

04-09-12 Preliminary Draft Comments from Clean Air Scientific Advisory Committee (CASAC) Lead Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

**Preliminary Comments from Dr. Michael Kosnett on
EPA's Integrated Science Assessment for Lead
(Second External Review Draft – February 2012)**

The following are my preliminary comments on the 2nd external draft Integrated Science Assessment for Lead (February 2012) prepared prior to the CASAC Lead Review Panel meeting in April 2012. They are subject to further revision as I continue my review and analysis of the document. These comments focus on Chapter 2, the Integrative Summary.

Key elements of the CASAC Lead Review Panel report on the 1st External Review Draft of the Integrated Science Assessment for Lead included a recommendation that the ISA improve its approach to causation assessment for the health effects of lead. Specifically, the CASAC report (December, 2011) recommended, “With respect to human health endpoints, a rigorous weight-of-the-evidence assessment is needed that transparently applies the criteria for the strength of evidence for causation” and “This weight-of-the-evidence assessment should be applied to specific health endpoints, in addition to broadly assessing impacts on whole organ systems.” I respectfully feel that the 2nd draft ISA has failed to satisfactorily address these major recommendations.

The “causation determinations” summarized in Chapter 2 continue to address broad organ system findings, without specifically focusing on key health endpoints within those endpoints. For example, in Section 2.6.2 (Cardiovascular Effects) page 2-18, the narrative states, “Collectively, the evidence integrated across epidemiologic and toxicological studies as well as across the spectrum of other cardiovascular endpoints examined is sufficient to conclude that there is a causal relationship between Pb exposures and cardiovascular health effects.” But the summary section on Cardiovascular Effects does not specifically indicate whether the endpoints subsumed under “Cardiovascular Effects” with respect to causality includes hypertension in adults, hypertension in children, cardiovascular mortality, or cerebrovascular mortality.¹ Nor, for virtually all the organ systems, have these causation determinations identified the magnitude of lead exposure that conclusively causes specific health effects. For a risk characterization document such as the lead AQCD to have optimal utility to risk managers and public health stakeholders, identification of specific health endpoints and the exposure (or dose) associated with causation are necessary. This is well illustrated by the narratives supporting the derivation of Reference Doses in EPA's IRIS database, which identify specific doses (e.g. LOELs) associated with specific health effects.

In addition to the lack of focus on specific health endpoints, the causation assessments included in the 2nd ISA fail to systematically address the causation criteria set forth in Table II of the preamble (p. Ivii). As stated in that table, a conclusion that a causal relationship exists between lead exposure and a human health effect requires that:

¹ In Summary Table 2-10, specific cardiovascular endpoints such as blood pressure, hypertension, and cardiovascular mortality are addressed, but the conclusion is limited to stating that the evidence supports “an association” between lead and these endpoints. As noted further in these comments, this terminology is ambiguous with respect to causal determination, which requires more than a summary finding of ‘association’.

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“...the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.”

The summary presentations in Chapter 2, and apparently most of those in Chapter 5, generally fail to present a critical analysis, in narrative terms, that addresses the adequacy with which the human epidemiological studies have ruled out the influence of bias and confounding, and the extent to which multiple high quality studies have reached consistent and replicate findings.

For example, with respect to “neurobehavioral effects” in children, Chapter 2 concludes, in Table 2-10:

Recent studies in children continue to support associations of Pb exposure with a range of effects, largely inattention and hyperactivity, and also misconduct delinquent behavior. In new studies, *the weight of evidence supports associations* with concurrent blood Pb in populations with lower mean blood Pb levels (2–5 µg/dL) than those in previous studies. New evidence indicates associations of concurrent blood Pb levels with ADHD diagnosis and contributing diagnostic indices in populations with mean blood Pb levels 2-4 µg/dL. [emphasis added]

The terminology in the foregoing paragraph, which is repeated frequently in other parts of Chapter 2 and Chapter 5, states that the “*weight of evidence supports associations*”. This phraseology is ambiguous, and fails to address the requisite elements of a “weight of the evidence” causation determination. A finding of an “association”, however strong, between lead exposure and a health endpoint in an epidemiological study is by itself inadequate to establish causation, particularly bias and confounding cannot be ruled out with reasonable confidence. As was stated in the CASAC report of December 2011:

“With respect to other [i.e. noncognitive CNS] endpoints in children, such as attention deficit hyperactivity disorder (ADHD), a more rigorous and transparent “weight of the evidence” analysis is recommended to establish the extent of any causal relationship. This analysis should devote more attention to the limitations of the existing studies with respect to consistency, reproducibility, bias, control for confounders, and shortcomings in statistical methodology.”

The discussion of neurobehavioral endpoints in Chapter 2 and Chapter 5 in the 2nd draft ISA continue to lack a sufficient critical discussion of such limitations. Contrary to the recommendations of the CASAC report, the tables that describe key studies addressing specific health endpoints have not been expanded to include a column that specifically addresses key limitations of each study. With respect to neurobehavioral endpoints in children, the narrative sections of Chapter 2 fail to note that virtually all of the studies of low level lead exposure have inadequately adjusted for parental psychopathology. This is a major limitation in studies of inattention in general and ADHD in particular, where epidemiological findings suggest that heredity accounts for 50 to 70 percent of the incidence. Accordingly, parental psychopathology, particularly parental ADHD or subclinical deficits in attention, merit major consideration as potential confounders. In contrast to most studies of the effect of lead on cognitive function in children, in which the influence of maternal intelligence is commonly adjusted for by

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including maternal IQ as a covariate in regression models, the studies of low level lead exposure and child behavior have been unable to include an acceptable measure of maternal or paternal inattentiveness or ADHD.² EPA's causation criterion requiring that confounding be ruled out with reasonable confidence has therefore not been satisfied.

EPA's causation criterion pertaining to "consistency" and "replication" by multiple high quality studies is likewise inadequately addressed in the narrative with respect to low-level lead exposure and behavioral endpoints. For example, neither chapter 2 nor the section 5.3.3 note that two major prospective studies of low lead level and child behavioral outcomes did not observe a significant association between lead and measures of attention (Wasserman et al, 2001; Canfield et al, 2003). In the prospective cohort study of Yugoslavian children in Pristina with BLL < 10 µg/dL studied by Wasserman et al (2001), blood lead was not significantly associated with either the attention subscale or the aggregate "externalizing" behavior score. In the prospective Rochester cohort of 4 to 5 year old children with mean BLL of 6.5 µg/dL studied by Canfield et al (2003), there were no significant associations in multivariable models between blood lead and performance on tasks of attention (see Table 2 in Canfield et al). In contrast, different studies conducted in these same cohorts have reported that low-level lead exposure was associated with decrements in cognitive function. Overall, the 2nd draft ISA has failed to present a critical review that distinguishes the well-validated causal relationship between low level lead exposure and cognitive function with the comparatively smaller and limited body of epidemiological evidence that has examined the relationship between lead and behavioral outcomes.

² The narrative in Section 5.3.3.1 comments that several of the studies of child behavior listed in Figure 5-14 and Table 5-9 have controlled for potential confounders such as SES and maternal IQ, while inexplicably failing to note the lack of adequate control for parental psychopathology. As demonstrated by Chen et al (2006), maternal IQ is not a significant covariate for child behavior. On page 5-127, the ISA narrative states, "While none of the studies examined the potential for confounding by HOME score, they did evaluate confounding by several other demographic and SES- related variables, as well as parental history of psychopathology, including ADHD (Cho et al., 2010; Nicolescu et al., 2010)." However, a careful assessment of these studies would raise substantial doubt as to the adequacy with which such potential confounding was in fact addressed. In the Korean study by Cho et al (2010), which in fact *failed* to report a consistent positive association between lead and indices of ADHD or attention in most of the measures that were examined, the adjustment for parental psychology consisted of having the parents of 590 children to note in a questionnaire whether they ever had ADHD or any other neuropsychiatric disorder. Implausibly, less than 5 percent responded affirmatively. Moreover, the variable was not included in the multivariable models. In the Romanian study by Nicolescu, parents were asked by telephone interview whether either had been diagnosed with "psychological/psychiatric problems." However, the extent of positive response was not reported, and even though "family psychopathology" was the factor with the *strongest* bivariate correlation with child ADHD rating by the parents, it was *not* included in the multivariable models of child attention or ADHD (see caption to Figure 2 in Nicolescu et al, 2010). The statement on page 5-132 of the 2nd draft ISA that refers to Nicolescu et al by stating, "Higher blood Pb level was associated with higher ADHD ratings in children in models with blood Pb level alone and in models that adjusted for parental psychopathology plus other covariates" is puzzling and should be corrected, because it appears to be contradicted by the details of the model reported in Figure 2 of that report. The narrative on page 5-132 also erroneously states, "It should be noted that for parental ADHD to be a confounder, parental Pb levels would have to be highly associated with ADHD in the parent and with blood Pb level in the child."

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As noted by Bellinger et al (1994), compared to models of cognition, models of behavioral outcome in children explain comparatively little of the overall variance (i.e. they have low R^2), raising the likelihood that even statistically significant associations may be relatively more vulnerable to residual confounding.³

In accordance with recommendations in the first CASAC report, sections of the 2nd draft SA in chapter 2 and chapter 5 pertaining to adverse effects of lead in adults appropriately note the effects cannot confidently be imputed to contemporary blood lead concentrations (i.e. < 10 µg/dL) because the populations in which they have been observed sustained higher blood lead concentrations in the past (i.e. general population BLLs of 10 to 25 µg/dL in the decades prior to 1980). Nevertheless for the endpoints of blood pressure, hypertension, and cardiovascular mortality, secular trends in blood lead and bone lead data would allow EPA to reasonably conclude that decades of blood lead concentration in the range of 10 to 25 µg/dL can cause elevated blood pressure and increased cardiovascular mortality in susceptible populations. The epidemiological data support this finding by virtue of consistent findings in multiple high quality studies that have adequately controlled for bias and confounding. In addition, toxicological and clinical data offer evidence of plausible biochemical mechanisms at this level of exposure.

The situation with respect to low level lead exposure and renal effects is quite different, and for this endpoint the 2nd draft ISA continues to lack a balanced and critical analysis of the strengths and limitations of the data. In its consensus response to charge questions, the first CASAC report (December 2011) noted with respect to the 1st draft ISA:

“In the case of renal effects, causal inferences are limited by the potential for reverse causation, inconsistency in the epidemiological observations, and the absence of a demonstrable nephrotoxic mode of action at a blood Pb concentrations 5 µg/dL....Failure to temper conclusions with study design limitations was particularly problematic for the review of the renal effects of Pb.”

These criticisms remain a major concern in the 2nd draft ISA. The summary section 2.6.3. “Renal Effects” essentially fails to acknowledge these limitations and concerns regarding the relevant literature. Chapter 5 addresses some of the concerns, albeit in a manner that would greatly benefit from a more balanced approach. Specifically, the new section, “5.5.2.5 Reverse Causality” appears to exist less as a critical analysis of the potential for reverse causation to explain (even partly) the inverse association of blood lead concentration and glomerular filtration rate, and more as a pointed attempt to refute its plausibility. This stands in contrast the comments on “reverse causation” put forth by authors of several key studies that have reported a significant BLL – GFR association. For example, in the discussion section of their longitudinal Normative Aging Study report on lead and serum creatinine, Kim et al (1996) state: “Our findings do not necessarily exclude the existence of an effect of impaired renal

³ The summary narrative in Chapter 2 and the expanded narrative in Chapter 5 fail to note other major limitations of many of the studies of the relationship between low-level lead exposure and behavioral problems in children. In contrast to the negative prospective studies of Wasserman et al (2001) and Canfield et al (2003), many of the “positive studies” are limited by a cross-sectional study design, combined with the fact that the single measure of blood lead available was obtained in late childhood. The cross-sectional design offers limited causal inference regarding low level lead exposure because it does not rule out that the possibility that a behavior problem preceded the development of an elevated BLL, and/or that BLL in early childhood may have exceeded the value measured in late childhood.

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function on levels of blood lead. In line with epidemiologic and toxicologic evidence that low-level lead exposure causes subclinical impairment of renal function is the physiologically plausible possibility that decreased glomerular filtration or decreased tubular excretion results in decreased excretion of lead. Further research is required to test the hypothesis of a bidirectional relationship.”

Unfortunately, the new section on “Reverse Causality” in the 2nd ISA offers no acknowledgement that such a bidirectional component remains an unanswered question. Similarly to the 1st draft ISA, the 2nd draft ISA dismisses the possibility of reverse causation in part by repeating the assertion that reverse causation is implausible because, “...the association was not limited to the segment of the population with potentially significant renal dysfunction in whom reduced Pb excretion would be more likely” (p 5-328). However, the 2nd ISA, like the first ISA, offers no citation or other substantiation for the supposition that there cannot be an inverse association between a filtered agent such as creatinine or lead and GFR in individuals whose creatinine or renal function falls within the “normal range”. The narrative did respond to my comment in response to the 1st draft ISA that, “...steady state serum creatinine is inversely proportional to GFR, and in any person, decrements in GFR are associated with increases in serum creatinine even when the serum creatinine remains in the normal range.” Two remaining points offered in section 5.5.2.5 to dismiss the possible contribution of reverse causation should be revisited. Two papers by Akesson et al (2005, 2006) were cited as finding no elevation of urinary lead in subjects with lower creatinine clearance. The narrative then argues, (line 17, page 5-328) “If reverse causality were the more likely hypothesis for these associations, lower creatinine clearance would be associated with lower urinary Pb, which it is not.” The citation of the studies by Akesson et al (2005, 2006) in this context is puzzling, because in neither of these papers did the investigators either measure or report values for lead in urine. The second point offered in Section 5.2.2.5 is that neither blood lead nor chelated lead is elevated in patients with renal disease of known (i.e. non-lead related) cause. However, studies not cited in Section 5.2.2.5 (e.g Muntner et al, 2007 and others to be supplied) actually do show a trend of increased blood lead in subjects with renal failure.

The sections of Chapter 2 and Chapter 5 pertaining to renal endpoints assert several times that the literature is “consistent” in reporting a significant relationship between low blood lead levels and markers of kidney dysfunction (e.g page 2-20, line 5; page 5-307, line 9: “studies consistently demonstrate associations between higher blood Pb level and lower renal function in adults. The studies in this category provided critical evidence that the effects of Pb on the kidney occur at much lower doses than previously appreciated based on occupational exposure data”). On the contrary, as was pointed out in the CASAC consensus comments of December 2011, an inverse relationship between blood lead and glomerular filtration has *not* been consistently observed. For example, in the large general population study of de Burbure et al (2003) there was no significant association between blood lead and serum creatinine or other biomarkers of renal function in multivariable regression models. In the normative aging study (Tsai et al, 2004) there was no significant association between either blood lead or bone lead and serum creatinine in subjects without hypertension or diabetes. A further inconsistency arises from some studies of subjects with occupational lead exposure (Weaver et al, 2003a; Roels et al, 1994), in which higher blood lead was associated with improved renal function. Although, as noted in the comments supplied in the first CASAC report, this might conceivably be a consequence of lead-induced hyperfiltration, the actual cause has not been determined, and the unexplained inconsistency, which weakens causal inference, should be acknowledged. Instead, without justification, the 2nd draft ISA, (p 2-21), dismisses these “paradoxical” observations as reflecting unspecified “limitations of the study

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design.” The observation by Evans et al, (2010) that individuals with low-level occupational lead exposure had a significantly decreased risk of developing renal insufficiency is another striking inconsistency. Evans and her co-author, C. Elinder, both of the Karolinska Institutet, wrote a review article in *Kidney International* in 2011 in which they contend that the available published literature does not allow the conclusion that low level lead exposure causes renal dysfunction. However, this important article was not cited in the 2nd draft ISA.

Finally, the observation in the first CASAC consensus comments that the absence of a discernible nephrotoxic mode of action of lead at low dose limits causal inference continues to lack acknowledgement in the 2nd draft ISA. Instead, contrary to the recommendation in the first CASAC report, the 2nd draft ISA continues to cite numerous studies of lead nephrotoxicity in animal models in which the lead dose greatly exceeds much lower human exposure that is of interest with respect to NAAQS and the AQCD. For example, on p 5-304, the narrative describes an animal study in which exposure of rats to 100 ppm ($\approx 100,000 \mu\text{g Pb/L}$) of lead acetate in water for 14 weeks is characterized as “low dose” exposure, when this exposure level is 4 to 5 orders of magnitude higher than typical human environmental lead exposure from water or diet.⁴

⁴ There are additional instances in which the sections of the ISA pertaining to renal effects appear not to have acknowledged comments offered in the CASAC report, even to the limited but still acceptable extent of disagreeing with them. The limitations of the studies of Yu et al (2004) and the related studies of Lin et al are not mentioned in the relatively lengthy discussion of these studies. On the contrary, without a detailed discussion of the major limitations of these studies, the 2nd draft ISA continues to favor the explanation that lead chelation has salutary effects on renal function in subjects with low level lead exposure. As noted in previous CASAC comments, EPA might prudently avoid offering an analysis of this controversial pharmacologic intervention in this document. The CASAC consensus comments recommended that “the practice of relying on extrapolation to characterize a dose-response relationship at a low blood Pb concentration (e.g., renal effects at a blood Pb concentration of $1 \mu\text{g/dL}$ in Figure 5-43) should be used sparingly, if at all, particularly when none of the studies included significant numbers of subjects with such a low blood Pb concentration, or when the validity of such extrapolation may be subject to considerable uncertainty. However, the 2nd draft ISA (p 5-343) continues to describe in the narrative the implicit adverse renal effect of an increase in blood lead from 1 to $10 \mu\text{g/dL}$, even though it was derived from a study of older adult subjects who had higher blood lead concentrations earlier in life.