3
4 **SUPPLEMENTARY MATERIAL**

Table I Excerpt from the ISA Table Presenting Summary of Evidence Supporting Causal Determinations for Nervous System Effects Related to Lead Exposure

Attribute in Causal Framework[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Cognitive Function Decrements in Children - Causal			
Consistent associations from multiple, high quality epidemiologic studies with relevant blood Pb levels	Evidence from prospective studies for decrements in FSIQ in association with prenatal, earlier childhood, peak, concurrent, lifetime average blood Pb levels and tooth Pb levels in children ages 4-17 yr in multiple U.S. locations, Mexico, Europe, Australia	Canfield et al. (2003a), Bellinger et al. (1992), Jusko et al. (2008), Dietrich et al. (1993b), Schnaas et al. (2006), Wasserman et al. (1997), Tong et al. (1996), Lanphear et al. (2005) Plus Table 4 3, Section 4.3.2.1	Blood Pb (various time periods & lifestages): Means 3-16 µg/dL With consideration of peak or early childhood blood Pb levels: Means 3-8 µg/dL for concurrent (age 4, 5 yr), age 2 yr
	Evidence from prospective studies for lower scores on tests of executive function and academic performance in association with earlier childhood or lifetime average blood Pb levels or tooth Pb levels in children ages 5-20 yr in multiple U.S. locations, U.K, New Zealand. Associations less consistent for learning and memory.	Canfield et al. (2004), Stiles and Bellinger (1993), Miranda et al. (2009; 2007a), Fergusson et al. (1997, 1993), Leviton et al. (1993), Chandramouli et al. (2009) Sections 4.3.2.3, 4.3.2.4, 4.3.2.5	Blood Pb (various time periods & lifestages): Means 4.8-7.2 µg/dL, Groups with early childhood blood Pb 2-16 µg/dL and 5-10 µg/dL Tooth Pb (ages 6-8 yr): means 3.3, 6.2 µg/g
	Supporting evidence from cross-sectional studies of children ages 3-16 yr, but most did not consider potential confounding by parental caregiving quality. Includes large NHANES III analysis.	Surkan et al. (2007), Kim et al. (2009b), Roy et al. (2011), Lanphear et al. (2000), Froehlich et al. (2007), Chiodo et al. (2007; 2004)	Concurrent (ages 3-16 yr) blood Pb : Means 1.7-12 µg/dL, Group (ages 6-10 yr) with blood Pb 5-10 µg/dL
	Outcomes assessed using widely-used, structured questionnaires.		

Attribute in Causal Framework[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
	Several studies indicate supralinear C-R relationship, with larger decrements in cognitive function per unit increase in blood Pb at lower blood Pb levels in children ages 5-10 yr	Canfield et al. (2003a), Bellinger et al. (1992), Jusko et al. (2008), Kordas et al. (2006), Lanphear et al. (2005) Plus Table 4 16	Groups with peak blood Pb <10 µg/dL: concurrent mean 3.3 µg/dL, age 2 year mean 3.8 µg/dL
Additional epidemiologic evidence to help rule out chance, bias, and confounding with reasonable confidence	Several epidemiologic studies found associations with adjustment for SES, maternal IQ and education, HOME score. Several adjust for birth weight, smoking. A few, nutritional factors.	Table 4 3, Table 4 5; Table 4 8, Table 4 9, Sections 4.3.2.1, 4.3.2.3 4.3.2.4, and 4.3.2.5	
	Epidemiologic studies had population-based recruitment, most with moderate to high follow-up participation not conditional on blood or tooth Pb level or cognitive function.		
	Pooled and meta-analyses demonstrate the consistency of association	Lanphear et al. (2005), Pocock et al. (1994), Schwartz (1994)	
Consistent evidence in animals with relevant exposures to help rule out chance, bias, and confounding with reasonable confidence	Impaired learning and associative ability in juvenile and adult animals as indicated by performance in tasks of visual discrimination, water maze, y maze, and operant conditioning with schedules of reinforcement with relevant dietary Pb exposure.	Stangle et al. (2007), Niu et al. (2009), Cory-Slechta et al. (2010), Altmann et al. (1993), Section 4.3.2.3	Blood Pb (after prenatal/ lactation, lactation only, prenatal/lifetime Pb exposure): 10-25 µg/dL
	Impaired learning, memory, executive function in adult monkeys as indicated by poorer performance on delayed spatial alternation and spatial discrimination reversal learning tasks with dietary Pb exposures.	Gilbert and Rice (1987), Rice and Karpinski (1988), Sections 4.3.2.3 and 4.3.2.4	Blood Pb (after lifetime Pb exposure from birth): 15, 25 µg/dL

Attribute in Causal Framework[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Evidence describes mode of action:	Decreased neurogenesis in hippocampus DG (involved in LTP and learning). Decreased NMDAR (involved in integration of new neurons into existing neuronal pathways). Decreased neurite outgrowth.	Sections 4.3.10.9 and 4.3.10.10	
Impaired neuron development	Found in animals with dietary gestational-lactational, lactational, post-lactational (3-8 weeks), lifetime from gestation Pb exposures.		
Synaptic changes	Decreased synaptic development. Changes in synaptic protein composition. Decreased ATP and AchE, which both mediate neurotransmission.	Section 4.3.10.4	
	Found in animals with dietary gestational with or without additional lactational Pb exposures.		
LTP	Decreased magnitude, increased threshold of LTP with gestational-lactational or lifetime Pb exposure.	Sections 4.3.12, 4.3.10.7, 4.3.10.8	
Neurotransmitter changes	Changes in dopamine metabolism. Increased sensitivity of dopamine receptor. Increased catecholamine transmission in cerebral cortex, cerebellum, hippocampus. Decreased glutamate and expression of glutamate receptor, NMDAR.	Section 4.3.10.8	
	Found in animals with dietary gestational-lactational, lactational, or post-lactational Pb exposure.		
Visual Function Decrements in Children - Inadequate			
The available evidence is of insufficient quantity, quality, or consistency	High maternal 1st trimester blood Pb associated with supernormal ERG in a study of children. No potential confounding considered. Uncertain functional relevance of ERG findings.	Rothenberg et al. (2002b) Section 4.3.6.2	Group with prenatal maternal blood Pb 10.5-32.5 µg/dL
	Higher than relevant Pb exposures did not affect visual acuity in infant monkeys but decreased visual acuity in adult monkeys.	Laughlin et al. (2008) Section 4.3.6.2	Blood Pb after postnatal day 8-week 26 exposure: 35-40 µg/dL
	Examination of retinal ERGs limited to adult rats (see below for Visual Function Decrements in Adults)	Section 4.3.6.2	

Attribute in Causal Framework[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Auditory Function Decrements in Adults – Suggestive			
Limited epidemiologic evidence with relevant bone or blood Pb levels, one high-quality study	Prospective study found association between tibia Pb level and higher rate of increase in hearing threshold over 23 yr in NAS. Population comprises only males, primarily white, but study examines multiple exposures and outcomes and has high follow-up participation. Results adjusted for age, race, BMI, education, diabetes, hypertension, smoking, occupational noise.	Park et al. (2010) Section 4.3.6.1	Tibia Pb mean: 22.5 µg/g, measured near end of follow-up
	Supporting evidence from case-control study finding higher blood Pb levels in workers from various occupations with hearing loss with adjustment for age, smoking, alcohol consumption, years of noise exposure, blood Mn, As, Se	Chuang et al. (2007) Section 4.3.6.1	Concurrent blood Pb geometric mean in cases: 10.7 µg/dL
Lack of animal evidence at relevant exposures	Increased hearing thresholds, decreased auditory evoked potentials in adult monkeys (ages 8-13 years) with gestational, lactational, lifetime dietary Pb exposure.	Rice (1997) Lilienthal and Winneke (1996) Laughlin et al. (2009) Section 4.3.6.1	Blood Pb after gestational, lactational, or lifetime exposure: 33-150 µg/dL

[a]Described in detail in Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the Pb biomarker levels with which the evidence is substantiated and blood Pb levels in animals most relevant to this ISA.

Source: Table 4-17 from U.S. EPA (2013b)