TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Protecting Texas by Reducing and Preventing Pollution

January 28, 2013

EPA Docket Center (EPA/DC)
U.S. Environmental Protection Agency
Mail Code 2822T
1200 Pennsylvania Ave, NW
Washington, DC 20460

Attn: Docket ID No. EPA–HQ–ORD–2011–0051

Re: Third External Review Draft of the Integrated Science Assessment for Lead

Dear Sir or Madam:

The Texas Commission on Environmental Quality (TCEQ) appreciates the opportunity to comment on the United States Environmental Protection Agency's (EPA) document published in the November 27, 2012, edition of the *Federal Register* entitled: "Third External Review Draft of the Integrated Science Assessment for Lead."

Enclosed please find the TCEQ's detailed comments relating to the EPA proposal referenced above. If you have any questions concerning the enclosed comments, please contact Dr. Michael Honeycutt, Toxicology Division, Office of the Executive Director, (512) 239-1793, or at michael.honeycutt@tceq.texas.gov.

Sincerely,

Zak Covar
Executive Director

Enclosure

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY'S (TCEQ) COMMENTS TO THE
U.S. ENVIRONMENTAL PROTECTION AGENCY'S (EPA)
THE THIRD EXTERNAL REVIEW DRAFT OF THE INTEGRATED SCIENCE ASSESSMENT FOR LEAD
DOCKET ID NO. EPA-HQ-ORD-2011-0051

On November 27, 2012, the U.S. Environmental Protection Agency (EPA) published a Federal Register notice (Federal Register doc. 2012-9752) of a 60-day public comment period (ending January 28, 2013) for the, "Third External Review Draft of the Integrated Science Assessment for Lead," hereafter referred to as the draft ISA (EPA/600/R-10/075C). The Texas Commission on Environmental Quality (TCEQ) has developed comments on the draft ISA to the extent practicable in the time allotted by EPA. The TCEQ provides the following comments for EPA consideration focusing on policy-relevant considerations.

General Comments

Because the ISA serves as the basis for later policy judgments regarding the requisite level of NAAQS for air-borne lead, it is crucial that every aspect of this document be accurate.

TCEQ urges EPA to accurately and thoroughly evaluate the studies that will ultimately direct attention and focus on addressing the effects of lead on the environment as well as the possible negative consequences of recommending a lower lead NAAQS. Specifically, we are concerned that as EPA focuses on air-borne lead concentrations, it draws attention away from the more direct and pervasive pathways of oral ingestion. Additionally, EPA should be very certain before drawing associative conclusions about lead exposure and neurological effects. The decisions of the EPA reach the public in a way that the vast majority of the scientific literature does not.

The EPA's request for comment on the draft ISA is impracticable given the short comment period allowed for review of relevant data.

The assessment of the health hazards associated with airborne lead (Pb) has significant regulatory implications. The 60-day comment period, which spans several major holidays, does not allow regulatory agencies and stakeholders to provide the most thorough and meaningful comments possible based on an in-depth review and analysis of the 1,762-page third draft ISA and plethora of associated citations. If EPA seeks detailed, meaningful public input and technical comments, the comment period for future documents should be extended to allow stakeholders to perform a more complete review of the relevant information and provide more detailed and specific comments regarding issues identified in the draft ISA. In addition, it would be extremely helpful if EPA would highlight sections of the document that were modified from earlier drafts.

The draft ISA often lacks transparency and would benefit from a more specific and structured approach when applying weight of evidence to causal determinations.

The framework for causality detailed in the Preamble discusses the Bradford Hill aspects as they apply to causality determinations. However, it is not clear how EPA applies the Bradford Hill aspects or how all aspects are considered as a whole. For example, the ISA says the strength of an association should be considered, but it provides no definition of what constitutes a strong association. Most associations in the cited epidemiology studies are weak, and because of the limitations inherent in such observational studies and limitations of applied statistical methodologies (e.g., multiple testing), findings could be due to chance. The ISA also does not

describe how it evaluates alternative hypotheses or what criteria are utilized to determine which hypothesis is most supported by the data.

With regard to the application of the framework, it appears that studies are not always evaluated in a consistent manner. Studies with the most rigorous methods should, appropriately, be given the greatest weight in an analysis, but it is not clear in the framework how individual studies are weighted. In general, the ISA highlights positive associations and often omits discussions of non-significant or negative associations, making results seem more consistent than they may be. Figures and tables throughout the ISA describe the results from various epidemiology studies which are of limited utility by virtue of their observational design and often lack statistical significance, but draw conclusions supporting causality based on the same. Given the reliance on observational data it is appropriate to include a discussion of the importance (or lack thereof) of statistical significance in observational epidemiology studies utilized to support the conclusions drawn in the ISA.

Within the draft ISA there is discussion of studies that have examined Pb doses and/or modes of action that are not pertinent to the environmentally-relevant low dose exposures to Pb. Given the acknowledgement (p. 5-246 line 35) that high and low dose exposures to Pb work by different modes of action, studies that expose animals or cells to very high doses of Pb not relevant to low level human exposure (e.g., rats exposed to 10,000 ppm in drinking water[1]) should be omitted or clearly noted with regard to their questionable ability to inform NAAQS determination. Similarly, epidemiologic studies are frequently enumerated throughout Chapter 5 without systematically discussing their relative strengths and limitations. Finally, additional discussion in Chapters 1 and 2 of remaining uncertainties, potential biases, and critical gaps in knowledge is necessary to provide the most accurate description to readers.

The estimated slopes for blood-to-air Pb relationships in humans in the draft ISA are not appropriate for current Pb exposure scenarios for the general public.
Blood Pb is a biomarker of Pb exposure. Therefore, blood Pb is associated with both air-related and non-air-related (e.g., dietary, soil/dust) exposure. The TCEQ agrees with the following text (emphasis added) from the draft ISA regarding the limitations of regression modeling for blood Pb concentration estimation from air Pb: *"However, regression models are based on (and require) paired predictor-outcome data, and,* ***therefore, the resulting predictions are confined to the domain of observations and are typically not generalizable to other populations.*** *Regression models also frequently exclude numerous parameters that are known to influence human Pb exposures (e.g., soil and dust ingestion rates) and the relationship between human exposure and tissue Pb levels, parameters which are expected to vary spatially and temporally.* ***Thus, extrapolation of regression models to other spatial or temporal contexts, which is often necessary for regulatory applications of the models, can be problematic.*** *" (Section 4.5)*

Based on these considerations, some of the studies selected in the summary of estimated slopes for blood-to-air Pb relationships in humans (Table 4-12 in the draft ISA) are not appropriate for current Pb exposure scenarios for the general public (children or adults) due to the study Pb sources and/or populations (e.g., leaded gasoline, workers, other countries) and limitations of

[1] page 5-10 line 4

regression models (e.g., exclusion of important parameters). Brunekereef (1984) specifically concluded in the meta-analysis of 19 studies that adjustment for confounders has been absent or incomplete in most, if not all, studies; therefore most estimations of blood Pb to air Pb relationships must be viewed with caution. Living circumstances (e.g., older homes with Pb-based paint), hand-to-mouth activity, child play habits/locations, etc., all serve to modify blood Pb as an indicator of exposure from all sources (Brunekereef 1984). Because confounders have not been taken into account and/or adequately adjusted for, these estimations of blood Pb to air Pb relationships cannot be used to develop a NAAQS which is scientifically-defensible. In fact, the draft ISA states that the coefficients shown in Table 4-13 are likely to overestimate the contribution of Pb from air to blood Pb concentrations.

Inhalation of Pb in ambient air is a minor source of Pb exposure compared to exposure by other routes.

Because air is a minor pathway for childhood Pb exposure when compared to other exposure routes, more strictly regulating Pb in air accomplishes little in terms of real risk reduction when compared to potential interventions targeting food, water, or household dust contaminated with lead paint. Typical child Pb intake from air is approximately 1.3E-02 µg/kg-day.[2] By contrast, typical child (1-6 year old) Pb intake from food is 150 times higher at 1.95 µg/kg-day (see Table 6-9 of ATSDR 2007). Similarly, typical (6 year old) Pb intake from drinking water is about 11.9 µg/day (see p. 366 of ATSDR 2007), which corresponds to a dose of 5.5E-01 µg/kg-day that is 42 times higher than that from air.[3] Child intake from air exposure is considerably less than intake from normal background Pb levels in soil and household dust. For example, using the estimated median background soil Pb concentration for Texas (15 mg/kg [4]), the corresponding central tendency Pb intake from soil and dust Pb for a 3-6 year old child (8.9E-02 µg/kg-day) is 7 times that from air.[5] For a 1-2 year old child, the central tendency Pb intake from soil and dust would be about 1.45E-01 µg/kg-day, which is a dose about 5 times higher than that for air exposure for a 1-2 year old of 2.86E-02 µg/kg-day.[6]

Thus, normal childhood Pb intake through food, drinking water, and soil/dust appears to be several orders of magnitude higher than typical Pb exposure through air. Given current childhood Pb exposure through air is approximately 200 times less than normal intake from other sources (e.g., food, water, soil/dust) it is highly unlikely that significant risk reduction would result from more restrictive air regulations. Moreover, EPA's Integrated Exposure Uptake Biokinetic (IEUBK) model for Pb in children supports this conclusion. When air concentrations of 0.15 µg/m^3 and 0.015 µg/m^3 are compared, using typical background soil Pb concentrations (i.e., 15

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[2] Average nonpoint source Pb air concentration of 0.02 µg/m^3 x 10 m^3/day x 1/15 kg child body weight = 1.3E-02 µg/kg-day.

[3] 11.9 µg/day x 1/21.7 kg 6 year old child body weight = 5.5E-01 µg/kg-day.

[4] Source: "Background Geochemistry of Some Rocks, Soils, Plants, and Vegetables in the Conterminous United States", by Jon J. Connor, Hansford T., Shacklette, et al., Geological Survey Professional Paper 574-F, US Geological Survey.

[5] 15 mg Pb/kg soil x 1 kg/1E+06 mg x 50 mg soil intake/day x 1/18.6 kg 3-6 year old child body weight + 15 mg Pb/kg dust x 1 kg/1E+06 mg x 60 mg dust intake/day x 1/18.6 kg 3-6 year old child body weight = 8.9E-02 µg/kg-day from soil and dust.

[6] 0.02 µg/m^3 x 8.0 m^3/day x 1/5.6 kg 1-2 year old child body weight = 2.86E-02 µg/kg-day.

mg/kg), the maximum predicted blood Pb level decreases by 0.2 μg/dL.[7] More importantly, at the current NAAQS the mean predicted blood lead level (1.02 μg/m^3) is significantly less than the 5 μg/dL blood lead reference value, and less than 0.04% of the population would be expected to exceed this value.[8]

Many studies included the draft ISA are inadequate to provide causal determinations.
While the toxic effects of exposure to high doses of lead have been known for centuries, the effects of low levels of lead exposure continue to be investigated. Many of the health outcomes reported in the draft ISA have complex etiologies (e.g., intelligence and academic performance) and uncertain dose-response relationships. Additionally, important confounders in epidemiology studies must be considered in the study design and adjusted for, otherwise the resulting health effects assessment for Pb will most likely be inaccurate. The draft ISA does not provide a study-by-study discussion of whether inclusion criteria were met, even for the studies ultimately utilized, leading to uncertainty as to whether these studies met such criteria. For example, Min et al. (2009) was included in the studies of associations of blood Pb levels with full-scale IQ (FSIQ) among children (Figure 5-2 and Table 5-3 in the draft ISA), but this study has many significant confounding variables. Children were exposed prenatally to multiple drugs including alcohol (77%), cigarettes (61%), cocaine (51%), and marijuana (31%).[9] Additionally, 4% of the study children had iron deficiency anemia, which has been associated with decreases in IQ (Bellinger 2011). This study should not be identified as sufficiently informative under Table 1, since there are many potential confounding factors associated with blood Pb levels and FSIQ.

The potential contribution of low blood lead levels to IQ is minimal in comparison to the effect of other covariates.
The relationship between exposure to high levels of Pb and various neurobehavioral indicators has long been recognized, yet the nature of that relationship and the importance of additional confounding variables continues to be debated. Reasons for the remaining controversy over the Pb–IQ link include: 1) the large number of confounders that must be considered when measuring an effect on children's intelligence; and 2) the frequent finding that the more covariates included in regression models, the smaller the effect of blood Pb level on IQ becomes (e.g., Bellinger and Dietrich 1994, Cooney 1995, Ernhart 1995).[10] This observation suggests that the 2-7 point decrement in IQ attributed in much of the literature to Pb exposure may result from residual confounding. The most important confounders are socioeconomic status (SES), parental IQ, parental education, and the quality of the home environment. Other factors associated with both IQ and blood lead level include sex, nutritional status, past history of ear infection, parental

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[7] Using IEUBKwin32 Version 1.1 Build 11, for 0.15 μg/m^3 the maximum predicted BLL is 1.2 μg/dL, while the maximum predicted BLL is 1.0 μg/dL for 0.015 μg/m^3.
[8] For 0.15 μg/m^3 Pb in air: the predicted geometric mean is 1.022 μg/dL and 0% of the population is predicted to exceed 10μg/dL, while 0.037% of the population is predicted to exceed 5μg/dL. For 0.015 μg/m^3 Pb in air: the predicted geometric mean is 0.907 μg/dL and 0% of the population is predicted to exceed 10μg/dL, while 0.014% of the population is predicted to exceed 5μg/dL.
[9] Exposure to these drugs would be expected to confound the relationship between Pb and IQ – see Koller et al 2004.
[10] Note that this it is also true for the key study by Lanphear et al. (2005) in Table 4 when comparing the unadjusted versus adjusted estimates, the adjusted estimates in every case are smaller.

smoking behavior, and paternal IQ (Koller et al. 2004). There is little doubt that socio-demographic factors affect intellectual development directly. However, they may also affect exposure to Pb, thereby confounding the association between Pb exposure and neurological effects.

Clearly, efforts must continue to mitigate childhood exposure to high levels of Pb, especially in populations with multiple risk factors for neurocognitive impairment, such as low SES. However, these efforts should be seen in perspective. The magnitude of the uncertain Pb-IQ dose-response relationship at low doses is small on a population basis and should be set against the far greater combined effect of SES as well as quality and stability of the home environment. Lead exposure (from all sources) accounts for a very small amount of variance in cognitive ability (1-4%) at most, whereas covariates such as social and parenting factors account for 40% or more (Weiss 2000). Moreover, it has been argued that, instead of *"chasing after an ever-receding Pb threshold,"* attention and funds should be focused on *"the more complex social ills that are associated both with continued Pb exposure and neurocognitive impairment in a small segment of the population"* (Gee and McKay 2002).

Subclinical effects of lead exposure have uncertain public health significance.
Section 2.9 of the draft ISA suggests that low levels of Pb exposure in ambient air continue to pose a significant public health threat, and if not addressed will exert downward pressure on the population-wide IQ. It is generally agreed that exposure to Pb is one component of a multitude of factors acting on IQ, and that Pb exposure accounts for a small proportion of variance in cognitive ability (1-4%) while social and parenting factors account for 40% or more (Weiss 2000). However, it is not clear that IQ decrements too small to be clinically significant for any particular individual (i.e., within the standard error of the test) can logically result in effects on the population as a whole vis-à-vis increases in number of individuals above or below a certain IQ score. The draft ISA would benefit from further discussion on this point.

Public health efforts to reduce exposure to lead in the general population have been and continue to be successful as evidenced by the observation that the vast majority of children have blood Pb level values well below both the 10 μg/dL level of concern previously set by the CDC as well as the recently adopted 5 μg/dL reference value.[11] In fact, the most recent data available from the CDC indicates that the geometric mean blood Pb level for children ages 1–5 is 1.17 μg/dL, with a 95th percentile of 3.37 μg/dL, and 1.21 % having blood Pb values ≥10 μg/dL.[12] Thus, significant changes in IQ and behavior would not be expected in the U.S. population as a whole.[13] However, the hypothetical analysis in Figure 2-1 implies that the public health

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[11] CDC Advisory Committee for Childhood Lead Poisoning Prevention January 2012 (http://www.cdc.gov/nceh/lead/ACCLPP/activities.htm)

[12]CDC- NHANES Fourth Report on Human Exposure to Environmental Chemicals, Updated Tables, September 2012 and Biomonitoring Summary at http://www.cdc.gov/biomonitoring/Lead_BiomonitoringSummary.html

[13] These results show that public health efforts to reduce exposure to lead in the general population have been and continue to be successful. However, certain populations of children are at higher risk for lead exposure (e.g., children living in homes containing lead-based paint) and lead exposure remains a concern for these specific populations. Note that the sources in footnote 9 do not provide data for percent of the population exceeding 5 μg/dL.

significance of small[14] change in blood Pb level is an increase in the number of individuals with an IQ below 70 (considered a disability by the US Social Security Administration). This figure is also based on the assumption that the impact of Pb exposure is the same across the entire range of IQ, which is unknown. Nevertheless, no evidence for this assertion is provided, and to the contrary Newschaffer et al. (2005) report no increase in this demographic over time. Therefore, the concern that population-wide declines in IQ will occur at current blood Pb levels is currently unsupported, especially given the (limited) data available that suggest the opposite trend is occurring (i.e., the Flynn Effect, Flynn and Weiss 2007).

Some key studies utilized by EPA in the draft ISA are inadequate to demonstrate that neurological effects are causally associated with blood Pb levels as low as 2 µg/dL in children. In response to the second draft of the ISA, one reviewer[15] noted that at increasingly low levels of Pb, blood Pb can still be measured with reasonable accuracy. However, other stronger variables such as maternal education or the impact of the child's home environment can be more difficult to measure and are subject to reporting errors. Moreover, SES and related variables are often entered as broadly categorical variables, while Pb is a continuous variable. Furthermore, at lower Pb levels, the effect of confounding may increase. The significant uncertainty introduced by studies not accounting or sufficiently adjusting for important known confounding factors are significant. For these reasons it is not clear that, at these low levels, effects that have been attributed to Pb are fully caused by Pb.

The issue that continues to elicit the most debate is the plausibility of a low-dose supralinear relationship between Pb and decrements in IQ. Explanations proposed to date regarding the shape of the dose-response cannot address residual confounding due to variable omission from study design. For example, though maternal data is often collected, results for paternal IQ, education, and SES are seldom reported. There is also limited availability of relevant medical history, such as childhood ear infections. The TCEQ agrees with the statement in the draft ISA that *"explanations for this supralinear relationship have not been well characterized by epidemiologic studies,"* but disagrees that toxicological studies currently available adequately support a nonlinear relationship. Studies such as those outlined in section 5.3.11 do not uniformly describe a supralinear relationship between Pb exposure and neurological effects. Moreover, the TCEQ agrees with Koller et al. (2004) who summarize the state of the research as follows: *"Mechanistically, no unifying theory explains the neurotoxicity of lead or how lead might affect cognition."*

The available evidence addressing the biological basis of a supralinear relationship in humans is minimal and questions remain regarding the veracity of this phenomenon. Some researchers suggest this is potentially a statistical artifact (Bowers and Beck 2006), and other explanations have been proposed including omission of confounding variables from study design, interaction of SES and home factors or bias in study population recruitment (Weiss 2000, Ernhart 2005, Kaufman 2001). The key study discussed in this section is the meta-analysis by Lanphear et al. (2005) relating blood lead level to FSIQ in children. This analysis, involving > 1,300 children

[14] The draft ISA states "As described in Section 5.3.2.1, most studies found that a 1 µg/dL increase in blood Pb level was associated with decrements in FSIQ in school-aged children in the range of <1 to 2 points…"
[15] Michael Rabinowitz

who participated in seven international prospective studies, identified a supralinear relationship over the range of 2.4–30 μg/dL. We note with interest that the current geometric mean blood Pb level for children ages 1–5 in the NHANES dataset is 1.17 μg/dL. Therefore, it is not clear that the specific dose-response identified in this study applies to the general population of the U.S. at contemporary blood Pb levels.

The studies included in the draft ISA have not demonstrated that Pb exposure is a causal factor in the increased frequency of attention deficit hyperactivity disorder (ADHD) in children.

A recent analysis of National Health and Nutrition Examination Survey (NHANES) 1999-2002 data cited by the draft ISA (5.3.3.4 - Braun et al. 2006) reported associations between blood Pb level and ADHD (parent-report of a diagnosis of ADHD or use of stimulant medication). However, the associations were not statistically significant.[16] Using the same NHANES dataset, restricting children ages to 8-15 years, Froehlich et al. (2009) found that prenatal tobacco smoke exposure and blood Pb levels are associated with ADHD, although prenatal tobacco smoke exposure was the greater risk factor. However, both studies have an important limitation due to their inability to adjust for parental psychopathology, which is one of the most important confounders in studying the associations of ADHD and environmental risk factors, since ADHD heritability has been estimated to be approximately 75% (Biederman and Faraone 2005). Therefore, for diseases with a complex etiology such as ADHD, confounding factors must be considered and adjusted for when attempting to elucidate any association, statistical or causal, between blood Pb exposure and ADHD.

Since Pb was phased-out of gasoline nationwide in 1996, the ambient air Pb concentrations have declined significantly as have the blood Pb concentrations in children. However, according to Centers of Disease Control and Prevention, rates of ADHD diagnoses have increased an average of 3% per year from 1997 to 2006 and an average of 5.5% per year from 2003 to 2007 (CDC-MMWR 2010). Significant decreases in child Pb exposure are inconsistent with concurrent increases in ADHD prevalence, and suggest that Pb exposure is not the key cause of ADHD.

Specific Comments

The expanded Table 1-1 is greatly improved from the second draft and highlights some important uncertainties with specific endpoints and indicates areas where additional data would be helpful.

Given the discussion on page lxiv regarding the difficulty of detecting thresholds in population-level data, the statement on page 1-8 on line 19 should contain a caveat to this effect.

Chapter 1 is admirable in its succinct description of an immense amount of literature. However, the evidence is, understandably, oversimplified and in many areas appears to underreport uncertainty and variability in the available data, especially as it pertains to specific environmentally-relevant doses. For example, CASAC has previously commented on the

[16] In Braun et al. Table 1 – overall p-value for lead: p=0.19

inconsistency in the literature with respect to renal effects, the potential contribution of reverse causation, and the paucity of toxicological studies that identify a mode of action for this end point, all of which should temper the causal inference for renal effects.

In Chapters 1 and 2, the section addressing effects of Pb exposure in children (page 1-8 and again at 2-16) seem to imply that deficits have been well-established for blood Pb levels as low as 2 μg/dL. Presumably the key study here is Lanphear et al. 2005, although neither Chapter 1 nor the referenced section 2.6.1.1 include citations for this point. In this study, the levels ranged from 2.5 to 33.2 μg/dL. Blood Pb levels were associated with deficits in IQ when comparing the 5th to the 95th percentiles in this dataset. Based on these results, it is not clear that levels as low as 2 μg/dL are associated with decrements in IQ. Additional discussion of this point in each of these locations would be helpful.

Chapter 4.1 states *that "...detectable quantities of Pb have still been observed to be bioacessible in various media types."* This is to be expected as Pb is a naturally occurring metal, however this point is not clear in this section of the ISA.

Page 4-138 on line 9 *"respectfully"* should read *"respectively"*.

In Table 5-1 include an additional column that indicates the experimental doses of Pb necessary to achieve the reported effect as well as the corresponding estimated blood Pb level.

Page 5-39 on line 11: include information regarding the relative toxicity of the various forms of inorganic Pb.

It is not clear how the data described in section 5.2.7.1 which is characterized as "equivocal" supports the statement in the summary on page 5-39, which states: *"Overall, evidence indicates that in vitro or in vivo exposure to various Pb compounds can increase risk of genotoxic effects, including DNA damage, clastogenicity, and mutagenicity."*

Page 5-60 on line 25, there are a number of other studies that should be mentioned here and represented in Tables 5-2 and 5-3 in order to give a more accurate depiction of the number of null studies and to give the appearance that the null data was given appropriate weight:

McBride et al. 1982 Med J Aust Jul 10;2(1):26-9
Smith et al. 1983 Dev Med Child Neurol Suppl. 47:1-54
Lansdown et al. 1986 Int Arch Occup Environ Health 57(3):225-35
Earnhart et al. 1987 May-Jun;9(3):259-70
Ernhart et al. 1989 Neurotoxicol Teratol. Mar-Apr;11(2):161-70
Ernhart and Greene. 1990 Arch Environ Health 45(6):342-54
Bellinger et al. 1992 Pediatrics 90:855-861 (for ages other than 24 months)
Wolf et al. 1994 J Dev Behav Pediatr Aug;15(4):224-31
Minder et al. 1998 J Learn Disabil Sep-Oct;31(5):494-502
Prpić-Majić et al. 2000 Cent Eur J Public Health 2000 Jul;8 Suppl:69

While it may be true that *"The few weak or null associations do not mitigate the otherwise strong evidence provided by other studies"* (page 5-67) the studies listed in this section of the ISA together with those listed above may provide useful lower bounds for risk estimates in the forthcoming Risk Assessment.

In section 5.3.2.1 the discussion of Lanphear et al. 2005 is critical, because this will probably be the key study going forward in the NAAQS review process. The text describing this study on pages 5-67 and 5-68 should address two issues raised by the author of one of the included studies (Ernhart EHP 2006 letter to editor): (1) the groups with peak blood lead levels ≤10 or 7.5 μg/dL were reportedly significantly different from the remainder of the study population based on race, maternal age, use of cigarettes and alcohol during pregnancy; and (2) there was no significant association of IQ and three of the four indices of lead exposure for the populations with peak blood Pb levels ≤10 or 7.5 μg/dL.

The last sentence on page 5-70 should be revised because the Cleveland cohort had comparable prevalence of prenatal alcohol use to the Boston cohort. Therefore, this statement is not accurate. This also applies to lines 15 and 16 of page 5-75, where it seems somewhat biased to point out the 50% incidence of alcohol use among mothers in the Cleveland cohort (null study) without mentioning the 52.6% incidence in the Boston cohort (positive study).

The caveats mentioned for the Miranda et al. 2007 study on page 5-112 should be repeated earlier in the discussion of the same study on page 2-28.

The statement on page 5-117 line 22 regarding confounding should be balanced by acknowledgment that other studies have found parental smoking to be an important confounding variable (e.g., Tong and Lu 2001).

Throughout the document "parental IQ" should be replaced with "maternal IQ" which better reflects the fact that cited studies report maternal, but not paternal IQ.

Table 5-17 and similar tables throughout Chapter 5 of the draft ISA are valuable additions because they summarize the evidence supporting the causal determinations. These could be further improved by indicating which studies were given greater weight, which had statistically significant results versus those that did not, the strength of the reported effect, and how uncertainties were incorporated in this weight of evidence determination.

In Section 5.4.5, it appears that the ISA determined the evidence was inadequate to infer a causal relationship for mortality. If so, it would be helpful to explicitly state this at the end of this section and also include in tables 1-1 and 2-2 in order to be consistent and transparent in causal determinations across the ISA.

Page 5-353 Lines 35 and 36: was this sentence intended to be a place-holder? It appears quite general and perhaps the authors intended to replace this with a more rigorous description of the *"usual caveats regarding population comparison mortality studies."*

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