Texas Commission on Environmental Quality's (TCEQ) Comments to the U.S. Environmental Protection Agency's (EPA) The Second External Review Draft of the Integrated Science Assessment for Lead Docket ID No. EPA-HQ-ORD-2011-0051

On February 2, 2012, the U.S. Environmental Protection Agency (EPA) published a Federal Register notice (Federal Register doc. 2012-2327) of a 60-day public comment period (ending April 2, 2012) for the, "Second External Review Draft of the Integrated Science Assessment for Lead," hereafter referred to as the draft ISA (EPA/600/R-10/075B). 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 including Ambient Lead: Source to Concentration and Integrated Health Effects of Lead Exposure – Nervous System Effects.

General Comments

The EPA's request for comment on the draft ISA is unreasonable 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 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 1,467-page second draft ISA and plethora of associated citations. Given the limitations of time and personnel, the comment period only allows a superficial review of the draft ISA at best, and leads to a less-than-desirable level of transparency and peer review, undermining confidence in the process. Consequently, TCEQ is only able to provide comments based on a cursory review. If EPA seeks detailed, meaningful public input and technical comments, the comment period should be extended to allow stakeholders to perform a more complete review of the relevant information and provide more detailed and specific comments regarding problematic issues associated with the draft ISA.

The draft ISA frequently lacks transparency and would benefit from a more specific and structured approach.

Within the draft ISA there is frequent discussion of studies that have examined Pb doses and/or modes of action that are not relevant to the actions of Pb potentially associated with low-dose human health effects. Studies that expose animals or cells to high doses of Pb not relevant to low level human exposure should be omitted or clearly noted with regard to their questionable ability to inform NAAQS determination. Similarly, epidemiologic studies are frequently enumerated without commentary addressing their relative value. There is often an appearance of multiple studies on a topic when, in fact, studies represent slight variants on analyses in the same population. This is generally not discussed. Furthermore, there is a failure to adequately describe uncertainties, biases, and gaps in knowledge, resulting in conclusions based on tenuous, speculative, or poorly-characterized studies.

There is one over-riding issue that is especially problematic: associations are frequently confused for causations. The choice of studies undermines the "causal" determinations asserted. Simply enumerating the ecological epidemiology studies that report associations between Pb and effects of interest does not demonstrate causality. There is little to no discussion of study quality or limitations, and data is often presented as if there is no ongoing debate within the field of study. This is especially apparent in the discussion of Pb exposure and intelligence quotient (IQ), where there continues to be uncertainties related to the frequency, timing, duration, and level of Pb exposure that may contribute to health effects. The ISA engages in the logical fallacy of *post hoc, ergo propter hoc*: simply knowing that a child has had elevated Pb level and also has deficits on neuropsychological testing does not mean knowing that Pb caused those deficits (Hebben 2001). It is clear that IQ is a malleable measure of global neurological function and is determined by a complex milieu of factors including genetics, maternal IQ, environment, education, and enrichment. Moreover, the TCEQ agrees with the following conclusion from the draft ISA regarding the plasticity of IQ:

> *"Collectively, these results suggest that cognitive development is not fixed early in childhood and can be affected negatively or positively by postnatal influences."*

Therefore, due to the inherent plasticity of IQ, it is difficult to conclusively link exposure to ambient levels of air-borne Pb and potential changes in IQ.

Ambient Lead: Source to Concentration

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.***

Based on these considerations, none of the studies selected in the summary of estimated slopes for blood-to-air Pb relationships in humans (Table 4-11 in the draft ISA) are 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 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). The TCEQ would add that since 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.

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

Air is a very minor pathway for childhood Pb exposure. Therefore, more strictly regulating Pb in air accomplishes little in terms of real risk reduction. Typical child Pb intake from air is approximately 1.3E-02 µg/kg-day.[1] By contrast, typical child (1-6 year old) Pb intake from food is 150 times higher at 1.952 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.[2] Child intake from air exposure also pales in comparison to 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[3]), 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.[4] 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.[5]

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 1.5 µg/m^3 and 0.15 µg/m^3 are used with typical background soil/dust Pb concentrations (e.g., 15 mg/kg), the geometric mean of blood Pb decreases by 1.2 µg/dL. More importantly, in both cases the mean predicted blood Pb level is significantly less than the 10 µg/dL blood Pb level of concern.[6] In fact, 0.05% or less[7] of children 0.5-7 years of age would be predicted to have blood Pb level exceeding this level of concern.

Integrated Health Effects of Lead Exposure - Neurological effects

Studies included the draft ISA are inadequate to provide causal determinations.

Since many of the health outcomes reported in the draft ISA have complex etiologies (e.g., intelligence and academic performance), important confounders in epidemiology studies must be considered in the study design and adjusted for, otherwise the dose-response assessment for Pb is most likely 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

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[1] 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.

[2] 11.9 µg/day x 1/21.7 kg 6 year old child body weight = 5.5E-01 µg/kg-day.

[3] 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.

[4] 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.

[5] 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.

[6] For 1.5 µg/m^3 the maximum predicted BLL is 2.17 µg/dL; for 0.15 µg/m^3 the maximum predicted BLL is 1.0 µg/dL.

[7] For 1.5 µg/m^3 Pb in air 0.054% of the population is predicted to exceed 10µg/dL; 0.15 µg/m^3 Pb in air 0% of the population is predicted to exceed 10µg/dL.

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 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%). 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 blood lead levels to IQ is minimal in comparison to the effect of other covariates.

The existence of a relationship between Pb and various neurobehavioral indicators has long been recognized, yet the nature of that relationship continues to be debated. Reasons for the 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 (Bellinger and Dietrich 1994, Cooney 1995, Ernhart 1995). 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 smoking behavior, and paternal IQ (Kaufman 2001). Although there is no doubt that socio-demographic factors affect intellectual development directly, they may also affect exposure to Pb, thereby confounding the association between Pb exposure and neurological effects. If two or more independent variables (risk factors) are strongly correlated, it is difficult to determine how much of the variation in the dependent variable (intellectual abilities) to allocate to each of the various risk factors (Needleman 2001).

Clearly, efforts must continue to mitigate childhood Pb exposure. 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 status 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). 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 with continued Pb exposure in a small segment of the population" (Gee and McKay 2002). The TCEQ agrees that the money spent attempting to comply with this overly-stringent NAAQS would be better spent in other areas.

Subclinical effects of lead exposure have uncertain public health significance.

Section 2.9 of the draft ISA suggests that low levels of Pb exposure continue to pose a significant public health threat, and if not addressed will exert downward pressure on the population-wide IQ. First, exposure to Pb accounts, at most, for a very small proportion of variance in cognitive ability (1-4%) while social and parenting factors account for 40% or more (Weiss 2000). Furthermore, the vast majority of children have blood Pb level values well below both the 10 μg/dL level of concern currently set by the CDC as well as the recently proposed 5 μg/dL level of concern[8]. In fact, the geometric mean blood Pb level for children ages 1–5 is 1.51 µg/dL, with 1.4 % having blood Pb values ≥10 µg/dL[9]. Thus, significant changes in intelligence and behavior would not be expected in the U.S. population as a whole. However, Table 2.6 implies that the clinical significance of a 1 µg/dL increase in blood Pb level and the purported <3 point decrement in FSIQ score is an increase in the number of individuals with an IQ below 70 (considered a disability by the US Social Security Administration). 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 assertion that population-wide decline in IQ is occurring is alarmist, especially given the wide acceptance that the opposite trend is occurring (i.e., the Flynn Effect, Flynn and Weiss 2007).

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 first draft of the ISA, one reviewer[10] noted that at increasingly low levels of Pb, blood Pb can still be measured with reasonable accuracy (often to 2 significant figures). However, other stronger variables such as maternal education or richness 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. The significant uncertainty introduced by studies not accounting or sufficiently adjusting for important known confounding factors cannot be overstated. For these reasons scientists should be skeptical that, at these low levels, effects that have been attributed to Pb are fully caused by Pb.

The issue that elicits the most debate is the biological plausibility of low-dose supralinear relationship between Pb and loss of IQ points. Explanations proposed to date regarding the shape of the dose-response cannot address residual confounding due to variable omission from study design. Specifically, though maternal data is often collected, paternal IQ, education, and SES are seldom reported. There has also been a failure to collect 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 nonlinear relationships. Studies such as those outlined in section 5.3.10 do not uniformly describe a supralinear relationship between Pb exposure and neurological effects. Moreover, 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 (Kaufman 2001).

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 (Braun *et al.* 2006) found a positive relationship between blood Pb

[8] CDC Advisory Committee for Childhood Lead Poisoning Prevention January 2012 (http://www.cdc.gov/nceh/lead/ACCLPP/activities.htm)
[9] CDC- NHANES Fourth Report on Human Exposure to Environmental Chemicals, Updated Tables, February 2012
[10] Michael Rabinowitz

level and ADHD (parent-report of a diagnosis of ADHD or use of stimulant medication). However, the associations were not statistically significant (Table 5-10 in the draft ISA).

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.

Summary
Current typical airborne Pb exposure for children (the sensitive population) is insignificant compared to normal exposure by other routes, and promulgation of increasingly stringent NAAQS for Pb will not significantly improve protection of public health from Pb toxicity, only create more burdensome and costly regulations. This is confirmed by results from EPA's own IEUBK model for Pb in children, which show that predicted mean blood Pb levels of children are not expected to exceed the blood Pb 10 µg/dL level of concern (or even the newly recommended 5 µg/dL, which is based on the 97.5th percentile of NHANESIII dataset[11]) using typical background soil/dust Pb concentrations and either a Pb NAAQS of 1.5 µg/m^3 or 0.15 µg/m^3.

Neurological effects such as IQ loss or poor academic performance depend on a multitude of factors. In such circumstances, epidemiology studies are limited in their ability to accurately identify and quantify adverse effects and have not adequately controlled for potential confounding by variables such as parental IQ, socioeconomic status, parent education, developmental delays, alcohol/drug use, and the home environment. Consequently, when the health outcomes of concern have complex etiologies and confounders have not been adequately adjusted for, a scientifically defensible and accurate dose-response assessment is unlikely. This is certainly the case for Pb-exposure and potential neurological effects.

Finally, the EPA should acknowledge that the dramatic decreases in ambient air Pb and children's blood Pb levels are inconsistent with their suggestion that Pb is a causal factor in the increased frequency of ADHD. The significant decreases in child Pb exposure are inconsistent with concurrent increases in the prevalence of ADHD. Moreover, the assertion that population-wide decline in IQ will occur if Pb levels in air are not further decreased is alarmist, as there is a general consensus that the opposite trend is occurring (i.e., the Flynn Effect).

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

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