques to calculate the GSD for children's PbB levels measured in NHANES II after excluding from the analysis those individuals that would not be expected to be substantially affected by changes in the lead NAAQS. Such children would be those likely to have higher than average pica activity and those exposed to excessively high concentrations of lead in dusts, particularly from lead in paint. A blood lead cutoff of 40 µg/dl was chosen as the lowest reasonable number above which air lead changes would not be important. [Logistic regressions of NHANES II data indicated that gasoline lead was a statistically significant predictor of PbB levels above 35 µg/dl.] After excluding all children with PbB levels over 40 µg/dl and adjusting the distribution to zero atmospheric lead, Schwartz (1985d) calculated a GSD of 1.419. [These results are consistent with a study, conducted by Shier and Hall (1977) and analyzed by Urban (1976), of children 6 years old and and younger randomly selected in Pittsburgh during 1974 and 1975; as in the Schwartz analysis of NHANES data, the GSD (1.37) for the general population in Pittsburgh did not change after excluding children from homes with lead-based paint (Pope, 1986b).] Thus, for the NHANES II population of children a GSD without attribution of any source of lead exposure except gasoline lead and industrial air lead emissions may be taken as a rounded-off value of approximately 1.42 (CD, p. 11-31). The staff recommends that a value of 1.42 be considered the most appropriate GSD for purposes of calculating the percent of children above a cutoff PbB

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; Tera et al., 1985).

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 may result in all of the shared variance between confounder and exposure variable 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 ± 0.58), and Yankel et al. (1.53 ± 0.064), yielding an unweighted median slope of 1.92 (CD, p. 11-105). 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).

It should be emphasized, however, that most of the children in these studies lived in the vicinity of lead point sources (i.e., smelters).

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 is deposited and 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 if the associated changes in the surface deposition of lead were accounted for, rather than simply inhaled air lead (Angle et al., 1984). 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 7-12) 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. (1984) 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 indirect 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). To only use an "adjusted" blood lead/air lead slope (i.e., inhalation slope) would result in an underestimation of 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 these 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 (i.e., disaggregate) relationships derived from regression analyses, the latter which refer to the blood lead/air lead relationships due to direct inhalation exposure.

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

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)

V-18

DUP050454899

TEH 0413512

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.

observed for industrial and urban areas at low and high PbB levels and for all ages of children. The apparent trend towards smaller 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 disaggregate 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 of different variables on PbB levels (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. Air lead was measured at 6 sites continuously for 2 months in 1978. Brunekreef (1984) estimates β (4.0) 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. After adjustment for parental education, the blood lead difference of about 8 μg/dl decreased to 7.2 μg/dl, 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 aged 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 above criteria used to determine key studies in the CD (p. 11-63), it appears that these series of studies near Arnheim and the subsequent analyses in Brunekreef (1984) are of sufficient quality to provide reliable aggregate slopes between blood lead and air lead.

2. The more recent study by Brunekreef et al. (1983) on Dutch city and suburban children 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 factors that covary with air lead (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; β = 5.9) groups with small differences in exposure at high exposure levels (i.e., <1 km vs. 2.5 km from smelter; β = 4.6) and groups with small differences in exposures at low levels (i.e., 2.5 km from smelter/urban vs. urban/rural; β = 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 may have 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 years of age. 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 β estimates 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 based on the 1974 data.

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 that underestimates the "true" impact of atmospheric lead on PbB levels. A range of values can be estimated from a) additional, and apparently relevant, studies

not used to derive inhalation slopes in the CD (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) peaks, 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., soil, 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 blood/air lead 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) yields a range of about 4 to 6. Use of these slopes to predict blood levels associated with alternative air lead levels is discussed in Section VII.C.3 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 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 cells 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; Angle et al., 1975;

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 functioning 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^{++}), sodium (Na+), and potassium (K+) (Holtzman et al. 1977; Bull, 1980; Van Rossum et al., 1985) occur at levels of lead as low as 15 micromolar in intact cellular systems. Because of the pervasive role calcium plays in regulating cellular

function, a wide range of linkages between lead's impact 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 lead concentrations as low as 50 micromolar, 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), as well as peripheral neuromuscular junctions (Cooper et al., 1984).

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 indirectly alter associated 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 tissues 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) normal mouthing

behavior (e.g., finger licking and immature dietary habits) which can transfer lead-contaminated soil and dust from their hands into the gastro-intestinal (GI) tract; 2) greater lead intake into the respiratory and GI tracts on a body weight basis; 3) greater lead absorption and retention rates; 4) greater prevalence of nutritional deficiencies which enhance lead GI absorption rates and toxicological effects; 5) 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; 6) a less developed blood-brain barrier that can allow greater entry of lead into the brain; and 7) an inherently greater physiological sensitivity of developing tissues and organs, as indicated by lower thresholds, and greater severity of 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 based on available estimates, approximately 240,000 live near point sources where lead exposure is generally higher (the latter figure may be an overestimate due to recent plant closures) (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.

As discussed in Section IV.F., for present purposes, exposures to and blood lead levels of children exposed to high levels of lead in paint will not be estimated in this assessment. Pope (1986a) estimates that in 1980, between approximately 6.2 and 13.6 million U.S. children under the age of 7 lived in homes containing > 0.7 mg/cm^2 lead in painted surfaces, a level considered by the Centers for Disease Control to be hazardous to young children. Lead-based painted housing with peeling paint, holes in walls, or broken or cracked plaster are considered to be particularly hazardous to children because of the relatively easy accessibility of paint chips or lead-contaminated dust. The estimated number of U.S. children residing in lead-based painted homes in 1980 with such deteriorating conditions ranges from 235,000 to 842,000 (Pope, 1986a).

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 appropriate criteria for averaging time and sampling frequency 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. Stated another way, its purpose is to prevent extremely high peak concentrations from being averaged out by extended periods of low concentrations if those high peaks represent a health hazard. 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 lead 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 risk of shorter term exposures to air lead concentrations 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 air quality 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. The following assessment of additional health and exposure information available since 1978 and other evidence suggests that a monthly averaging time may be more appropriate than a calendar quarter. Whether a quarterly average standard can provide adequate protection at a level that minimizes the risks associated with even short-term exposures is also discussed.

1. Equilibration Period for Blood Lead in Children

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). Few direct measurements have been made on the equilibration period for blood lead in children, 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).

A population of poor, urban children with pretreatment PbB concentrations greater than 50 µg/dl received chelation therapy and were then followed prospectively for the next 2 to 2 1/2 years (Chisolm et al., 1985). Following therapy, blood lead levels increased within one month to varying degrees, depending on the housing conditions the children returned to, and stabilized after three months. Individual records showed that PbB levels increased usually in 3 months by approximately 10 µg/dl in children who moved from lead-free or renovated housing to old housing with some

lead-paint hazards and that PbB levels decreased in a similar fashion in those who moved in the opposite way. The authors conclude that such observations suggest that PbB is "quite sensitive to changes in exposures to lead" (Chisolm, 1985), although these results may not be directly applicable to the substantially different exposure conditions associated with lead in ambient air.

A more rapid equilibration rate for blood lead in children is indicated by regression analyses of NHANES II data in which individual children's PbB levels were most closely correlated with the previous month's gasoline lead consumption compared to the current month and second previous month's gasoline lead use (the third previous month's gasoline lead coefficients were not significant) (Schwartz, 1985a). A one month lagged gasoline lead also best fit blood lead in regression analyses of New York and Chicago screening data (Schwartz, 1985a) and of cord blood lead in Boston (Rabinowitz et al., 1984b). In addition, for the prevalence of children then reported (1976-1980) to have lead toxicity (PbB > 30 µg/dl) in CDC quarterly screening reports and in NHANES II, a greater portion of the variance was explained by one month lagged gasoline lead, compared to concurrent or previous gasoline lead use (Schwartz 1985a).

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 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 bloodstream

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 the above data, it appears 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. Based on the analyses of NHANES II and gasoline lead data, children's PbB levels and the number of children with elevated lead levels appear to be responsive to monthly changes in air lead emissions.

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. PbB levels and ALA-D activity in workers experiencing occupational lead exposure for the first time were significantly altered after only a few days of exposure, and concentrations of urinary lead and urinary ALA changed significantly after about two weeks (Tola et al., 1973). Hemoglobin and hematocrit levels were significantly lower in the workers at the end of the observation period (about 3 months). Similar results were seen under controlled conditions in which 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).

The sensitivity of these biochemical parameters to short-term changes in lead exposure is consistent with the fact that lead is rapidly transported via blood plasma into target tissues such as bone marrow. However, in light of the extremely high exposure levels in these studies (e.g., air lead in the work areas studied by Tola et al. were up to 2-4 mg/m^3 and the average PbB level rose from approximately 12 µg/dl to 40 µg/dl in 3 weeks), it is difficult to relate these findings directly to children exposed to ambient concentrations of lead, primarily through indirect pathways such as soil and dust.

Although the health significance of short-term exposures to lower levels of lead that are relevant to ambient air conditions is difficult to determine for children at present, there does appear to be some cause for concern. This concern is based on the following findings: 1) based on limited occupational and experimental studies, short-term exposures (< 2 weeks) to high levels of lead result in significant changes in heme biosynthesis; effects on other physiological processes associated with similar short-term exposures and effects of short-term exposures more typical of ambient conditions remain to be studied; 2) 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); 3) 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 4) limited epidemiological evidence indicates that children's blood lead levels respond to month to month variations in air lead emissions.

In summary, it appears that a monthly standard would be more protective of children's health than the current quarterly standard, especially around point sources where emissions may be more sporadic. Not only would a monthly standard when compared to a quarterly standard set at the same level reduce short-term increases in children's lead exposure, it would also reduce average long-term air lead levels and deposition, since controls would be necessary to meet the standard in months with increased emissions, and would thereby reduce the number of children with long-term elevated blood lead levels. Although a monthly lead standard appears to be the most appropriate averaging time, if the implementation of a monthly standard is impractical due to monitoring limitations (see Section 7.B), a quarterly averaged standard could provide equivalent health protection by adjusting the level to reduce the probability of short-term (e.g., monthly) air lead concentrations above whatever target level is considered adequate.

In evaluating the adequacy of the current quarterly average standard, it is necessary 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. Recent data on monthly and quarterly air lead averaged concentrations are considered below. Air quality analyses were performed on all available SAROAD data (10,711 monitor-quarters) collected from stationary source, microscale (for mobile source emissions), and neighborhood scale monitors between 1980 and 1984 (Battye, 1984). Table 7-1 presents the results of comparing maximum monthly average lead concentrations to quarterly average lead

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)

concentrations at different types of monitoring sites. These ratios are largely independent of average lead concentration (Battye, 1984) and suggest, for example, that in order to protect against a maximum monthly average concentration of 1.5 $\mu g/m^3$ around point sources, a quarterly average concentration of approximately 1.1 $\mu g/m^3$ (using a mean ratio of 1.4) would be required. If the more conservative 90 percentile value of 1.82 is used, a quarterly average concentration would have to be adjusted to approximately 0.82 $\mu g/m^3$. Without such adjustments, a quarterly average of 1.5 $\mu g/m^3$ around point sources would allow monthly maximum averages as high as 2.1 $\mu g/m^3$ using the mean ratio, and 2.7 $\mu g/m^3$ assuming the 90 percentile ratio.

The magnitude and potential health significance of such excursions in air lead levels over a given quarterly average standard, especially if repeated, suggests that in addition to the reasons previously outlined, a monthly standard would be more protective. If a quarterly standard is retained, it would have to be adjusted so as to preclude excessive excursions above the monthly target level. A quarterly standard adjusted in an appropriate manner could provide health protection roughly equivalent to that of a monthly standard around point sources. At non-point source sites where lead concentrations are less variable, an adjusted quarterly standard would be somewhat over protective.

B. Form of the Standard and Sampling Frequency

1. Alternative Forms of the Standard

Any ambient standard is defined not only by its averaging time and level, but by the characteristic way attainment with that standard is determined, i.e., its form. Compliance with the current lead NAAQS is deterministic--the maximum arithmetic mean average over a calendar quarter is not to exceed 1.5 $\mu g/m^3$. The staff recommends that the primary lead NAAQS

be stated in a statistical form rather than the current deterministic form.

A statistical form can offer a more stable target for control programs and, with reasonably complete data, is less sensitive to 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. Under a deterministic form, compliance with the standard, and consequently emission control requirements, can theoretically be determined on the basis of a single "atypical" month or quarter. 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, a statistical standard could be expressed in many different forms. There are several approaches in determining the form of the standard that would directly recognize the statistical variability associated with the estimated maximum monthly or quarterly average concentrations. In general, two different types of standards have been forwarded. The first is the "parametric" approach, in which the underlying distribution of air quality data would be explicitly taken into account in determining compliance with the standard or in setting targets for control programs. Hypothetically, if correct assumptions regarding these distributions could be made, potential errors in the classification of areas as either attaining or not attaining the standard could be reduced.

An alternative method that has been cited as a way of accounting for the variability in air quality estimates involves the development of a tolerance interval so that a site would not be classified as attain-

ment unless the measured concentration is below the standard level by more than this tolerance interval. Conversely, non-attainment would not be considered unless the maximum monthly or quarterly average concentration was above the standard by an amount greater than the tolerance interval. Within this tolerance interval, attainment status would be "too close to call" -- additional data would be needed before a definite attainment determination could be made.

Although standard forms that explicitly account for the variability in air quality measurements by way of tolerance intervals have certain advantages, only preliminary analyses have been undertaken to date (Hayes et al., 1985). This initial work clearly indicates that considerably more analyses of the statistical properties of air quality data, the implications of these standard forms on attainment policy, and the difficulties in implementation must be undertaken before the Agency can move ahead and specify an appropriate tolerance interval. While EPA plans to further consider this approach and its associated issues in future NAAQS revisions, further consideration of a standard using a tolerance interval would be premature at this time.

For this review three different statistical approaches have been examined. [Each one is equally appropriate for both monthly and quarterly averaging periods.] The alternatives include an expected maximum calendar month (quarter), expected maximum month (quarter), and expected highest 3 months (quarters) standard. The computational scheme for an expected maximum calendar month (quarter) standard is to compute the average over the past 3 years for each calendar month (quarter) (i.e., average all the Januarys, Februarys, etc. or all first quarters, all second quarters, etc.). For an expected maximum month (quarter) standard, the maximum monthly (quarterly)

average would be identified for each calendar year within the 3-year period and the average of these maximum months or quarters would be computed. Computationally, the expected highest 3 months (quarters) average is equivalent to the expected maximum month (quarter) average, unless a single year contains two or more of the highest 3 months (quarters). In essence, each of the alternatives involve a different averaging convention using three years of data. Other forms, such as an expected exceedance rate (requiring that the expected number of monthly averages greater than x ug/m^3 should be less than 1 in three years, for example, were discounted in part because limited data points would be available upon which to base the computations (36 in three years for a monthly average).

The following hypothetical data set will be used in Table 7-2 as an illustrative comparison of each of the alternative forms of a quarterly average standard. In this instance, the critical value would be used to determine attainment or non-attainment, by comparing it against a given standard level.

Hypothetical Data Set For Example Calculations in Table 7-2

Quarterly Lead Average (ug/m^3)

Year	1	2	3	4
1981	1.18	2.55	3.34	2.77
1982	2.98	3.21	1.94	2.68
1983	0.76	5.44	1.29	3.67

As expected, Table 7-2 indicates that the deterministic approach of using the maximum quarterly average in a single year results in the highest critical value because it is determined by a single high quarter. The three alternative forms produce somewhat lower values as a result of averaging over a three year period. The difference between the expected maximum quarter

TABLE 7-2. COMPARISON OF ALTERNATIVE FORMS USING HYPOTHETICAL DATA[a]

Alternative Forms	Computation Scheme	Critical Value in 1983	Comment
Maximum quarterly average (deterministic approach)	Choose maximum quarterly average in a 1 year period	5.44 $\mu g/m^3$	Single "atypical" quarter can dominate result
Expected maximum calendar quarter	Compute average over 3 years for each calendar quarter (i.e., average all first quarters, all second quarters, etc.) to reflect the highest of these four averages	3.73 $\mu g/m^3$	Most applicable where data are consistently seasonal; effect of single high values is averaged out
Expected maximum quarter	Choose maximum quarterly average in each calendar year within the 3-year period; average these maximum quarters	4.00 $\mu g/m^3$	Effect of single high value averaged out; better accounts for non-seasonality in data
Expected highest 3 quarters	Compute average of the 3 highest quarterly averages over 3 years	4.15 $\mu g/m^3$	Similar to expected maximum quarter alternative unless a single year contains two or more of the three highest quarterly averages; provides some control of the second and third highs in a given year

[a]Hypothetical data are listed on previous page.

and the expected highest 3 quarters results from the first and second highest quarters falling in the same year. The expected maximum calendar quarter produces the lowest value.

As a further comparison of the alternative forms, modelled data for a secondary lead smelter were examined for each of the 3-year periods of meteorological data ending in the years 1975, 1976, 1977, and 1978 (See Table 7-3). Similarly, Table 7-4 compares the modelled data for a lead battery plant for each of the 3-year periods of meteorological data ending in the years 1967, 1968, 1969, 1970 and 1971. In both cases, emissions were assumed to be constant.

As in the above example, the rank order of the alternative forms in terms of stringency is the maximum quarterly (monthly) average; expected highest 3 quarters (months); expected maximum quarter (months), and; expected maximum calendar quarter (months), but the difference in the average critical values is small. This comparison illustrates how the maximum quarterly (monthly) average, the deterministic approach, can vary sharply from one year to the next. The alternative forms tend to smooth these fluctuations out.

In selecting the most appropriate form for the standard, the focus should be on identifying the form that best reflects the overall health objective and produces a reasonably stable target for control strategy development. Based on these initial analyses of the three alternatives forms considered, the expected highest 3 months (quarters) appears to best satisfy these objectives. This form permits averaging to smooth out year to year fluctuations due to meteorological conditions and to ensure that an "atypical" value does not dominate, yet provides some control over the second and/or third high months (quarters) should they occur within the same calendar year.

2. Sampling Frequency

In reaching a decision on the standard,the averaging period (monthly

Table 7-3. Comparison of Critical Values[a] of Modelled Quarterly and Monthly Averages Around a Secondary Lead Smelter

Quarterly	Predicted Critical Value in 1975	1976	1977	1978	Average Critical Value	Relative Reduction in Average Critical Value
Max. Quarterly Avg.[b]	4.42	3.72	3.62	3.64	3.85	0
Exp. Max. Cal. Qtr.	3.49	4.04	3.88	3.50	3.73	-3%
Exp. Max. Qtr.	3.49	4.04	3.92	3.54	3.75	-3%
Exp. Highest 3 Qtrs.	3.80	4.04	3.92	3.61	3.84	0
Monthly						
Max. Monthly Avg.[b]	5.07	4.62	4.86	4.36	4.72	0
Exp. Max. Cal. Month	3.95.	4.55	4.50	4.12	4.28	-10%
Exp. Max. Month	4.38	4.82	4.73	4.55	4.55	- 4%
Exp. Highest 3 Months	4.66	4.82	4.81	4.71	4.71	0

Source: Hunt, 1985.

Table 7-4. Comparison of Critical Values[a] of Modelled Quarterly and Monthly Averages Around a Lead Battery Plant

Quarterly	Predicted Critical Value in 1967	1968	1969	1970	1971	Average Critical Value	Relative Reduction in Average Critical Value
Max. Quarterly Avg.[b]	0.64	0.64	0.85	0.84	0.61	0.72	0
Exp. Max. Cal. Qtr.	0.63	0.64	0.71	0.72	0.70	0.68	-6%
Exp. Max. Qtr.	0.67	0.64	0.71	0.72	0.70	0.69	-4%
Exp. Highest 3 Qtrs.	0.70	0.64	0.71	0.72	0.71	0.70	-3%
Monthly							
Max. Monthly Avg.[b]	0.89	0.85	1.08	1.05	0.96	0.97	0
Exp. Max. Cal. Month	0.91	0.90	0.85	0.90	0.81	0.87	-11%
Exp. Max. Month	0.91	0.90	0.92	0.90	0.96	0.92	-5%
Exp. Highest 3 Months	0.94	0.93	0.95	0.93	0.97	0.94	-3%

Source: Hunt, 1985.

a) The critical value would be used to determine attainment/non-attainment by comparing against a given standard level. For max. quarterly avg. it is the highest quarter in the specified calendar year. For the alternative statistical forms, it is the computed value for each 3-year period ending in the specified calendar year.
b) Max. quarterly or monthly average is comparable to a deterministic form of the standard.

vs. adjusted quarterly), form (deterministic vs. statistical), and frequency with which ambient air lead samples are collected should be considered. Given the normal operation of the current one-in-six day lead sampling schedule, with normal 75% data capture, it is clear that the number of samples collected in the course of a month (3) would not provide a statistically valid estimate of the actual air quality for the period (Thrall et al., 1984). Consequently, it is recognized as will be discussed below that should a monthly average lead NAAQS be chosen, it would be necessary to increase ambient air lead sampling to more frequently than one-in-six days, especially during periods and in areas of relatively high air lead concentrations. Recent analyses also suggest that the precision associated with one-in-six day sampling for a quarterly average (deterministic form) lead standard may be unacceptable (Hunt, 1986).

Hunt examined the precision associated with alternative sampling frequencies (every sixth day, every third day, every other day, and every day) with 75% and 100% data capture for monthly and quarterly averaging periods and for both deterministic (using one year of information) and statistical (using three years of information) forms of the lead standard. Precision estimates were calculated for 95% confidence intervals for the following categories of monitoring sites: 1) source-oriented sites with maximum annual quarterly averages less than the current standard of 1.5 $\mu g/m^3$, 2) source-oriented sites with maximum annual quarterly averages greater than the current standard, and 3) National Air Monitoring Stations (NAMS) urban maximum concentration sites.

Using the criterion that the true monthly or quarterly arithmetic mean for a specific time period (e.g., a given month (quarter) or the average of 3 highest months (quarters) in a specific three year period) should lie within

± 10% of the sample arithmetic mean, the initial results from this analysis suggest the following:

1) The standard with the best precision and requiring the least frequent sampling would be a statistical quarterly average;
2) The required sampling frequency with data capture ranging from 75 to 100% could vary according to site type. For NAMS maximum urban concentration sites, the required sampling frequency would be one-in-three days. For source-oriented sites with maximum quarterly averages less than the current standard, every other day sampling would be needed. For source oriented sites with maximum quarterly averages greater than the current standard, the sampling frequency would have to increase to every day.

If a monthly average is selected, the statistical form again would be more desirable than the deterministic in terms of precision and sampling frequency. The sampling frequency for a monthly statistical standard would have to increase compared to a statistical quarterly average. For NAMS maximum urban concentration sites, the sampling frequency would have to increase to once every other day with 100% data capture. For source-oriented sites with maximum quarterly averages less than the current standard, every day sampling would be needed with approximately 75% data capture. Sampling frequency would have to be increased to every day with 75-100% data capture for source-oriented sites with maximum quarterly averages greater than the current standard.

The analysis also suggests that if the data collected are to be used to predict future events (i.e., a given month or a 3-year average is considered typical of all future months or 3-year periods), then the sampling frequencies presented above would have to be increased and in some instances a precision of ± 10% could not be achieved even with every-day sampling with 100% data

capture. While this analysis clearly suggests that more frequent sampling may be required, it is premised on the assumption that the coefficients of variation estimated from past data will resemble future conditions when ambient lead levels are lower and the variability in lead data may decrease. Thus, these results should be viewed as conservative and future sampling requirements could probably be less intensive.

As an alternative to increased sampling frequency using the hi-volume sampler, the States could seek approval for a modification to the Federal Reference Method for lead and replace the specified high-volume air sampler with a similar, "low-volume" sampler that operates with a sample flow rate approximately 1/10th that of the high-volume sampler. The low volume sampler is operated continuously for a period of one month to yield monthly integrated ambient lead samples, which are analyzed conventionally. In approving such a modification for the State of Connecticut, the Agency noted that while there was acceptable agreement between lead samples collected by the low-volume and high-volume samplers at a colocated urban site in Connecticut, it was not clear that such agreement would necessarily be found in all areas of the country. Therefore, additional testing would be necessary before the low-volume sampler could be approved for use in other areas, especially in areas of relatively high lead concentrations and/or where coarse mode particles are predominant, or for universal use as an equivalent method. It was also noted that the level and degree of documentation of the design, construction, operation, and quality assurance procedures of the modified sampler, while adequate for use of the sampler within Connecticut, are not sufficient to readily allow use or adoption of the sampler by other States (Purdue, 1984; McElroy, 1984).

REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR LEAD:

ASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

OAQPS DRAFT STAFF PAPER

Strategies and Air Standards Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, N.C. 27711

February, 1986

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR LEAD: ASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

OAQPS STAFF PAPER

I. PURPOSE

This paper evaluates and interprets the most relevant scientific and technical information reviewed in the draft EPA document "Air Quality Criteria for Lead" (EPA, 1984) in order to better specify the critical elements that EPA staff believes should be considered in the possible revision of the primary and secondary National Ambient Air Quality Standards (NAAQS) for lead. This assessment is intended to help bridge the gap between the scientific review contained in the criteria document and the judgments required of the Administrator in setting ambient standards for lead. As such, particular emphasis is placed on identifying those conclusions and uncertainties in the available scientific literature that the staff believes should be considered in selecting the averaging times, forms, and levels for the primary and secondary standards. While the paper should be of use to all parties interested in the standards review, it is written for those decision makers, scientists, and staff who have some familiarity with the technical discussions contained in the criteria document (hereafter referenced as "CD").

II. BACKGROUND

Since 1970 the Clean Air Act, as amended, has provided authority and guidance for the listing of certain ambient air pollutants that may endanger public health or welfare and the setting and revising of NAAQS for those pollutants. Primary standards must be based on health effects

criteria and provide an adequate margin of safety to ensure protection of public health. As several recent judicial decisions have made clear, the economic and technological feasibility of attaining primary standards are not to be considered in setting them, although such factors may be considered to a degree in the development of state plans to implement the standards (D.C. Cir., 1980, 1981). Further guidance provided in the legislative history of the Act indicates that the standards should be set at "the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population." Also, margins of safety are to be provided such that the standards will afford "a reasonable degree of protection . . . against hazards which research has not yet identified" (Committee on Public Works, 1974). In the final analysis, the EPA Administrator must make a policy decision in setting the primary standard, based on his judgment regarding the implications of all the health effects evidence and on the requirement that an adequate margin of safety be provided.

Secondary ambient air quality standards must be adequate to protect the public welfare from any known or anticipated adverse effects associated with the presence of a listed ambient air pollutant. Welfare effects, which are defined in section 302(h) of the Act, include effects on vegetation, visibility, water, crops, man-made materials, animals, economic values and personal comfort and well-being. In specifying a level or levels for secondary standards the Administrator must determine at which point the effects become "adverse" and base his judgment on the welfare effects criteria.

The current primary standard for lead (to protect public health) is 1.5 micrograms per cubic meter ($\mu g/m^3$), maximum arithmetic mean

averaged over a calendar quarter. The current secondary standard for lead (to protect public welfare) is identical to the primary standard. For both primary and secondary standards, lead and its compounds are measured as elemental lead and currently are collected using a high volume air sampler.

In addition to the lead NAAQS, several other federal regulations have been adopted in order to control human exposures to lead. These include EPA's schedule for the phased reduction of the allowable lead content in gasoline and the national drinking water standard for lead, as well as the Department of Housing and Urban Development's goals to eliminate lead-based paint hazards in federally-funded housing, the Food and Drug Administration's regulations on the lead content of foods and ceramic products, the Consumer Product Safety Commission's limit on lead content in paints, toys, and furniture, and the Occupational Safety and Health Administration's standards for occupational exposure to lead. In addition, the Centers for Disease Control have established criteria for health classification of children screened by lead poisoning prevention programs.

III. APPROACH

The approach used in this paper is to assess and integrate information derived from the criteria review in the context of those critical elements that the staff believes should be considered in the review of the primary and secondary standards. Particular attention is drawn to those judgments that must be based on the careful interpretation of incomplete or uncertain evidence. In such instances, the paper states the staff's evaluation of the evidence as it relates to a specific judgment, sets forth appropriate alternatives that should be considered, and recommends a course of action.

The principal focus of this paper is on the effects of inorganic lead either airborne or deposited from the air onto dusts, soils, vegetation, food, and water. The impact that lead from non-atmospheric sources, such as paint and solder, has on human exposure is also considered. The effects of organic lead vapors which are not commonly found in the atmosphere (see Section IV.A) will not be addressed.

Section IV presents relevant features of human exposure to atmospheric and non-atmospheric sources of lead through various pathways. Section V presents different approaches to estimate the impact of alternative air lead levels on lead body burdens as indicated by blood lead levels. Section VI addresses other essential elements with regard to the primary standards; these include the following:

1) identification of possible mechanisms of toxicity;
2) description of health effects and their relation to exposure levels; and
3) identification of the most sensitive population groups;

Drawing from the analyses of the criteria document information contained in Sections IV, V, and VI, and the associated appendices, Section VII identifies and assesses the factors the staff believes should be considered in selecting an averaging time, form, and level of the primary standard. Selecting an appropriate standard level includes a determination of an acceptable blood lead level and the impact a given air standard would have on the distribution of blood lead levels in the population of concern. Staff conclusions regarding alternative policy options in each of these areas are also presented.

Section VIII contains an examination of information in the criteria document the staff believes is most relevant with respect to the secondary standard. This discussion includes:

1) identification of the levels at which lead-induced changes in terrestrial and aquatic ecosystems have been demonstrated;

2) assessment of the available data base (laboratory and field studies) to identify quantitative relationships necessary for the prediction of environmental impact; and

3) staff recommendations concerning a secondary standard.

and major roadways (i.e., microscale) reported the majority of concentrations over 1.5 $\mu g/m^3$. Only one population-oriented or neighborhood site had a quarterly average greater than 1.5 $\mu g/m^3$ between 1980 and 1983, whereas 14% and 16% of quarterly averages in source-oriented and microscale site-years, respectively, exceeded this value.

Trends in maximum quarterly averages between 1980 and 1983 are illustrated in Figure 4-2. Because of recent changes in lead monitor siting guidelines, the lead monitor network currently is being expanded and changed. In order to avoid biases relating to changes in the monitoring network, the trends analysis included only sites where valid data were available for three of the four years studied (Battye, 1985a). It should be noted, therefore, that these trends data, with the exception of those for "all" monitoring sites which include currently unclassified site-types, are based on a limited number of available monitoring sites that remained in service since 1980 (e.g., 27 stationary source sites, 9 neighborhood scale sites). Despite the new siting guidelines implemented in 1982 that added sites closer to traffic emissions, microscale readings have been declining, corresponding to the phasedown of the lead content in gasoline and reductions in leaded gasoline usage due to the gradual phase-out of older cars burning leaded gasoline. Similarly, annual and maximum quarterly average lead levels near point sources have also decreased since 1980, partly due to increased controls by lead-emitting sources in compliance with state implementation plans as well as to decreased industrial production at lead-emitting facilities (Silvasi, 1985).

B. Lead in Soil

The natural occurrence of lead in the earth's crust averages 5-50 µg lead/g soil [one µg/g is equivalent to one part per million or 1 ppm] lead in various soils (Shacklette et al., 1971; McKeague and Wolynetz, 1980). Much of the lead in the atmosphere deposits on terrestrial surfaces

Table 4-2. FREQUENCY DISTRIBUTIONS OF MAXIMUM QUARTERLY LEAD CONCENTRATIONS BY TYPE OF SITE[a]

Site type/time frame	Percent of site years in concentration ranges[b] <0.5	0.5-1.0	1.0-1.5	1.5-2.0	>2.0	Mean	Total site-years	Total number of sites
1980 through 1983								
All monitors[c]	69	22	5	2	2	0.53	1189	414
Stationary source	62	16	8	3	11	0.95	159	56
Microscale roadside[d]	17	40	27	13	3	0.99	30	18
Middle scale	39	42	18	0	0	0.68	33	15
Neighborhood scale	61	32	5	0	2	0.51	62	29
1983 only								
All monitors[c]	71	19	5	1	3	0.51	360	360
Stationary source	53	24	9	2	11	0.88	45	45
Microscale roadside[d]	16	47	32	5	0	0.83	19	19
Middle scale	53	33	13	0	0	0.60	15	15
Neighborhood scale	72	28	0	0	0	0.40	29	29

[a]Data are from the SAROAD system and represent the numbers of site-years for which the maximum quarterly concentrations fall within the designated concentration ranges. To be included, a site-year must have four valid quarters of data.

[b]Concentration ranges are in units of $\mu g/m^3$.

[c]Includes sites previously classified into categories (e.g., urban) that do not meet any of the current definitions.

[d]Microscale sites are within 5-15 meters from a major roadway and 2-7 meters above the ground.

Source:Battye, 1984

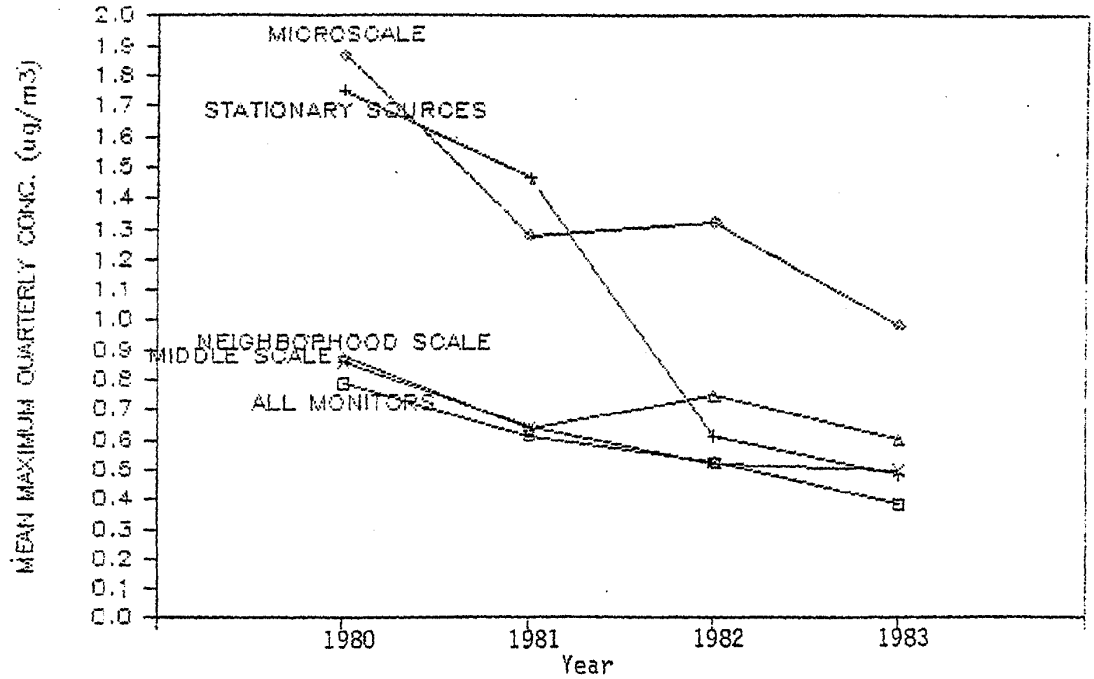

Figure 4-2. Trends in maximum quarterly lead concentration for various monitor types. Source: Battye,1984

photoreaction (Huntzicker et al., 1975) and are readily adsorbed onto atmospheric particles (Edwards et al., 1975), their presence in the atmosphere is transitory. Therefore, any health hazards associated with organic lead exposure are most likely to occur in an occupational setting and will not be assessed here.

In contrast to automobile exhaust, atmospheric lead emissions from industrial plants processing lead and its products contribute little to the overall pollution load across large, regional areas although fallout from these sources can be severe on a local scale. The high concentration levels which are found around lead smelters in particular result mainly from fugitive emissions predominately made up of large (>7 μm) lead particles resulting from materials handling, furnace upsets, and furnace charging and tapping operations (Landrigan et al., 1975; Jennett et al., 1977; GCA, 1984). Beyond the immediate area (0.25-1 km) of lead stationary sources, process emissions from stacks, predominately as lead sulfates and oxides with a size range between 1 and 10 μm, become the major source of lead in soils and air (Dorn et al., 1976; Roels et al., 1980; Davidson and Osborn, 1984).

2. Ambient Concentrations

As indicated in the CD (Section 7.2.1), lead levels in urban areas and near point sources have been markedly reduced since 1977 by the use of unleaded gasoline in new cars equipped with catalytic converters, the lead-in-gasoline phasedown program, and steady reductions in emissions from all types of industrial and commercial sources in compliance with the 1978 lead NAAQS. Recent (1980-1983) air quality data for 414 stationary source sites, micro-scale roadside sites, middle scale roadside sites, neighborhood scale roadside sites, and other non-classified sites are summarized in Table 4-2 (Battye, 1985a). The monitoring sites located near stationary sources

A. Airborne Lead

1. Physical, Chemical and Spatial Characteristics

In general, about 50% of automotive lead emissions deposits within a few hundred meters of major roadways (Daines et al., 1970; Huntzicker et al., 1975; Ingalls and Garbe, 1982) while the remaining particles are small enough to remain airborne and travel hundreds or thousands of kilometers. This likely accounts for the surface contamination of polar glaciers, oceans, and other remote locations around the globe (Murozomi et al., 1969; Duce et al., 1975; Davidson et al., 1981b,c, 1982; Settle and Patterson, 1982). In general, U.S. urban and rural airborne lead particles have a mass median aerodynamic diameter* (MMAD) consistently between 0.3 and 0.7 micrometers (μm) with most of the mass associated with submicron particles, although a distinct peak is seen in the upper end of many of the particle size distributions between 5 and 10 μm (Davidson and Osborn, 1984).

Inorganic lead is emitted from automobiles as lead halides, hydroxides, and oxides and reacts with atmospheric ammonia and acid sulfates to form principally lead sulfate (e.g., $[NH_4]_2\ SO_4 \cdot PbSO_4$) with minor amounts of lead carbonates and halides remaining (Habibi, 1970; Ter Haar and Bayard, 1971; Dzubay and Stevens, 1973; Biggins and Harrison, 1978, 1979). Small amounts of lead additives used in gasoline (tetraethyl- and tetramethyl-lead) may escape to the atmosphere by evaporation from fuel systems or storage facilities. Relatively low concentrations of these organic lead compounds have been typically found in atmospheric samples (1 - 6% of total lead) except in special situations such as gasoline stations or garages (Skogerboe, 1975; Harrison et al., 1979). Because these organic lead compounds decompose by

*MMAD is used as an indicator of particle size of a lognormally distributed aerosol such that half the mass lies on either side of the MMAD.

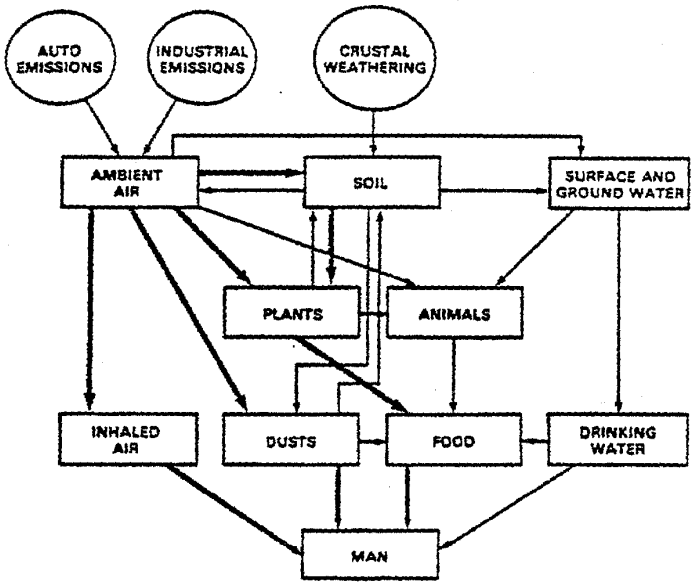

Figure 4-1. Principal pathways of human exposure to lead. Heavy arrows are those pathways discussed in greatest detail. From CD, Figure 7-1.

Table 4-1. Typical Lead Concentrations in Various Exposure Media

Medium	Rural Area	Urban Area	Near Point Source(s)[a]	References
Ambient Air ($\mu g/m^3$)[b]	0.01 - 0.3	0.03 - 4.4	0.2 - 10.2	Tyler, 1984; Yarn, 1984
Indoor Air ($\mu g/m^3$)[c]	0.003 - 0.2	0.01 - 0.4	0.07 - 3.1	Yocum, 1982; Cohen and Cohen, 1980; Rabinowitz et al., 1984b
Soil (ppm)	5 - 30	30 - 4500	150 - 15,000	CD, Table 7-11; Mielke et al.; 1983; See Tables B-1 and B-2
Street Dust (ppm)[d]	80 - 130 (90)	100 - 5,000 (1500)	(25,000)	Nriagu, 1978; CD, Table 7-26
House Dust (ppm)[d]	50 - 500 (300)	50 - 3,000 (1000)	70 - 100,000 (10,000)	U.S. EPA, 1977; Landrigan et al., 1975; Morse et al., 1979; Angle and McIntire (1979)
Typical Foods (ppm)	0.002 - 0.98	Same	Same	CD, Table 7D-1
Water ($\mu g/l$)	<1 - 180 $\mu g/l$	Same	Same	Sharrett et al., 1982; EPA, 1985a
Paint[e]	<1 - >5 mg/cm^2	Same	Same	Billick and Gray, 1978

[a]Within 2-5 km of sources including primary and secondary lead smelters, battery plants.

[b]Represents quarterly averages monitored between July 1982 and July 1984.

[c]Range of indoor/outdoor ratios used (0.3 - 0.8) from Yocum, 1982 except near point sources where large particles predominate and infiltration into homes is low, ratio appears to be closer to 0.3 (Cohen and Cohen, 1980).

[d]Values in parentheses represent estimates provided in CD (Tables 7-24 and 7-26) as typical averages.

[e]Since there may be several layers of lead-based paint on a given surface, absolute concentration of lead is less useful than mg/cm^2. Surveys by HUD in Pittsburgh showed that more than 70% of pre-1940 dwelling units and 20% of post-1960 units had at least one surface with more than 1.5 mg/cm^2 lead paint (NAS, 1980).

IV. LEAD EXPOSURE: MULTIMEDIA CONSIDERATIONS

In order to assess the risks associated with alternate lead NAAQS, it is necessary to understand the influence exerted by atmospheric lead on the total lead exposure of the population(s) of concern through the various exposure pathways. Relevant data on these pathways and the relationships between air lead and lead in other media are summarized in this section. Section V presents methodologies to estimate blood lead levels associated with alternative air lead levels.

The sources and pathways of human lead exposure are diagrammed in Figure 4-1 and typical levels of lead in different media to which U.S. populations are exposed are presented in Table 4-1. Up to the current time, between 85-90% of airborne lead in the U.S. originated from gasoline combustion, with the remainder from stationary industrial processes such as primary and secondary lead smelting, battery plants, lead alkyl production, iron and steel production, ore pulverizing, copper smelting, and combustion of oil, coal, and waste oil. Atmospheric emissions can influence human exposure through direct inhalation of lead-containing particles and through ingestion of lead which deposits onto soil, dusts, vegetation, and other environmental surfaces. This deposition can occur by either or both of two mechanisms: 1) continuous dry deposition due to various mechanisms which may include gravitational settling or wind-related deposition; and 2) episodic wet depostion due to either washout of coarse mode particles (>2.5 micrometers in diameter) which are found mainly near emission sources, or the "rainout" (incloud precipitation scavenging) of smaller particles which are more widely dispersed. Human exposure to lead can also be traced to lead in paint pigments and solder in canned foods and plumbing.

where it is retained in organic complexes near the soil surface (CD, p. 7-28). The ability of soil to immobilize lead largely depends on soil pH and organic content (i.e., fulvic and humic substances). Many U.S. soils appear to have a large capacity to bind lead with only a small fraction dissolved in soil moisture where it is available for plant uptake (see Section VIII). The environmental impact of lead on the biota of terrestrial and aquatic ecosystems is discussed in Section VIII.

The upper layer of roadside soils may contain atmospheric lead from 30 to 2000 ppm in excess of natural levels within 25 meters of the roadbed beyond which concentrations decline abruptly in relation to traffic density and vehicle speed (Page and Ganje, 1970; Quarles et al, 1974; Wheeler and Rolfe, 1979; Pierson and Brachaczek, 1976). In contrast, soil lead concentrations around various lead point sources generally decrease exponentially within a 3-10 km radius from 100-60,000 ppm down to background levels (CD, Appendix 7-C). However, elevated soil lead levels have even been found at distances exceeding 20-25 km from some smelters (Wixson, 1978). Limited data indicate that lead in soil near primary and secondary lead smelters occurs as lead oxides, sulfide, sulfate, and elemental lead (Olson and Skogerboe, 1975; Corrin and Natusch, 1977).

Urban soils are contaminated by lead from a combination of automotive and point source deposition as well as from paint chips from indoor and outdoor surfaces. Elevated soil lead concentrations (as high as 2000 ppm) have been found within 10 feet of wood frame houses painted with lead-based paint (Ter Haar and Aronow, 1974). Accumulations of lead in soils (and dusts) around brick or stone structures have also been found, and can be partially attributed to washoff lead collected on roofs, ledges, and exterior walls (Wheeler and Rolfe, 1979), and possibly to an aerodynamic effect of

the structures on deposition of Pb from nearby sources. Vegetable garden soil samples collected in a 30-mile radius of downtown Baltimore had lead levels up to 10,900 ppm with a median value of 100 ppm (Mielke et al., 1983). Much of this lead was attributed to automotive exhaust and industrial emissions because of the near absence of lead painted houses and the clustered pattern of lead levels around downtown. Soil lead concentrations in a sample of city parks have also been reported to be quite high, ranging from 200 to 3300 ppm (Chow et al., 1975; Zimdahl and Hassett, 1977).

The contribution that lead in soil can make to total lead exposure under alternative air lead levels is addressed in the modeling approaches presented in Section V.

C. Lead in Dust

Dust is a normal component of the home (i.e., "house dust") as well as the outdoor environment where it can be found on sidewalks, playgrounds, driveways, and other hard surfaces. Anthropogenic materials deposited on these outdoor surfaces will be referred to as "street dusts". In addition, the very top layer of soils (including leaf litter) to which people, particlarly children, come in direct contact, are considered in the criteria document to be "soil dusts".

Both house dust and street/soil dust contain lead from atmospheric deposition, "natural" soil, and paint chips. As with roadside soil, significant correlations between lead concentrations in street dust and the proximity and density of traffic have been found (Rolfe et al., 1977; Lau and Wong, 1982). As summarized by Nriagu (1978), street dusts from different U.S. cities contained between 300 and 18,000 ppm lead. A survey of street dusts in 77 midwestern cities showed an average lead content of 1,636 ppm in residential neighborhoods and 2,413 ppm in commercial and industrial areas (NAS, 1980). Limited chemical analyses of roadside soils and dusts from

U.S. cities found lead predominately as sulfate, along with minor amounts of oxide and halide salts (Olson and Skogerboe, 1975; Corrin and Natusch, 1977). Gutter debris in Dearborn, Michigan contained mostly large lead particles ranging between 40 and 1000 μm (Pierson and Brachaczek, 1976).

Airborne lead deposited on streets, sidewalks and driveways is subject to further distribution by wind and water. Windblown particles associated with dust are apt to be redeposited within the urban environment because of the complex wind currents caused by buildings and street canyons. There is somewhat conflicting evidence on the persistence of lead in street dust. Laxen and Harrison (1977) found that only a light rainfall (2 to 3 mm) is sufficient to remove 90% of the lead from the road surface, mainly to surrounding soil and to waterways. A survey of rainwashed areas in the U.K. and New Zealand concluded, however, that the acidity of rain (pH between 4 and 5) was insufficient to completely dissolve and transport lead particles, and that residue near streets pose a health hazard to children who are prone to ingest street dusts (Day et al., 1979). The rate of removal of lead from dusts is also dependent on the frequency and efficiency of street cleaning operations. In the absence of empirical data regarding this mechanism, it is reasonable to assume that lead concentrations in urban street, curb, and sidewalk dust will rise between precipitation and street cleaning episodes, and drop thereafter.

Lead levels in house dust can be expected to vary considerably depending on house cleaning practices, the presence and condition of lead-based painted surfaces, the presence of cigarette smoke, the amount of dust and soil blown into or carried into the house on clothing and shoes, (especially on those occupationally exposed to lead), indoor sources of lead other than paint (e.g., soldering), the permeability of the home to outdoor air (which can

vary with season), and the outdoor concentrations of air lead. Surveys of a diverse set of homes indicate a wide range of house dust lead levels between 18 and 16,000 ppm (EPA, 1977; Harrison, 1979; Angle and McIntire, 1979) and as high as 100,000 ppm within 2 km of smelter (Landrigan et al., 1975).

It is well established that children who play in dust and soil, especially in urban areas and on sites polluted by long-term fallout from industrial emissions, ingest lead in these media through normal mouthing behavior. Significant correlations have been found between blood lead levels and lead in soil, household and street dusts, and on children's hands (Lepow et al., 1975; Sayre et al., 1974; Angle and McIntire, 1982; Quah et al., 1982; Brunekreef et al., 1983).

In order to assess the impact of atmospheric lead on children's total exposure, it is necessary to estimate the contributions of different air lead levels to outdoor and indoor soil/dust lead levels as well as the amount of dirt a child may ingest, both inadvertantly and deliberately. These issues are addressed in the modeling approaches presented in Section V.

D. Lead in the Diet

The ingestion of food appears to be a major component of most individuals' total lead uptake, although the exact amount is a function of the size and type of diet. The occurrence of lead in the diet may be a result of a) natural sources of lead; b) deposition of airborne lead particles onto vegetation, soils, and water; and c) the harvesting, processing, transportation, packaging, preparation, and storage of food during which lead can be introduced at every stage either by atmospheric deposition or through metallic contamination, particularly from solder.

As would be expected from the differences in the handling of various

foods, lead contents vary considerably, ranging from 0.002 to 1.65 ppm (average is 0.65 ppm) (CD, Table 7D-1). Lead in unprocessed foods such as fresh fruits and vegetables comes from atmospheric deposition on vegetation surfaces and uptake from soil moisture through roots (Schuck and Locke, 1970; Motto et al., 1970). The potential for lead uptake through the roots is determined primarily by the soil's organic content and pH; at normal soil pH levels (4.5 to 8) and with sufficient organic content, lead is bound to organic complexes in preference to other metals that are plant nutrients, e.g., zinc, calcium, manganese, magnesium (CD, p. 6-32). With changes in soil properties such as reduced organic content and lower pH, a greater fraction of total soil lead may become mobilized and its potential for uptake by plant roots enhanced (CD, p. 6-38).

Several studies have shown that lead on the surface of leaves (and bark) is closely related to traffic density and distance from the highway, (or more specifically to air lead concentration and particle size distribution), and that not all of the lead particles deposited on plant surfaces can be washed off (Motto et al., 1970; Schuck and Locke, 1970; Lagerwerff et al., 1973; Pilegaard, 1978; Garty and Fuchs, 1982; Tanaka and Ichikuni, 1982). Leafy aboveground vegetables whose edible portions are exposed to atmospheric lead (e.g., spinach, lettuce) tend to have the highest lead levels (Spittler and Feder, 1978) while for many crops, the edible internal portions (e.g., corn and wheat kernels) may have considerably less lead than the outer exposed parts such as stems, leaves, and husks (Ter Haar, 1970), depending on food processing methods. Belowground crops such as potatoes and onions are only partially protected from atmospheric deposition since their roots accumulate lead from the soil as well as indirectly via translocation from the leaves (CD, p. 7-34). Meat products that enter our

food chain may also be affected by atmospheric as well as from lead via the deposition and accumulation of lead on forage subsequently eaten by livestock (Graham and Kalman, 1974; Crump and Barlow, 1982).

Recent studies on lead content of various foods, both before and after processing, packaging, and preparation, and on food consumption patterns in the U.S., provide information on dietary lead intakes for different populations (Beloian and McDowell, 1981; Wolnik et al., 1983; National Food Processors Associations, 1982; Pennington, 1983; U.S. FDA, 1983, 1984). Based on these data, the CD has apportioned lead in "typical" child and adult diets to the following sources: natural soil lead, atmospheric lead, lead in solder, and lead whose origin cannot be determined at present. These estimates and their associated uncertainties are discussed in terms of their application to estimating lead exposure in Section V.

E. Lead in Water

Lead is a natural, usually minor, constituent of surface and ground waters. Atmospheric lead can enter the aquatic system through direct fallout or in surface runoff as suspended particles or adsorbed to soil particles. Under most conditions (pH, temperature, alkalinity), lead forms insoluble salts and precipitates to sediments, which probably accounts for the low lead content of U.S. source water supplies; the average concentration ranging between 3 and 4 micrograms Pb per liter water (µg/l) (NAS, 1980).

In contrast, lead levels in household drinking water can be much higher due to plumbing corrosion and subsequent leaching of lead, ranging between 10 and 30 µg/l on average. The combination of corrosive (i.e., soft or acidic) water and lead pipes or lead soldered joints in distribution systems create localized zones of high lead concentrations (Worth et al., 1981) as high as 380 µg/l. In general, levels are highest in samples of hot and/or stagnant "first draw" water.

Drinking water is a major source of lead exposure among many infants while they are dependent on baby formulas during their first year. EPA's Office of Drinking Water is currently reviewing the degree of protection afforded by the existing lead standard of 50 µg/l against health risks in this sensitive population.

The CD's estimates of the contributions that natural, atmospheric and solder lead make to young children's total lead exposure via drinking water and total diet are addressed in the modeling approaches presented in Section V.

F. Lead in Paint

Ingestion of lead-containing paint is considered to be the most frequent cause of severe lead intoxication among children (Chisolm, 1971; CDC, 1985). Significant correlations have been found between the quantity and condition of lead painted surfaces in homes and blood and fecal lead levels in inner city children (Urban, 1976; Hammond et al., 1982). Significant differences in blood lead levels have been found in relation to housing condition among children as young as nine months with highest levels in children living in deteriorating pre-World War II housing, intermediate levels in well-maintained and rehabilitated older housing, and lowest levels in children in public housing and newer units free of lead paint (Clark et al., 1984). Other recent investigations indicate that in addition to peeling lead-based paints, intact lead-based paint contributes to elevated blood lead levels in children (Gilbert et al., 1979; Galke et al., 1975).

Despite numerous reports extending back to the turn of the century linking childhood lead poisoning and ingestion of paint dust and flakes, it was not until 1971 that the Lead-Based Paint Poisoning Prevention Act was passed. Under the Act, which has since been amended, the Department of Housing and Urban Development has regulatory and research responsibilities

for eliminating the hazards of lead-based paint poisoning in federally funded housing. In 1977, the Consumer Product Safety Commission banned as hazardous, household paint (including toy and furniture paint) containing more than 0.06% lead. Prior to 1940, some interior paints contained more than 50% (500,000 ppm) lead. Use of lead pigment paints declined slowly between 1940 and the late 1960's after which it declined at a rapid rate (NAS, 1972). Pope (1986a) estimates that in 1980, the interior and/or exterior surfaces of between 21.5 and 47.3 million households in the U.S., mostly built before 1960, contained greater than 0.7 mg/cm^2 lead in painted surfaces, a level considered hazardous to young children by the Centers for Disease Control (CDC). Between 6.2 and 13.6 million children under the age of 7 are estimated to have resided in lead-based painted housing in 1980 (Pope, 1986a). Even if coated with low level-leaded paint, the underlying layers of lead-based paint in older homes represent a large reservoir of lead exposure in children, particularly if there is peeling paint, broken or cracked plaster, or holes in the walls. The number of lead-based painted homes with these deteriorating conditions (i.e., "unsound") in 1980 is estimated to have been between 800,000 to 2.9 million with approximately 235,000 to 842,000 children under age 7 living in such homes (Pope, 1986a).

Lead-based paint continues to be the major source of high-dose lead exposure and symptomatic lead poisoning for children in the U.S. (Chisolm, 1971; CDC, 1985), and it appears that exposure to lead-based paint will continue to be a problem for decades to come. Between 1973 and 1980, only 10% of remaining pre-1940 housing units and 5% of remaining housing units built in the 1940's had been removed from our nation's housing stock by demolition, disaster, or by other means such as conversion to commercial space (Bureau of the Census, 1983). Less than half of these units were

located in central city areas where lead poisoning is most prevalent. In addition, poor urban families often have no choice but to live in poorly maintained older housing because the vast majority of new housing units created from 1973 to 1980 is located outside of central city areas, and acute shortages of modern and lead-free, low income rental units exist in many cities (Farfel, 1985).

Although exposure to peeling and intact lead-based paints are implicated as major sources of elevated blood lead levels in children, it is important to note that no single source of lead in the environment accounts for elevated blood lead levels in all children. For example, in fiscal year 1981, the U.S. Centers for Disease Control screened 535,730 children and found 21,897 with lead toxicity. Among the children identified, 15,472 dwellings were inspected and 10,666 or approximately 67 percent were found to have lead paint hazards (CD, Table 11-65). Conversely, approximately one third of the homes of affected children inspected did not have identified lead paint hazards, [however, failure to demonstrate a linkage between lead paint and elevated blood lead does not mean that no exposure to lead paint exists.] Even for those children for whom a potential lead hazard has been identified, contributions from other lead sources are difficult to determine. Furthermore, it is apparent that the precise contribution that paint makes to total exposure to lead is likely to be highly variable. For example, fecal lead excretions of 1,000 µg/day were independently found in children exposed to flaking paint in old housing at times when they had blood lead concentrations between 60 and 80 µg/dl (Chisolm and Barltrop, 1979). In children with lead encephalopathy and average blood lead concentrations of 333 µg/dl, fecal lead excretions ranging from 5,000 to 104,000 µg Pb/day were reported (Chisolm and Harrison, 1956).

Most importantly, high exposures to lead in those children living in older housing with flaking or intact paint will not be significantly influenced by any changes in atmospheric lead emissions. Children with pica for paint chips or others living in lead-based painted homes who are excessively exposed to lead contaminated dust through normal hand to mouth activity cannot be expected to be protected by any lead NAAQS no matter how stringent. For this reason and because exposure to paint lead is so highly variable, the staff will make no attempt here to quantitatively estimate exposures of children who are excessively exposed to lead-based paint under various air lead levels in Section V, as is done for other exposure media. It is clear that any exposures and blood lead levels predicted for children under various air lead levels using the approaches in Section V will be significantly higher for children with high paint lead exposure. As will be discussed further in Section VII, preventing excessive exposure to existing sources of lead in and around housing is a problem that must be specifically addressed by an appropriate combination of legislation, housing code inspection and enforcement, financial incentives, parental education, and other social welfare programs.

V. ESTIMATING LEAD EXPOSURES AND BLOOD LEAD LEVELS

In order to assess the health risks associated with alternative air lead levels, it is necessary to estimate the blood lead (PbB) levels that would be distributed in the population(s) of concern under various air lead concentrations. [The amount of lead measured in whole blood is an index of the rapidly diffusible fraction of the total body burden of absorbed lead and is generally used as the dosage, or index of exposure, in investigating the various human health effects associated with lead.] Three approaches are examined that can be used to estimate or predict the impact of inhaled and ingested lead aerosols and compounds on the body burden of lead as indexed by blood lead. These approaches are presented for consideration for possibly using one, two, or all three (with any necessary modifications using improved data) in assessing the protection afforded by alternative lead NAAQS.

The first approach is to use measured rates of "uptake" of lead through different pathways (e.g., inhalation, ingestion) from experimental studies together with available mathematical models from lead balance studies to project either total body burden or the amount of lead in any of the presumed "physiological" kinetic compartments (e.g., blood, soft tissue, bone) at any time (Hammond et al., 1981). This "uptake/biokinetic" modeling approach attempts to account for the following: a) the amount of lead in the body at any one time is the product of dynamic interactions of partially offsetting processes of absorption, distribution, storage, mobilization, and excretion; b) these processes vary with the route and rate of exposure, a person's age, nutritional and health status, and baseline exposure; and c) uptake from all sources by all absorption routes can be modeled, thus providing an estimate of the relative importance of atmospheric lead exposure, either directly or indirectly, to total body burden.

The level of lead in one tissue (e.g., blood) and its relationship to levels of lead in other tissues responds to many external and internal factors. A discussion of lead's absorption, excretion, retention, and distribution within a child's body under different exposure and physiological conditions is provided in Appendix A. Any application of this model's outputs, should however, recognize the limitations of the data and the significant variability among populations in their behavioral, exposure, and physiological characteristics.

The second modeling approach is to estimate separate empirical relationships between average levels of lead in air, food, water, dust, soil and in blood, which are available from experimental exposure and observational, or epidemiological, studies of different populations (i.e., "disaggregate" approach) (CD, Section 11.4). The third is referred to as the "aggregate" approach whereby a relationship between blood lead and air lead is derived that reflects both direct inhalation exposure and indirect exposures via secondary deposition processes. The validity of these latter two approaches, which rely primarily on epidemiological data, requires that the input of lead from all sources must have been reasonably constant long enough for virtual equilibration to occur between blood lead and environmental lead levels (Hammond et al., 1981). The nature of the relationships detected between lead concentrations in blood and various environmental media, and the merits and limitations in using empirical relationships to represent lead exposure through multiple pathways, will be discussed in Section V.B.

A. Integrated Lead Uptake/Biokinetic Model

There have been several studies measuring the intake, uptake, and metabolism of lead in volunteers, from which balance schemes have been constructed (Kehoe, 1961; Chamberlain et al., 1978, Rabinowitz et al.,

1976, 1977). These balance schemes are derived from limited data obtained under experimental conditions and their application thus far has been restricted to adult males. It is also possible to construct balance schemes by making estimates about lead intakes and various metabolic factors. This approach suffers from the fact that the data and assumptions employed are based on the results of many separate pieces of research, and therefore important variables may be omitted. However, provided the data exist, balance schemes can be constructed for different groups with different exposures to lead to assess the importance of specific exposure factors under variable conditions (e.g., alternative lead NAAQS, phaseout of lead in soldered cans and in gasoline).

The staff has attempted to devise model balance schemes for U.S. children, aged 2 years, under alternative air lead levels. Because this analysis assumes that the various air lead levels are maintained constantly, averaging time (considered in Section VII) will not affect the uptake estimates. As discussed in Section VI.C, pre-school age children ($\leq$ 6 years old) and pregnant women (as exposure vehicles for the fetus) are specified in the CD as particularly sensitive to lead. Of this group, children between 2 and 3 years old experience, in general, the highest blood lead levels (Mahaffey et al., 1982; Billick et al., 1979), most likely due to their greater hand-to-mouth activity as well as to various metabolic processes (Harley and Kneip, 1985). In order to predict the maximum impacts on young children, uptake estimates are calculated for 2 year olds and PbB levels will be estimated for those children and presented in Section VII. The results summarized in Table 5-1 give a broad outline of the actual and relative magnitudes of average intakes and uptakes of lead by different pathways and from different sources. It is important to recognize the limitations of this exercise, which involves

Table 5-1. MODEL BALANCE SCHEMES FOR AVERAGE LEAD INTAKE AND UPTAKE IN 2 YEAR OLD CHILDREN UNDER CONSTANT AIR LEAD LEVELS[1]

	0.25 μg/m³		0.5 μg/m³		0.75 μg/m³	
	General[2]	Point Source[3]	General[2]	Point Source[3]	General	Point Source
1. Outdoor air lead (μg/m³)	0.25	0.25	0.5	0.5	0.75	0.75
2. Indoor air lead (μg/m³)	.08-0.2	.08	0.15-0.4	0.15	0.23-0.6	0.23
3. Time spent outdoors (hours/day)	2-4	2-4	2-4	2-4	2-4	2-4
4. Time weighted average (μg/m³)	.09-.21	.09-.11	.18-.42	.18-.21	.27-.63	.27-.32
5. Volume of air respired (m³/day)	4-5	4-5	4-5	4-5	4-5	4-5
6. Lead Intake from air (μg/day)	0.4-1.1	0.4-0.6	0.7-2.1	0.7-1.1	1.1-3.2	1.1-1.6
7. % deposition/absorption in lungs	15-30	35-60	15-30	35-60	15-30	35-60
8. Total lead uptake from lungs (μg/day)	0.06-0.3	0.1-0.4	0.1-0.6	0.3-0.7	0.2-0.9	0.4-1.0
9. Dietary Lead Consumption (μg/day)						
a) natural lead, indirect atmospheric	2.4	2.4	2.4	2.4	2.4	2.4
b) from solder or other metals	3.8	3.8	3.8	3.8	3.8	3.8
c) atmospheric lead	0.4	0.4	0.4	0.4	0.4	0.4
d) undetermined sources	1.2	1.2	1.2	1.2	1.2	1.2
10. % absorption in gut	42-53	42-53	42-53	42-53	42-53	42-53
11. Dietary lead uptake (μg/day)	3.3-4.1	3.3-4.1	3.3-4.1	3.3-4.1	3.3-4.1	3.3-4.1
12. Street dust/soil lead (μg/g)	55-200	100-525	150-500	350-800	275-875	600-1225
13. Indoor dust lead (μg/g)	85-225	160-500	250-400	350-700	400-650	550-850
14. Time weighted average (μg/g)	83-221	150-504	233-417	350-733	379-688	554-975
15. Amount of dirt ingested (g/day)	0.1	0.1	0.1	0.1	0.1	0.1
16. Lead intake from dirt (μg/day)	8.3-22.1	15.0-50.4	23.3-41.7	35.0-73.3	37.9-68.8	55.4-97.5
17. % dirt lead absorption in gut	30	30	30	30	30	30
18. Lead uptake from dirt (μg/day)	2.5-6.6	4.5-15.1	7.0-12.5	10.5-22.0	11.4-20.6	16.6-29.3
19. Total lead uptake from lung and gut (μg/day)	5.9-11.0	7.9-19.6	10.4-17.2	14.1-26.8	14.9-25.6	20.3-34.4

[1]Assumptions and calculations are described in Appendix B by row number.
[2]Refers to children living in typical urban or rural environments.
[3]Refers to children living near one or more lead point sources.

Table 5-1. MODEL BALANCE SCHEMES FOR AVERAGE LEAD INTAKE AND UPTAKE IN 2 YEAR OLD CHILDREN UNDER CONSTANT AIR LEAD LEVELS[1]
(Continued)

	1.0 µg/m³		1.25 µg/m³		1.5 µg/m³	
	General	Point Source	General	Point Source	General	Point Source
1. Outdoor air lead (µg/m³)	1.0	1.0	1.25	1.25	1.5	1.5
2. Indoor air lead (µg/m³)	0.3-0.8	0.3	0.38-1.0	0.38	.45-1.2	0.45
3. Time spent outdoors (hours/day)	2-4	2-4	2-4	2-4	2-4	2-4
4. Time weighted average (µg/m³)	.36-.83	.36-.42	0.45-1.0	.45-.54	0.54-1.25	.54-.63
5. Volume of air respired (m³/day)	4-5	4-5	4-5	4-5	4-5	4-5
6. Lead Intake from air (µg/m³)	1.4-4.2	1.4-2.1	1.8-5.0	1.8-2.7	2.2-6.3	2.2-3.2
7. % deposition/absorption in lungs	15-30	35-60	15-30	35-60	15-30	35-60
8. Total lead uptake from lungs (µg/day)	0.2-1.3	0.5-1.3	0.3-1.5	0.6-1.6	0.3-1.9	1.1-1.9
9. Dietary Lead Consumption (µg/day)						
a) natural lead, indirect atmospheric	2.4	2.4	2.4	2.4	2.4	2.4
b) from solder or other metals	3.8	3.8	3.8	3.8	3.8	3.8
c) atmospheric lead	0.4	0.4	0.4	0.4	0.4	0.4
d) undetermined sources	1.2	1.2	1.2	1.2	1.2	1.2
10. % absorption in gut	42-53	42-53	42-53	42-53	42-53	42-53
11. Dietary lead uptake (µg/day)	3.3-4.1	3.3-4.1	3.3-4.1	3.3-4.1	3.3-4.1	3.3-4.1
12. Street dust/soil lead (µg/g)	500-1150	750-1450	600-1250	850-1600	700-1400	1000-1750
13. Indoor dust lead (µg/g)	525-875	800-1150	625-1000	1000-1400	750-1150	1200-1700
14. Time weighted average (µg/g)	521-967	792-1250	621-1083	987-1467	742-1233	1167-1717
15. Amount of dirt ingested (g/day)	0.1	0.1	0.1	0.1	0.1	0.1
16. Lead intake from dirt (µg/day)	52.1-96.7	79.2-125.0	62.1-108.3	98.7-146.7	74.2-123.3	116.7-171.7
17. % dirt lead absorption in gut	30	30	30	30	30	30
18. Lead uptake from dirt (µg/day)	15.6-29.0	23.8-37.5	18.6-32.5	29.6-44.0	22.3-37.0	35.0-51.5
19. Total lead uptake from lung and gut (µg/day)	19.1-34.4	27.6-42.9	22.2-38.1	33.5-49.7	25.9-43.0	39.4-57.5

[1]Assumptions and calculations are described in Appendix B by row number.
[2]Refers to children living in typical urban or rural environments.
[3]Refers to children living near one or more lead point sources.

many uncertainties and assumptions due to a lack of sufficient data. These limitations along with details of the available data and calculations are provided in Appendix B. The children considered in the model do not include the whole U.S. population; they comprise groups with different exposures to lead, some of them extreme, in order to illustrate the variations in lead exposure and absorption in different situations. Section V.A.2 presents methodologies to relate estimates of average lead uptake under alternative air lead levels to blood lead levels. Although this approach predicts hypothetical outcomes and the absolute numbers should not be used uncritically, the model does strive to use the available data, with all its limitations, to the fullest extent possible and to provide a useful tool in eventually distinguishing the health impacts of alternative lead NAAQS.

1. Estimates of Lead Uptake

The method employed to estimate the degree to which each environmental source of lead contributes to a child's total daily lead uptake is based on the maximum ambient air lead level allowable for each level considered, probable exposure conditions with respect to other exposure media such as food and dust, and average biological absorption rates for each exposure route. The method consists of a four-step process:

1) definition of ambient concentrations of lead for major exposure sources (i.e., air, food, soil, dust);

2) determination of daily lead intake according to the relationship:

$$I_i = C_i \cdot [Pb]_i$$

where I_i is the daily lead intake from source i, C_i is the ingestion or inhalation (i.e., consumption) per day of each lead source i and $[Pb]_i$ is the concentration of lead in each source i_i;

3) calculation of the amount of lead absorbed from each exposure source i:

$$U_i = I_i \cdot A_i$$

where U_i is lead uptake for each exposure source i, I_i is the daily lead intake from each source i, and A_i is the percent absorption of lead, via the appropriate exposure route for the particular source; and

4) calculation of the total lead uptake from all sources, U_μ:

$$U_\mu = \Sigma (I_i \cdot A_i)$$

Certain assumptions are required to calculate the average daily intake and uptake of lead for children living in the two general areas specified -- urban/rural and near (within 2-5 km) one or more point sources. The assumptions and estimates used in the calculations presented in Table 5-1 are discussed in Appendix B.

2. Uptake and Blood Lead Concentration

To estimate children's blood lead (PbB) levels under different exposure scenarios, several different kinds of studies can be used to derive a relationship between absorbed lead (or lead uptake) and blood lead. Available studies include population surveys in which the blood lead concentration of individuals or groups is correlated with measured lead concentrations in air, food, water, soil, or dust; experiments in which volunteers are exposed to controlled air lead concentrations and their PbB levels measured; and lead balance studies of individuals with measured lead intakes. The most relevant of these studies are discussed in Appendix C along with descriptions of the analyses used to derive uptake/PbB relationships. Data on children from population surveys are discussed in Section V.B. Because of significant metabolic differences, experimental data on adults are used for comparative purposes only.

Figure 5-1 compares the relationships derived from the Ryu et al. (1983) dietary intake study on infants, the Chamberlain and Heard (1981)

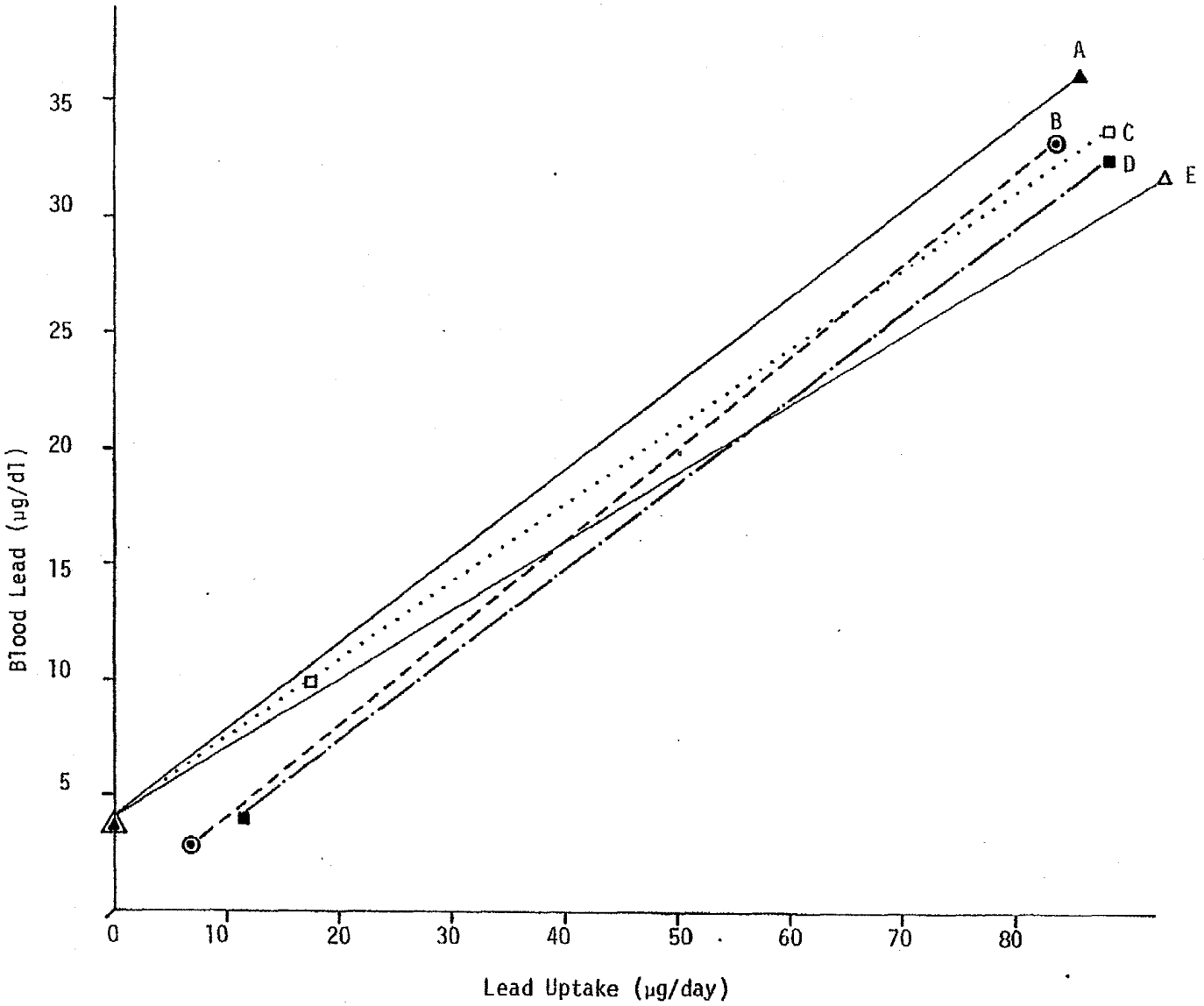

Figure 5-1. Summary of relationships between daily lead uptake and blood lead, derived from: a) Ryu et al. (1983)--curves A (▲) and E (△) represent estimates using 0.42 and 0.53 for lead absorption rates through the gut; b) Harley and Kneip (1985)--curve B (◉) represents estimates for 2 year old children; c) Chamberlain and Heard's (1981) analysis of epidemiological data on adult men (curve C); and d) Rabinowitz et al.'s (1976) metabolic study on adult men (curve D;■).

analysis of the adult epidemiological data, and the metabolic lead balance/ compartmental models of Rabinowitz et al. (1976) and Harley and Kneip (1985). Despite the diverse nature of the populations, study designs, and methodologies, there is a fair degree of consistency in the relationships. Each study found that a linear function provided as good a fit, if not better, than other non-linear forms at the relatively low exposure levels investigated. Some experimental and epidemiological evidence suggests however, that the 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 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 (CD, 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 uncertainties associated with it. Because this model 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.3 (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 to 2) evaluate 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 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 exposure to lead that has deposited 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, i.e., air lead. Before discussing these approaches, several important factors in interpreting

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).