Peer Review of Indicators For America's Children and the Environment, Third Edition

June 10, 2011

Final Peer Review Report
EPA Contract Number EP-W-08-008
Work Assignment 2-6

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June 10, 2011

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Re: Work Assignment #2-06 to Contract EP-W-08-008 – Peer Review of Indicators and Proposed Statistical Methodology for America's Children and the Environment, Third Edition

Dear Mr. Axelrad,

Attached, please find a compilation of reviewers' responses to the EPA ACE3 charge questions. Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. Additionally, all peer review comments are organized by topic, indicator, and charge question.

Please feel free to contact me if you have any questions or comments. We, at EnDyna, really appreciate the opportunity to work with you on this important project.

Best regards,
ENDYNA, Inc.

Dr. Smita Siddhanti

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SUBTASK 3.3B: PURPOSE AND OBJECTIVES

EnDyna has coordinated with the all approved America's Children and the Environment, Third Edition (ACE3) peer reviewers as stipulated in Work Assignment (WA) #2-06. Provided below is the Final Peer Review Report for all ACE3 Topics and Indicators, which contains the verbatim written comments from each of the three approved peer reviewers per indicator.

This Final Peer Review Report is being submitted to EPA for review and comment (e.g., regarding layout or formatting). Following receipt of EPA comments, EnDyna will incorporate all necessary changes.

Additionally, EnDyna will provide these comments in a comment-response matrix format, in order to facilitate EPA's response to these comments at a later time. The comment-response matrices to be developed include: 1) topic-based matrices and 2) thematic-based matrices. If during the creation of all comment-response matrices the Final Peer Review Report is found to require corrections, the document will be edited and a Revised Final Peer Review Report on all ACE3 Indicators will be provided to EPA.

CHARGE QUESTIONS

Question 1 – Topic Text

Does the topic text appropriately and clearly describe the topic and its importance for children's environmental health?

Are there additional aspects of the topic's importance for children's environmental health that should be included?

Is the relevant literature appropriately summarized?

Are there other important references that should be added?

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Question 2 – Indicator Text

Does the indicator text provide sufficient information about the data set and the indicator calculation to enable an understanding of the indicator?

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Question 3 – Indicator Presentation

Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data?

Are there ways in which the presentation and description of the indicator values could be improved?

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Please comment on the appropriateness of the comparisons made in the indicator(s) and whether other comparison populations and/or benchmarks may be informative to the public.

Question 4 – Context and Utility

For each indicator, please comment on whether the text appropriately and objectively reflects the strengths and limitations of existing knowledge regarding relationships between environmental conditions and children's health that are relevant to the topic.
For each indicator, please comment its utility and appropriateness addressing the three principal objectives of ACE:

a) To presents concrete, quantifiable indicators of key factors relevant to the environment and children in the United States. These indicators are designed to offer a basis for understanding time trends for some factors and for further investigation of others.

b) To inform discussions among policymakers and the public about how to improve federal data on children and the environment.

c) To provide indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children.

Question 5 – Documentation

Is the documentation complete and transparent?

1.0 BIOMONITORING

1.1 Bisphenol A

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Dana Barr
- Diane Heck
- Erica Phipps

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

General comments on ACE introductory information:

The term "concrete, quantifiable measures" seems to infer that there is no uncertainty in the interpretation of these data. Temporal variability, analytic variability, creatinine correction issues, diurnal variability and sampling of population dense areas are introduce some bias in the interpretation. Somewhere in the report these issues should be succinctly addressed and not mired in the small print as they are in CDC's National Report on Human Exposure to Environmental Chemicals. For example, the sampling by design limits the representation from less population-rich areas such as the West that may have different exposures to BPA. So while these data are representative, they may not identify particularly unusual exposures that may occur in certain areas. Limitations in interpreting biomonitoring data should be given…. Not simply the standard language that "just because you have a chemical in your body it doesn't mean disease" type of limitation statement but the true complexities in trying to present these data in some form of interpretable framework.

Definition of body burden should be included in the glossary of terms. Body burden is NOT equivalent to a biomonitoring measurement and should not be used interchangeably.

Further define "exposure" in the glossary. Exposure does not necessarily mean the chemical has entered the body. Biomonitoring data can help evaluate exposure but are not equal to exposure.

Should stick to facts in glossary of terms. Definition of benzene for example is factual but to define "dioxins" as a "group of harmful chemicals" is not strictly factual. Furthermore, cadmium is a known renal toxicant and that is not indicated in the glossary. Methyl mercury. Most mercury (~90%) found in living organisms are in this form. Organophosphorus pesticides, not organophosphate pesticides. They are closely related in structure but not toxicity. Should clarify. Again, classifying PCBs as "toxic" is not strictly factual. Toxic in relation to what other chemicals? Organophosphorus insecticides are not referred to as toxic in the glossary although they have a real acute toxicity that can cause death. "Volatile Organic Pollutants" are more widely known as "Volatile Organic Compounds" or VOCs.

Deciliter. Should also add 100 milliliters.

Body burden. Body burdens can be calculated from blood measurements with supplementary toxicokinetic information. A body burden measurement and a biomonitoring measurement are NOT equivalent. This section should be rewritten to refer to biomonitoring measurements only.

The front matter is transparent but many terms are incorrectly or non-factually defined.

The topic information adequately links the topic to exposure but does a less successful job in relating it to health.

The language seems to simplistic even for lay persons.

Reviewer 2:

The topic text does topic text appropriately and clearly describes the topic and its importance for children's environmental health, however information on the topic is rapidly evolving and frequent updates to this area are recommended.

Additional aspects that should be considered for inclusion: In the time since the literature review was conducted there has been a growing but not yet definitive body of evidence associating pre and post natal exposure to BPA to low birth weight, prematurity, and externalizing behaviors in toddlers. There is also increasing evidence that exposure to BPA is associated with cardiovascular, immune and metabolic disease in adults.

Representative References:

Casas L, Fernández MF, Llop S, Guxens M, Ballester F, Olea N, Irurzun MB, Rodríguez LS, Riaño I, Tardón A, Vrijheid M, Calafat AM, Sunyer J; On behalf of the INMA Project. Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children. 2011, Environ Int. [Epub ahead of print, 2011 Mar 24.]

Miao M, Yuan W, Zhu G, He X, Li DK. In utero exposure to bisphenol-A and its effect on birth weight of offspring. Reprod Toxicol. 2011[Epub ahead of print, 2011 Mar 30.]

Golub MS, Wu KL, Kaufman FL, Li LH, Moran-Messen F, Zeise L, Alexeeff GV, Donald JM. Bisphenol A: developmental toxicity from early prenatal exposure. 2010
Birth Defects Res B Dev Reprod Toxicol. 89(6):441-66. Review. Erratum in: Birth Defects Res B Dev Reprod Toxicol. 2011, 92(1):95.

Cantonwine D, Meeker JD, Hu H, Sánchez BN, Lamadrid-Figueroa H, Mercado-García A, Fortenberry GZ, Calafat AM, Téllez-Rojo MM., Bisphenol a exposure in Mexico City and risk of prematurity: a pilot nested case control study., 2010, Environ Health. 18;9:62.

Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM, Lanphear BP.
Prenatal bisphenol A exposure and early childhood behavior. 2009, Environ Health Perspect. 117(12):1945-52.

Clayton EM, Todd M, Dowd JB, Aiello AE., The impact of bisphenol A and triclosan on immune parameters in the U.S. population, NHANES 2003-2006. 2011, Environ Health Perspect.,119(3):390-6.

Meeker JD., Exposure to environmental endocrine disrupting compounds and men's health. 2010, Maturitas. 66(3):236-41.

Lubick N., Cardiovascular health: exploring a potential link between BPA and heart disease. 2010, Environ Health Perspect. 118(3):A 116.

Canelas MM, Gonçalo M, Figueiredo A. Contact allergy to epoxy resins--a 10-year study. 2010, Contact Dermatitis. 62(1):55.

The text is clear and accessible for individuals with varying levels of scientific and medical expertise.

Reviewer 3:

To fully describe the concerns for children's health (including fetal development), additional information is needed, specifically on suspected links between low-dose *in utero* and/or early life exposures to BPA and increased likelihood for breast and other forms of cancer;[1] altered metabolism of sugars and fats;[2] and neurodevelopmental and behavioral impacts, including impaired learning, increased aggressiveness and hyperactivity.[3] In this context, it should be made

[1] See, for example, Soto AM et al (2008) Does Breast Cancer Start in the Womb? *Basic and Clinical Pharmacology and Toxicology*, 102:125-133; Ho SM et al (2006) Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. *Cancer Research*; 66:5624-5632

[2] See for example, Alonso-Magdalena P et al (2005) Low doses of bisphenol A and diethylstilbestrol impair Ca2+ signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. *Environmental Health Perspectives;* 113, 969–977.

[3] See, for example, Braun JM et al (2009) Prenatal Bisphenol A Exposure and Early Childhood Behavior, *Environmental Health Perspectives*; 117:1945-1952; Ishido M et al (2004) Bisphenol A causes hyperactivity in the rat concomitantly with impairment of tyrosine hydroxylase immunoreactivity. *Journal of Neuroscience Research*; 76:423–433; Kawai K et al (2003) Aggressive behavior and serum testosterone concentration during the maturation process of male mice: the effects of fetal exposure to bisphenol A. *Environmental Health Perspectives*; 111:175–178; Miyagawa K et al (2007) Memory impairment associated with a dysfunction of the hippocampal cholinergic system induced by prenatal and neonatal exposures to bisphenol-A. *Neuroscience Letters;* 418(3):236–241.

clear that the health effects are not only during childhood, but that there are likely to be lifelong implications for health, including increased risk of developing certain chronic diseases (many of which are on the rise in the human population). Further explanation could also be given to the complexity of mechanisms of action, including epigenetics.

Sources of exposures should be broadened beyond dietary sources to include, in particular, house dust.[4] There is also evidence of contamination in air, water, sediments, industrial waste water and sewage sludge. This intro should make it clear that exposures to BPA are ubiquitous, given its use/presence in many facets of everyday life. Perhaps also mention infant exposure via formula cans.

Line 8: Use of BPA in the PVC industry is referred to in past tense. This needs to be checked, as I believe this use continues. The acronym "PVC" should be inserted after polyvinyl chloride as some people will be familiar with the former and not the latter.

Second paragraph about higher exposures in children should also mention the point, raised at the very end, that immature animals (possibly including human fetuses and infants) are less able to metabolize BPA than older animals. In other words, it is not just their higher/more rapid intake, but also the likelihood that their bodies are less able to deal with it efficiently.

Line 13 should also mention *in utero* exposures and highlight the fact that BPA can cross the placental barrier,[5] with BPA measured in amniotic fluid at levels up to five times higher than in maternal blood.[6]

Line 16: Suggest replacing "prevalent" with "widespread" or other more commonly understood term.

Line 26-27: This comparison to natural estrogen may leave the reader with a false sense of security. Suggest adding a sentence about the bioactivity of hormones (including endocrine disrupting chemicals - EDCs) at exceedingly low levels.

Suggest also adding here a brief explanation in lay terms of the non-monotonic dose-response curve, to make the point that extremely low doses of an EDC, such as BPA, may be of greater (and different) concern than high dose exposures.

May need to address/explain the apparent contradiction between the delayed time to onset of puberty mentioned in line 33 and the early onset mentioned in line 39.

Page 2, line 1-4: this should be put in context with a specific mention of the Endocrine Society Scientific Statement (Diamanti-Kandarakis, et al, 2009) about the broad range of health concerns (and precursors, such as metabolism and obesity) associated with EDCs. This paragraph should also

[4] Environment Canada, Health Canada (2008) Screening Assessment for the Challenge: Phenol, 4,4'-(1-methylethylidene)bis- (Bisphenol A); Rudel RAet al (2003) Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine disrupting compounds in indoor air and dust. *Environmental Science and Technology* 37:4543-4553.

[5] Nishikawa M et al (2010) Placental Transfer of Conjugated Bisphenol A and Subsequent Reactivation in the Rat Fetus. *Environmental Health Perspectives*; 118:1196–1203.

[5] Balakrishnan B et al (2010) Transfer of bisphenol A across the human placenta. *American Journal of Obstetrics and Gynecology*; 202:393.e1-7

[6] Ikezuki Y et al (2002) Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Human Reproduction;* 17(11):2839–2841.

acknowledge that BPA is one among many EDCs and that potential synergies/interactions among multiple exposures to multiple contaminants are not well understood, particularly for the developing fetus and child.

Line 30: This sentence could more clearly state that the concern is about risks posed to the developing fetus in the womb, and perhaps restate the higher exposures received in the womb and in early childhood. The concern about maternal exposure is also presumably about infants being exposed via breast milk, but this is not explicitly stated.

Line 32: could state explicitly that data are not available for younger children.

Overall, I find the literacy level too high – including unexplained use of technical terms – if this document is indeed going to be of use to concerned parents and others who may not have a scientific background or higher levels of education.

Question 2 – Indicator Text

Reviewer 1:

General comments on BPA Biomonitoring section:
Page 1, line 25. Change to "early and adolescent development"

Line 29. Restructure sentence to avoid "There has been"

Clarify that biomonitoring levels do not equal exposure levels

Howe do animal concentrations associated with health outcomes compare to human biomonitoring levels?

It is important to stress that this analysis is for total BPA and only free BPA is biologically active, thus, it is impossible to tell which proportion of those exposed may be at risk for developing health outcomes. Would be good to provide range of numbers for what percentage of total BPA is actually free in the body … I think it is around 2%.

Should include reference to Rees Clayton 2011 paper on immune parameters derived from NH data. EHP 119:390-396.

Creatinine adjustment. This section leaves out the important information that creatinine excretion is dependent upon muscle mass thus children and the elderly will have much lower excretion rates than adults. Females will excrete less than men. I will suggest later that you eliminate creatinine adjustment because I firmly believe that the findings with children are purely artifactual and not real. However, if you leave this section, you need to state clearly that this makes comparing child and adult concentrations difficult and will tend to make child concentrations appear falsely higher (typically about 2 times higher as their creatinine excretion is about ½ of that of adults).

Page 4, second paragraph. "Urinary creatinine concentrations "can" vary…" The DO vary SIGNIFICANTLY with the variables listed.

Creatinine correction does NOT improve the comparability of urinary chemical measurements across populations when the populations differ in age, sex, race/ethnicity.

Temporal trends. NCHS does indicate that 3-cycles is necessary to address "trends" (although they abhor the use of that word); however, significant differences in the two cycles can and should be evaluated.

What was the minimum cell number requirement for statistical evaluation?

Was there a poverty-creatinine interaction term?

I firmly believe that the child findings are not real but an artifact of creatinine correction.

I was disappointed to see the environmental data separated from the biological data. Without the former, this looks like a regurgitation of CDC's report and uses similarly medicinal language that fails to make any interesting assertions or conclusions about the data.

I liked the use of adjustment of age-specific natality. Great concept.

Reviewer 2:

The indicator text provides sufficient information about the data set and the indicator calculation to enable an understanding of the indicator. In addition the text is clear and accurately conveys the information.

However one problem was evident. In reference to line 14-18, "Measured levels in the U.S. population may be composed predominantly of the inactive metabolites..." a profound bias is evident. In this regard, little is known about the biochemical activity of BpA and its metabolites and the pharmacokinetics and pharmacodynamics of BpA in humans therefore it is inaccurate to refer to BpA metabolites as inactive.

Reviewer 3:

In general, the description of the data source and indicator calculation is adequate, if a bit high literacy.

Title of the indicator should state "women of childbearing age" or other similar reference to the concern about *in utero* exposure.

Overview paragraph, last sentence: I have the same comment here as noted above about the lack of explicit mention of potential risks *in utero* to the developing fetus and implications for subsequent health effects as well as potential exposures via breast milk. If contamination of breast milk is mentioned, however, it would be wise to state that breast milk remains the ideal food for babies and also to point out that formula can also be a source of BPA exposure, due to packaging and possible BPA content in older baby bottles.

Line 18: Point about conversion of metabolites to active form when crossing the placenta should also be made in the introductory section (page 1).

Line 43: some explanation (an example, perhaps? E.g., a family of 4 with total income of less than $x/year) should be given about how the poverty level is defined.

Question 3 – Indicator Presentation

Reviewer 1:

1) Should note statistical significance on graphs.

2) Tables. Should define NA.

3) Color scheme was not particularly appealing.

Reviewer 2:

The indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data.

To better facilitate the use of the data by the general public it is suggested that he use of < and > should be clearly defined or replaced by descriptive text such as "greater than or equal to".

The comparisons made were accurate and correctly convey conclusions supported by the data. They are clearly described and should be easily understood by all concerned stakeholders.

Reviewer 3:

Re: Indicator BPA1 Graph:

Title of the indicator should state "women of childbearing age" or other similar reference to the concern about *in utero* exposure.

Bullet 1 refers to the data points illustrated at the bottom of the graph. Perhaps the "all races/ethnicities" data should be at the top of the graph?

It is not clear what the word "this" at the end of line 5 refers to. Is it referring to the differences among the three values provided? Is so, it should be plural, i.e., "these differences."

Bullet 1: it might be helpful as context to state the median concentration in the general US population.

The sub-bullet under the first bullet (Lines 7 and 8) is not clear. Perhaps this note should be inserted after the values for the race/ethnicity breakdowns have been introduced.

Bullet 3: Readers will have questions about why the lower-income groups seem to show greater median concentrations. Despite the qualifier that these differences "frequently" are not statistically significant, it would be helpful to provide some information about reasons why different income brackets may experience higher/lower exposures levels. (This comment also applies to Indicator BPA2 so the explanation might be better placed in the intro text.)

An additional bullet should note that the levels in women of childbearing age are cited as proxies for fetal exposures (and exposures via lactation, if that is indeed part of the objective) and should

also note that BPA crosses the placenta and, further, that these may be underestimates in light of evidence that levels in the womb can actually be higher than those measured in the mother's body.

Re: Indicator BPA2 Graph:

Bullet 1: It would be helpful to provide some information about reasons why children in different income brackets may experience higher/lower exposures levels.

Bullet 2: It seems a bit awkward to present data points in a summary bullet, only to have it followed by a technical statement saying that the differences are not statistically significant. The bullet and sub-bullet should be merged and expressed in common language to help the reader interpret what he/she is reading. Many readers will skip over something that is labeled "statistical note" and will come away with the impression that the impoverished "other" category has significantly higher exposures.

Bullet 3: Same comment as above: the main bullet and technical bullet should be merged and expressed in plain language.

Bullet 4: The comparisons are helpful, including the comparison with women, although a comparison with the general population might be more logical than a comparison just with women of childbearing age.

Bullet 5: It would be more direct and relevant to children's environmental health protection objectives to say that younger children have higher BPA concentrations. As stated, it could sound as though body burdens decline gradually over time (as they might for a persistent substance). The current statement skirts around the point that younger children are somehow receiving higher doses on an ongoing (daily) basis and/or are less able to metabolize BPA. These two reasons should be mentioned here to help the reader understand the data and the differences found.

Other comments re: indicator graphs:

An additional graph should be included based on Data Table BPA2b – the comparison of median and 95th percentile values in children of the various age groups. Bullets to highlight the relevance of this information, along the lines of comment above for Bullet 5, should be included. It is a very important point – of direct relevance to the objective of this report -- that the younger children are showing evidence of being more highly exposed.

Comments on data tables and related text:

Table BPA1a: Explanation is needed for the 24.5 level for all races – unknown income.

Table BPA2a: Explanation is needed for the 61.3 level for all races – unknown income and for white non-Hispanic – unknown income.

Question 4 – Context and Utility

Reviewer 1:

The limitations of this report are not worded strongly enough.

It is not clear how this report differs too much from CDC's existing report on biomonitoring data.

It would be more valuable to integrate environmental information in with the biomonitoring data.

Reviewer 2:

In general the text appropriately and objectively reflects the strengths and limitations of existing knowledge regarding relationships between environmental conditions and children's health. However the text principally addresses potential estrogenic effects, few of which are supported by human data. The current state of the art indicates that BpA mediates a broad array of effects. Currently it is unclear which, if any, of these effects will most deleteriously affect children's health. In addition, mechanisms underlying observed effects mediated by BpA in animals and humans are poorly understood. Therefore this reviewer recommends that until the field is better understood the potential for BpA mediating estrogenic effects be limited and that the non-estrogenic health effects receive more emphasis.

A. The document presents concrete, quantifiable indicators of key factors relevant to BpA in the environment and children in the United States.

B. With some content modification (suggested above) the document will inform discussions among policymakers and the public about how to improve federal data on children and the environment.

C. The document provides indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children.

Reviewer 3:

<u>Indicator BPA 1 (BPA levels in women of childbearing age):</u>

Reflection of existing knowledge: Text could be expanded to include implications of exposure, including potential for exposure to the fetus and the fact that animal evidence suggests that prenatal exposures are of particular concern (and are also higher). As written, the bullets describing the data do not make any link to the children's environmental health relevance of the data being presented.

Objective (a): Yes, this objective is met. Trend information will be valuable, once available.

Objective (b): Somewhat. The text could make it more clear that the levels in women of childbearing age are a surrogate for exposure information for fetuses. Further, the text could note that levels of exposure in the womb may indeed be higher than levels measured in/from the woman's body, as noted above. (Research finding that amnio levels 5x greater than maternal blood levels). It would be ideal to have more insight/information on sources of exposure and their relative importance.

Objective (c): Somewhat. This objective will be more adequately served once trend information is available. It would also be aided by incorporation of more contextual information about the concerns, as noted in my suggested additions above.

Indicator BPA 2 (BPA levels for children):

Reflection of existing knowledge: Text could be expanded to include the health and developmental implications of exposure. As written, the bullets describing the data do not make any link to the children's environmental health relevance of the data being presented.

Objective (a): Yes, this objective is met. Trend information will be valuable, once available.

Objective (b): Somewhat. The text could point out that data not available for younger age groups and that exposures are of greatest concern for children, including infants and young children in particular (and fetuses, as noted in Indicator BPA1). It would be ideal to have more insight/information on sources of exposure and their relative importance.

Objective (c): Somewhat. This objective will be more adequately served once trend information is available. It would also be aided by incorporation of more contextual information about the concerns, as noted in the suggested additions above.

Question 5 – Documentation

Reviewer 1:

Yes, the transparency is to be applauded EXCEPT with the creatinine correction issue. I still feel like this is a faulty finding.

Reviewer 2:

The documentation was relatively complete however biased towards reproductive and developmental toxicity. As noted in the Topic Text section, in this rapidly developing field additional outcomes potentially are more significant than endocrine disruption. It is recommended that newer references be added.

Reviewer 3:

Yes, the documentation appears to be complete and transparent.

The section "Race/Ethnicity and Family Income" should include additional information on how the poverty level is defined, including some illustrative examples (e.g., family income of $xxxxx/year for family of x people living in major metropolitan area…)

1.2 Cotinine

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Larry Lowry
- John Meeker
- Jennifer Straughen

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

Topic text section was well written with one exception: Page 1, lines 28-29. This sentence has too many "hedge" words making it pure speculation in appearance. The words "suggest" and "some" are in question. I suggest rewording the sentence to be more positive or if the data is really that soft, eliminating it.

Reviewer 2:

Overall the topic text seems appropriate and clear for its intended use. One inconsistency in the background literature is that wording like "increased risk" is used for respiratory effects and birth outcomes, whereas the more definitive "cause" or "causal" were used to describe relationships with SIDS and breast cancer. I might suggest using similar "risk" language for these latter outcomes since I doubt the existing evidence is any stronger for SIDS and breast cancer in relation to ETS compared to respiratory effects or effects on birth outcomes.

I don't know of any additional references that should be included, and I feel it is written in a way that is understandable by the wide range of target audiences.

Reviewer 3:

Overall, I think it is fine. However, it may be helpful to those outside of science or medicine if you mention that ETS exposure is commonly referred to as second-hand smoke exposure.

Question 2 – Indicator Text

Reviewer 1:

Page 3, NHANES section, lines 1-3. Data for 1988-1991 and 1991-1994 cover children 4 years and older. Children 3 years and older are used from 1999-2000 on. The next statement: "NHANES data from 1988-2008 are used for Indicator B5 for children 2 to 17 years ..." Where did you get the data on 3 year olds for the years 1988-1994?

Page 3, NHANES section, lines 3-4. NHANES data for women ages 16-49 are used. If you go to the NCEH website where the data is located, they are broken down into 3-11, 12-19, and 20+. I realize that the data can be queried to defined groups but if the reader goes to the NCEH website, they will see different tables and data grouping.

Page 3, line 6. Recent updates from the NHANES website now includes ages 1 and up. I realize that this data became available after this ACE-3 update was written but reference to age 1 and up data now being collected would be appropriate.

Comment: There is no mention of the half-life of cotinine in serum in either children or women. Mention of this would give the reader/reviewer some idea of what period of exposure the serum level represents. I do not know what the half-life is but if it is short, the value obtained could be due to a recent visit to a restaurant where smoking was present. If that visit was some time ago, the value of serum cotinine would not reflect that exposure. Determine what the half-life is in serum and add a statement that indicates over what period of time this indicator measures.

Reviewer 2:

Yes, I believe the indicator text provides sufficient information about the dataset and calculation for most readers. Researchers with an interest in more details will be able to find it with the links to more information. I believe it is written in a language that should be clear for most people.

Once sentence, line 14-15 on Page 2, that describes why blood is preferred because cotinine stays “relatively stable” seemed unclear to me.

Reviewer 3:

Yes. The overall description of the indicator is clear. However, I think a few points could be better clarified:

On page 2, lines 14-18 the authors mention that blood cotinine is preferred because it is stable. However, hair cotinine is more stable, yet the way the way the text is phrased seems to imply that hair cotinine is not stable. Perhaps some additional details about why blood is used can be added.

Page 3, line 17: In most places, "nonsmoker" is used, whereas on line 17 "non-smokers" is used. It is somewhat trivial, but worth noting.

Page 24, line 24, "pre-natal" should be "prenatal".

Question 3 – Indicator Presentation

Reviewer 1:

Page 5, Lines 7 and 10. Add (see Table B5) at the end.

Page 6, Lines 1-10. It seems strange that there is discussion of data that is not presented but no discussion of results supported by data tables.

Page 6, Line 17. Why was the data set from 2005-2008 used and not other data sets or combined data sets?

Page 6, Lines 23. There is no discussion of the data in Tables B5b and B5c. Why present the tables and not the discussion?

Page 7, Lines 4 and 8. Add (see Table B6)

Page 8. Comment: There was no discussion of Tables B6a or B6b. Why present the tables and not the discussion?

Page 8, Lines 1-3. Comment: It seems strange that there is discussion of data that is not presented but no discussion of results supported by data tables.

Reviewer 2:

I think the graph, bullet points, and data tables were well-organized, and the comparisons that were made statistically seem appropriate.

Was the inclusion of sample size in the main figures considered?

The CDC's National Reports on Human Exposure to Environmental Chemicals typically presents 95% confidence intervals around all point estimates they report. Was that considered here?

Also, did the authors consider presenting figures to display the reported race/ethnicity and poverty differences? I think those illustrations could be useful.

Were the women's concentrations not further analyzed by race/ethnicity and income? Why not?

Finally, given that the median and 95th percentile cotinine concentrations among the children were higher than those among adult women, is there any way this could be concluded in the bullet points? This seems like an extremely important result here and public health message since many of the children are likely unable to control their ETS exposures as much as adults. This is an

especially unfortunate situation given how preventable ETS exposures should be at the individual level compared to many of the other biomarker indicators covered in this report.

Reviewer 3:

I prefer that measures of statistical significance (p-values or confidence intervals) be presented in summary points below the bar graphs, such as that on page 5.

Is it possible to present some statistics for trend over time on pages 5-8? I think the change over time is of importance.

Further, it would be helpful to compare the measures from the most current year with years other than the 1988-1991 cotinine measures.

It would also be helpful to present racial differences in changes in cotinine in a similar format to the graphs on pages 5-8 as this may assist in identifying at risk populations for groups interested in racial disparities or intervention research.

Graphical figures as opposed to large data tables are better for diverse audiences as they are generally easier to understand.

Question 4 – Context and Utility

Reviewer 1:

Discussion of selected data and reporting on data not shown makes the overall presentation weaker. Discussion should be based on data presented and data presented should be discussed.

There is no summary of the findings that provide the take home message that would address in a concise manner, the significance of these data and data trends. They have a significant public health message in my opinion but this is not stated in clear text.

Reviewer 2:

The text appropriately and objectively reflects the strengths and limitations in our current knowledge of this indicator. I think this report represents a very important consolidation of national data for a wide range of audiences. These indicators should be highly referenced by researchers and policymakers alike, and should serve as a useful resource for medical professionals, other various groups, and citizens.

Reviewer 3:

Although the information presented is potentially very useful, I think some of the utility of the presented indicators is limited by a few factors. First of all, the document uses women aged 16-49 to represent women of childbearing age. Most of the published literature on "women of childbearing age," including that by other government agencies defines women of childbearing age

as either 18-44, 18-45, or 16-44 years of age. Altering this category makes it difficult to compare and generalize the data presented here with previously published studies. Further, a 49 year old pregnant woman is rarely representative of the population of women giving birth.

Secondly, I was disappointed to see that the comparisons presented were focused on comparing data from 2007-2008 to 1988-1991. I think there is a great deal of interest to know whether some of the more recent policy changes (i.e. making restaurants completely smoke free, not allowing smoking in public places, or at some job sites) has impacted ETS exposure. Further, there is a failure to mention that the reduction in cotinine levels may be due to policy changes such as those mentioned above. Instead the authors choose only to mention the reduction in active smokers (page 8, lines1-3).

Question 5 – Documentation

Reviewer 1:

References appear to be representative of the literature.

Metadata: Again, this is a generic document. It is my opinion that the metadata table should reflect the data that is used for this indicator.

Methods: Page 19, line 16-18. How can indicator B5 cover ages 3-17 when two data sets (1988-1994) contain only data for ages 4-17?

Page19, lines 22-25. These two sentences are out of place and seem to repeat what is said in lines 18-19. If this section is necessary, have it follow the discussion of indicator B5 as it has nothing to do with indicator B6.

Page 20 Detection limits. The text does not indicate why the detection limits are lower in recent years. Describe briefly the changes in analytical methodology that lead to the lower detection limits.

Page 20 top table. The heading shows ages 3-17 but data from 1988-1994 did not include 3 year olds. Explain or redo the table.

Pages 30-34 contain many detailed tables of data but there is no general summary of the findings specifically as it relates to children's health and ETS as assessed by serum cotinine.

Comment: I cannot comment on the quality of the statistical treatment because I lack the expertise in this area. The data tables provide a concise summary of the data comparisons and the significance (for those with the appropriate statistical training, but not for the lay audience and general public or government official).

Reviewer 2:

Yes, the documentation appears to be complete and transparent.

Reviewer 3:

It seems to be complete, but I think the layout is confusing. All of the tables from page 30 onward would benefit from some restricting. They are redundant and unclear. Headings should not be Race1, Race2, etc., nor should the word "cotinine" be repeated endlessly.

Table 2, on page 31: What does PL stand for? Poverty level? There is really no way to know because it is not defined in a footnote. Similarly, RACEINC1 and similar column headings are challenging to interpret and understand. If you want to include the variable name, perhaps that can be a separate row. I think that these tables are very confusing, and probably more so for someone who is not a statistician, epidemiologist, or other professional familiar with data analysis.

1.3 Lead

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Carla Campbell
- Bruce Lanphear
- Larry Lowry

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

SUGGESTED INSERT: Page 1, Lines 26-28: Exposure to lead in house dust tends to be highest for young children, due to their frequent and extensive contact with floors, carpets, WINDOW AREAS, and other surfaces where dust gathers, as well as their frequent hand-to-mouth activity.

SUGGESTED CHANGE: Page 3, lines 11-12: Once absorbed, MOST OF THE LEAD some lead is stored in bones, where it can stay many years, while other lead goes into the blood and can be eliminated more quickly. (Over 50% of body lead is stored in bones, with a very long half-life, as is indicated).

SUGGESTED CHANGE: Page 3, lines 32-34:
Mothers who are exposed to lead can transfer lead to their unborn children during pregnancy.[58]
Cognitive and behavioral effects of prenatal exposure to lead have been observed in young infants and children across numerous studies.[16,39,57,59]
ADD: The CDC has recently published guidelines for screening pregnant and lactating mothers for possible lead exposure to better protect the fetus from adverse effects of this.
Reference: Advisory Committee on Childhood Lead Poisoning Prevention. Guidelines for the Identification and Management of Lead Exposure In Pregnant and Lactating Women. Atlanta: Centers for Disease Control and Prevention: 2010.

Reviewer 2:

With a few exceptions, described in the responses (below) and the attached PDF, the text does adequately describe lead epidemiology and its particular relevance to children's health.

The relevant literature is adequately cited. One additional behavioral problem associated with lead that deserves to be described is conduct disorder. This should be included in the sentence describing the association of lead with delinquency and criminal behaviors. This is important because two studies indicate that antisocial behaviors occur in US children at levels relevant to contemporary children:

Braun JM, Froehlich TE, Daniels JL, Dietrich KN, Hornung R, Auinger P, Lanphear BP. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004. Environ Health Perspect 2008;116:956-962.

Chiodo LM, Jacobson SW, Jacobson JL. Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol. 2004 May-Jun;26(3):359-71.

There are a few sections that need to be re-organized. In particular, the exposure and absorption of lead in children should be described together (see attached PDF with comments).

Ideally, and most relevant to the US EPA, the document should describe what regulatory efforts are contributing to the ongoing decline in children's blood lead levels. Are there regulations undergoing review? Shouldn't these efforts be discussed?

This is an opportunity to talk about – even boast about – what EPA regulations have done and will be doing to protect children's from lead toxicity. Ideally, and most relevant to the US EPA, the document should describe what regulatory efforts are contributing to the ongoing decline in children's blood lead levels.

Reviewer 3:

Page 1, line 36. Add at the end: In this case, all liquid intake by the child comes from tap water, a very different scenario from older children and adults.

Page 1, line 41. Include vinyl mini-blinds, keys etc often from foreign sources where controls for lead content are lax.

Page 2, line 20: Although lead content of US made items is controlled or banned, this is not the case from items imported from Asia, as evident by the many recalls of products by the Consumer Product Safety Commission.

Page 2, line 31. Consider adding the following: It should be mentioned that these behavioral changes could also be influenced by socio-economic status.

Page 2, line 32. Might want to add that lead from mother exposure before birth can be transferred to the infant through breast milk.

Question 2 – Indicator Text

Reviewer 1:

SUGGESTED CHANGE: Under Race/Ethnicity, Page 5, Line 24-25. I would add a suggested change. The data are also tabulated across three family income categories: all incomes, below the poverty level, and greater than or equal to the poverty level.
ADD: The greater than poverty level category is further broken down in the Data Tables by whether the family's income status is at 100-200% or > 200% of the poverty level.

SUGGESTED CHANGE: Under the Indicator B1 figure I would change the last bullet, found on page 8. In 2007–2008, children ages 6 to 10 years had median blood lead levels of 1.0 µg/dL; the median for children ages 11 to 15 years was 0.8, and for ages 16 to 17 years the median was 0.7 µg/dL. The 95th percentile blood lead levels were 2.6, 2.1, and 1.7 µg/dL, respectively, for ages 6 to 10, 11 to 15, and 16 to 17 years. (See Table B1a.)
ADD: the data for the 1-5 year-old children in this bullet, for easy comparison with the older children

Reviewer 2:

There is actually TOO MUCH information about NHANES methodology and how the data were analyzed. The vast majority of people – I would reckon 99.9% of readers – will actually be discouraged from reading the report because there is too much attention to the NHANES methodology.

The text to describe the data set and the indicator should be no longer than one page. In fact, most of the data needed is already provided in the biomonitoring section. Anything else is unnecessary. If, for some reason you do need it, it should be in an appendix so it doesn't distract from the results.

Reviewer 3:

Page 4, line 7 NHANES. It should be mentioned that the representative population sampled includes those who may have lead exposure from the environment or parental exposure and that these data cannot be assumed to represent "normal" or acceptable values, just representative of the population sampled.

Question 3 – Indicator Presentation

Reviewer 1:

SUGGESTED CHANGE: I thought the labeling of the Figure analogous to Indicator B1 was better in the 2003 ACE document; it added for the 95th percentile (10 percent of children have this blood lead level or greater) and for the median value (50 percent of children have this blood lead level or greater). That seemed to be useful for lay and non-technical audiences. It was on page 53 of the 2003 version of this document.

The two figures shown are simple and well done. The text is helpful in providing a detailed explanation of what is being shown.

Reviewer 2:

Yes, there are ways that the tables can be made to be more useful. I would suggest you use the figure format used by Jones R, et al. (Jones R, et al. Pediatrics 2009;123:e376-e385) in their recent publication on blood lead levels in US children (see Figure 1). The tables in this report are excessive and ultimately detract from the report. They can be whittled down to one or two figures using the format used in Jones R, et al. Pediatrics 2009;123:e376-e385 publication.

You should also consider adding figures that show blood lead levels by floor dust lead loading values from NHANES (see article by Dixon S, et al. EHP 2009;117:468-474). This is particularly relevant for US EPA Report because the focus should be on environmental exposures, not race or poverty.

Similarly, you should consider examining the mean blood lead levels and percent of children with blood lead levels > 5 micrograms per deciliter who live in older versus newer housing. If possible, you should categorize children by poverty and age of housing to create a four category graph with median blood lead levels and percent of children having a blood lead level > 5 micrograms per deciliter.

Reviewer 3:

General comment: There is inconsistency in the way data in the charts, the bullet points and data tables are presented. Not all parts of the chart are explained, just selected items that gives the appearance of "cherry picking". It is my view that the charts should be followed by bullet points explaining each item and that this discussion be in the same order as the data tables. This is not the case. Some specific examples:

Page 7 lines 5 and 8. Add (see table B1) to be consistent with bullet points on page 8.

Page 9 chart. The order from top to bottom is white, black, Mexican, Other, and all. The first bullet point is the median for all (lines 3-6) without reference to Table B2.

Page 9, line 8. The next bullet talks about black-non Hispanics again without reference to Table B2

There is no discussion of the other data on the chart and the table B2 does not follow the same sequence as the chart on page 9. This is very confusing.

Page 10, lines 6-13. These bullet points refer to two time periods, 1991- 1994 and 2005-2008 but there is only reference to Table B2b covering the earlier period without reference to the Table B2 which covers the latter period. It took me some time to find where the figures cited in the bullet points came from.

Question 4 – Context and Utility

Reviewer 1:

B1: I think this is well done. Please see my comment above regarding B1.

B2: I think the figure and text are well done and give the key points in the figure.

This does give time trends and demographic breakdown, as well as differences in various ages of children which are all important information for lead toxicity.

Just the thought articulated below. Comparing data from different time periods will give the readers information about the trends in BLLs, which have been positive ones over the last few decades. This report summarizes and illustrates that trend well.

c) One thought in reviewing this document is that many studies have used geometric mean blood lead level as the exposure variable, in contrast to the median blood lead levels collected by NHANES and used in this document. That obviously is a design of the NHANES surveys, but I have seen published papers (in the past) giving the geometric mean levels from NHANES data, rather than the median. So the geometric mean levels may be available for presentation.

Reviewer 2:

No, it doesn't because it fails to recognize the primary sources of lead exposure for children. Why shouldn't this report provide an overview of regulations for air, water, soil and dust? Why shouldn't it present trends in air lead levels over the past 3 decades to compare with children's blood lead levels? Shouldn't EPA's report be on something different than what CDC or the American Academy of Pediatrics would produce?

Blood lead levels are one key indicator, but the sources of exposure, such as air lead concentrations and floor dust lead loading are equally important, especially for the US EPA to report on state of children's health and environment.

Once again, from an environmental perspective, this report fails. From a policy perspective, this report should be boldly proclaiming that the dramatic declines in blood lead levels were due to EPA (and, to some extent, HUD and CPSC) regulations. But then it should also describe what is known about these major sources of lead, wherever national data exist (e.g., the relationship of lead-contaminated house dust with children's blood lead levels using NHANES.) If there are insufficient data for air lead levels because EPA failed to maintain this critical source of exposure dat, then it should state this and indicate what is being done to rectify it.

See comment above. Ultimately, US EPA should emphasize the major sources of exposures in addition to children's blood lead because policymakers must rely on exposure measurements to continue to reduce children's blood lead levels.

Reviewer 3:

As stated above, consistency between charts, bullet points and tables would clarify the presentation.
Regarding the three principle objectives, there is no summary of the findings that provide the take home message that would address in a concise manner, the significance of these data and data trends. They have a very significant public health message in my opinion but this is not stated in clear text.

Question 5 – Documentation

Reviewer 1:

The Metadata tables seem appropriate and are understandable to an informed public and lay audience.

The Methods section seems appropriate although I am not a statistician, so can't give an expert opinion on this.

Reviewer 2:

See comments above.

Reviewer 3:

References: Appears to be representative, not checked.

Metadata: The information seems complete but is general. Can these be adapted for the indicator of interest, in this case lead? For example, the bottom of page 19 states that for some data sets, there are a large percentage of values below the detection limit. This is not true for blood lead.

Methods: Question: How were blood samples collected? Were they venous, finger sticks or similar, and were precautions taken to clean the area prior to the stick/prick? Were the same sampling techniques used for all ages and for all time intervals?

Comment: The documentation of data sources and data handling seems complete. I cannot comment on the quality of the statistical treatment because I lack the expertise in this area. The data tables provide a concise summary of the data comparisons and the significance (for those with the appropriate statistical training, but not for the lay audience and general public or government official).

1.4 Mercury

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Alan Becker
- Larry Lowry
- Mike Wilson

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

I base my "content" assessment on the *utility* of the information as presented in the document, from the perspective of the scientific community, the public, and policy makers. I base my "organization" assessment on the presentation and readability of the information.

Question 1 – Topic Text

Reviewer 1:

a.) Information related to absorption of the different mercury species in the gut is an important point on why organic mercury by mouth is particularly of concern. Also some information related to inhalation of mercury vapors from metallic mercury. See the below reference for information.

Clarkson T., Laszlo M., (2006). The Toxicology of Mercury and Its Chemical Compounds. Critical Reviews in Toxicology, 36:609-662.

b.) Liquid mercury is also a threat to children in that the mercury thermometers and blood pressure devices may be present at doctor's offices and clinics. When these devices are broken children can be exposed to increase amounts of mercury vapor (e.g. closer to floor, hand to mouth exposure and higher respiration). Also ritualistic use of metallic mercury in the Hispanic and Haitian communities used in ceremonies involving children and stored in households.

United Nations Environmental Program (2006). Cultural uses of Mercury, Retrieved March 22, 2011 at http://www.chem.unep.ch/mercury/awareness_raising_package/G_01-16_BD.pdf

c.) An updated literature search needed. I have provided articles from 2010-2011 that needs to be reviewed to update the background. More emphasis should be related to children.

Yoshida M., Suzuki M., Yasutake A., Watanable C., (2011). Neurobehavioral effects of combined prenatal exposure to low-level mercury vapor and methyl mercury.Journal of Toxicological Science; 36(1); 73-80.

Ramon R., Murcia M., Aguinagalde X., et al. (2011). Prenatal mercury exposure in a multicenter cohort study in Spain. Environmental International 37(3) 597-604.

Strom S., Helmfrid I., Glynn A., Berglund M., (2011). Nutritional and toxicological aspects of seafood consumption—An integrated exposure and risk assessment of methyl mercury and polyunsaturated fatty acids. Environmental Research; 111(2): 274-280.

Tezer H., Erkocyglu M., Kara A., et al. (2011) Household poisoning cases from mercury brought from school. European Journal of Pediatrics. 170(3): 397-400.

Price C.S., Thompson W.W., Goodson B., (2010). Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. Pediatrics. 156-64.

Bose-O'Reilly S., McCarty K.M., Steckling N., Lettmmeier B., (2010). Mercury exposure and children's health. Current Problems Pediatric Adolescent Health. 40(8): 186-215.

Tian W., Egeland G.M., Sobol I., Chan H.M., (2011). Mercury hair concentrations and dietary exposure among Inuit Preschool children in Nunavut, Canada. Environmental International 37(1): 42-48.

Salehi Z., Esmaili S.,Sari A., (2001). Hair mercury levels in pregnant women in Mahshahr, Iran: Fish consumption as a determinant of exposure. Science International. 408(20): 4848-54.

Davidson P.W., Leste A., Benstrong E. et al. (2010). Fish consumption, mercury exposure, and their association with scholastic achievement in the Seychelles Child Development Study. Neurotoxicology. 31(5): 439-47.

The following paper seems to strengthen the use of blood levels collected in the NHANES Data.

Halbach S., Welel G., (2010). Levels of organic and inorganic mercury in human blood predicted from measurements of total mercury. Journal of Applied Toxicology; 30(7): 674-9.

Reviewer 2:

Topic text section was well-written with only a few questions.

Page 1, line 17 and 20. The word high can be emotional as it does not have a qualifier. Suggest adding a qualifier or using the word "increased".

Page 1, line 19. The term bacteria referring to the conversion of mercury to methyl mercury is not inclusive of the process. Suggest that the term biota be used to include biotransformation occurring in the water column as well as within smaller fish/biota in the food chain.

Reviewer 3:

Content

1) Overall, the text reports the facts of mercury biomonitoring findings from NHANES, but it does not *interpret* these facts effectively for the reader. It therefore reads like a CDC, not an EPA, document. Important research findings from New York and Massachusetts are buried in the document amongst text pertaining to health outcomes reported in various studies.

2) Specifically, the text is reasonably descriptive regarding the sources and levels of mercury identified in certain populations, but it does not provide information that would help the reader decide if these are levels to be concerned about, or not. ACE2, for example, notes the EPA's Reference Dose level of 5.8 ppb and translates this for the reader from 0.1 ug/kg/day. ACE2 is thus able to report a percentage of women of childbearing age who exceed this blood mercury level in the population (8%) for the 1999-2000 time period. This is an effective way of translating biomonitoring findings into useful public health information. The ACE3 draft does not presently provide this important interpretive information.

3) The text would be strengthened by including reference to the EPA mercury RfD; in addition, the text does not report concentration or dose values on p. 1 lines 30-39 and p. 2 lines 1-8 in the summary of research findings. The reader is therefore not able to interpret this information in this section; the reader cannot place the study findings in context. These studies should be reported with their dose levels in units of ug/kg/day, or ppb Hg in blood, or ug/lit (with interpretation of the units provided in the text) so the reader can place the health effects reported in these studies in reference to the RfD.

4) Specifically, the significance and utility of research findings reported on pp 1-2 are lost by the lack of dose values and the use of vague terms. For example,

p. 1:

Line 32: "high-dose mercury" (What is "high dose?")

Line 34: "moderate mercury levels" (What is "moderate?")

Line 36: "increased prenatal mercury exposure" (Increased above what?)

p. 2:

Line 1: "prenatal mercury exposures" (At what levels?)

Lines 3-4: "levels within the range of typical levels" (What are these levels?)

Line 5: "increased prenatal mercury levels" (Increased above what?)

Line 6: "early life exposures" (At what ranges of exposure?)

5) It is especially troubling that the important findings from Lederman (2008), Oken (2008) and Oken (2005) are buried in the text (p. 2 lines 2-5). If appropriately reported and highlighted, this information would be a great interest to the public and to policy makers, in that it provides a

glimpse into findings that could call into question the existing EPA mercury RfD. These findings should be flagged in this report and placed in the context of the biomonitoring findings for mercury.

6) In general, this report should interpret the CDC data for use by the public. This could be done by giving an estimate of the number of women of childbearing age at risk and/or providing an estimate of the number of babies born each year potentially at risk of neurodevelopmental deficits attributable to mercury exposure.

7) ACE2 is relatively clear about the linkages between the coal industry and environmental mercury contamination: "The largest human-generated source of mercury emissions in the United States is the burning of coal." (p 58) Why does ACE3 step away from this important point? On p. 1, lines 8-13, the role of coal in mercury contamination is obscured. The reader wants to know: "What is the contribution of the coal industry to mercury in the bodies of women and potential health effects among infants?" The EPA mercury webpage (at http://www.epa.gov/hg/exposure.htm) notes that "The U.S. power sector is estimated to account for about 1 percent [of] total global emissions." This statement, or something similar, should appear in the document text, with a follow-up statement noting that coal provides about 90% of U.S. power. It is important that EPA make these links for the public.

8) I appreciate the mention of the role of the work environment in mercury exposure (p. 2 line 38). It would be very useful if this document could elaborate on this statement and provide the reader with information on this potential pathway of exposure. Are women at risk in the workplace, perhaps more so than from eating fish? Are there certain occupations where mercury exposures are of particular concern? How are workers protected from mercury exposures, or not? While this might appear to be somewhat tangential to the matter of children's health *per se*, the fact that women of childbearing age are usually working in the U.S. makes the issue of occupational exposures relevant to this report and to the public interest.

9) In general, the text could better interpret the CDC data for use by the public; it could provide more exposure or dose numbers from previous studies and compare these against the RfD. It could note that the RfD might not be protective in light of refs 18-20, which would be consistent with the historical trajectory of Hg "safe levels". The text should give an estimate of the number of women of childbearing age at risk and provide an estimate of the number of babies born each year potentially at risk of mercury- attributable neurodevelopmental deficits.

Organization

1) It is not clear that the term "mercury" in the text refers to "methylmercury" (pp 1-2).
The reader is left to deduce this on p. 2, line 38, when the terms "elemental and inorganic mercury" reappear for the first time. On p. 1, it is not clear whether "mercury" or "methylmercury" are of concern (see lines 26-27, for example). A more disciplined use of terms is needed here.

2) Pages 1 to 3 should be categorized by sub-headings, written in the form of either a question or truncated phrase. There is a need for a more logical flow of information:

Page 1
Lines 2-7: What is mercury?

Needed: What have we learned about mercury and children's health since 2000?

Cite references #18-20 here for concerns about RfD, existing levels. c. Line 8-17: How does mercury enter the environment?

Lines 18-25: How does mercury enter people's bodies?

Page 2
Lines 2-7: How does mercury affect the health of children?

Lines 9-15: Is eating fish hazardous due to mercury contamination? c. Lines 16-25: Where can I find information about mercury and fish? d. Lines 26-37: Is there a problem with mercury in vaccines?

Needed: Is mercury exposure a problem in the workplace?

Lines 38-line 10 page 3: Is there a problem with mercury in schools?

Lines 11-20: How is mercury measured in biomonitoring studies?

Lines 21-31: What levels of mercury in people have been identified by biomonitoring?

Lines 32-25: What has the federal government learned about mercury exposures and children's health since the last ACE study report in 2003?

Question 2 – Indicator Text

Reviewer 1:

I think the indicator is understandable and the information pertaining to the data set is straight forward and easy to read. I would like to see an expanded indicator related to children 1-5.

Reviewer 2:

Page 4, line 7 NHANES. It should be mentioned that the representative population sampled includes those particularly in the "other" category that consume more fish than the named categories. This may skew the results. The use of these values, particularly the median values should not be used as "normal" as they include those with fish consumption patterns that vary.

Page 4, lines 13-17 NHANES. The indicator chosen (B4) is for women 16-49 years covering the survey years 1999-2008 (Note line 17 says 1999-2006). The rationale is that there is risk to the developing fetus from exposure of the pregnant mom, a reasonable statement. However, the section goes on to state that there are data for ages 1-5 from 1999 to 2008 and for ages greater than 1 from 2003 on. Why were these data not used as they represent actual data in children rather than indirect measures in the mom?

Page 4, lines 18-25. The text states that total blood mercury was reported from 1999 on and inorganic mercury starting in 2003-2004. This is a bit confusing. I believe that total mercury was measured in all periods, a necessary process to be able to compare data from different survey periods. As the authors note, the influence of fish consumption and the presence of methyl mercury

is a large fraction of the total body burden of mercury so measurements only of inorganic mercury, primarily from occupational and environmental sources, would underestimate exposure.

Page 4, line 26. It should be noted in this section, that the biological half-life of methylmercury in blood is about 158-170 hours (ATSDR Tox Profile, page 189) whereas the biological half-life of total mercury is about 60 days. The implications of the short half-life for methyl mercury is that blood measurements will only reflect recent fish consumption and may not be representative of an individual's risk of adverse health effects.

Page 4. General comment: NHANES data exist for mercury in urine for women 16-49 years old as well as children 1-5 over most of the time periods. Why were these data not used as an indicator of environmental exposure of children and the risks associated with that exposure? Mercury in urine reflects environmental exposure in contrast to mercury in blood that assesses mostly dietary exposure. Elimination half-lives are generally longer reflecting representative exposures rather than very recent exposures. In the interests of transparency, I believe that the existence of the urine data should be acknowledged along with a reason why this indicator was not used.

Reviewer 3:

Content

1) The indicator text suffers from the same problem as the Topic Text, described above: It does not give the RfD and other values against which the reader can compare the levels presented in Indicator B4, for example.

2) In general, this section is heavy on explanations of statistics and descriptions of results, but it provides little to no information that would allow the reader to *interpret* what s/he is reading. How do these results compare with the RfD, for example? If 5.8 ppb ≈ 5.8 ug/lit, this would be a simple thing to do. If I have the conversion incorrect, it is still a simple task to include this in B4.

3) It is important for the reader (including health care providers, policy makers, public health scientists etc.) to also have a sense of the uncertainties in the data. This gives the reader the opportunity to make an independent decision about a course of action. For example, this section could report something about the findings of citations 18-20, and in a qualified way, illustrate these findings in Indicator B4, perhaps with a dotted line to indicate "preliminary evidence." Without interpretation and without some indication of the uncertainties, the reader is left with questions about the report's findings and with uncertainties about what actions to take.

4) The median data (B4c & B4d) show an increase of 100% from ages 3-6 to ages 6-11; i.e., 0.2 ug/l to 0.4 ug/L, yet this is not discussed in the text. This seems significant. Is exposure somehow increasing during this growth period?

Organization

1) This section could be more effectively communicated using sub-headings, bulleting of information, use of boxes, comparisons with the RfD, providing an estimate of the number of women and newborns potentially at risk.

Question 3 – Indicator Presentation

Reviewer 1:

I would like to see the 95th percentile and race ethnicity of the 1-5 age group.
Also the 95th percentile of income including the 1-5 age group.
Also can the data be presented by regions (coastal, Midwest, etc.)

Reviewer 2:

Page 5, line 8. Add (see Table B4) at the end.

Page 5, line 12. There is no discussion of Table B4a. Even if there is nothing remarkable about the data for medians, some mention of that should be mentioned.

Page 6, line 4. It should be mentioned that the "other" category included populations that have much higher consumption of fish like Asians and Native Americans, non-Hispanic. This may skew the data as shown.

Page 7, line 28. There is no discussion of the data from Table B4d. From my view, a comment that the median and 95 percentile values from the 2005-2008 time period did not show significant differences across age groups. This is an important fact that is not reported.

Reviewer 3:

Content

1) The graph, bullet points, and data tables do not have interpretive information and are therefore not very useful to the reader. I have described this in some detail above. In short, it is not possible for the reader to know "what this information *means* for the health of children." Answering this question is the central goal for improving this entire document, including the Figure and Tables.

Organization

1) Table B4a is not discussed in the text.

2) It is difficult to track down the Table numbers in the explanatory text.

3) Statistical significance could be indicated in the tables with the use of (*).

4) Conversions should be provided to allow the reader to compare with ACE2; e.g.: 0.1 ug/kg/day ≈ 5.8 ppb ≈ 5.8 ug/L.

5) What does the doubling of the median concentration in B4d from 3-6 to 6-11 mean?

Question 4 – Context and Utility

Reviewer 1:

a.) More detailed analysis for the 1-5 age group needs to be included.

b.) I did not find anything on how to improve the data. There also needs to be a section on the limitations of the data set. Again the 1-5 age group was not part of the indicator and not represented in the data analysis. Yes I understand from the literature review that you are mostly concerned with fetus involvement, however I think that 1-5 and maybe up to 20 should be include to evaluate these children. Recommendations were not made on ways to improve the NHANES data base.

c.) Although there is a mention of fish consumption in the background. One of the most effective ways to minimize the impacts on children is the fish consumption and public health outreach to educate the general populations on risk to the fetus and effects that may manifest through childhood by consuming fish high in mercury levels.

Reviewer 2:

Regarding the three principle objectives, the data presented in this document do not represent data from children as the authors chose to ignore that data from NHANES in favor of the data on women ages 16-49. Although one can assume that exposure during pregnancy will impact the child, why use that data when you have direct data on children?

There is no summary of the findings that provide the take home message that would address in a concise manner, the significance of these data and data trends. They have a significant public health message in my opinion but this is not stated in clear text. Of course the lack of any analysis of data from children is a major shortcoming in my opinion.

Reviewer 3:

a) I have described this in detail above. The document describes data gathered by the CDC, but it does not effectively make this information useful as a "key factor relevant to the environment and children" because it offers no interpretation. It also obscures potentially very useful data from the research community by using phrases (such as moderate level etc) without offering a quantitative interpretation of what those phrases mean in terms of dose or concentration.

b) I do not think this draft will effectively improve discussion as currently drafted because the information is so difficult to use, as noted above. The document leaves the reader thinking, "We collected all of this information and there is plenty of science involved here, but I don't quite see how it relates to public health, children, or the environment."

c) Again, the report misses an opportunity to be clear. It does not provide interpretive information of the biomonitoring data, and it side-steps naming the key source of mercury contamination in the U.S.: the generation of power using coal. If the report were clear on naming this source and quantifying it, policy makers and the public could begin to make informed choices about the trade-offs in using coal as a source of power. A quantitative decline in cognitive function in some

portion of the next generation, for example, might be enough to shift the policy debate, but that will only happen if this important CDC biomonitoring information is presented in a way that is understandable and usable.

Question 5 – Documentation

Reviewer 1:

A new section is needed on limitations to the current data and general recommendations on improving future data collection analysis.

Reviewer 2:

References: Appears to be representative of the literature.

Metadata: The information seems complete but is general. Can these be adapted for the indicator of interest, in this case mercury? For example, page 16, the years of available data should be specific for mercury. In addition, the question of analytical methods and the reporting of inorganic, metallic and organic mercury referred to previously in this review, need to be clarified.

Methods: Summary section, lines 15-18. There is confusion by listing the different methods used to determine mercury in blood taken at different time intervals when total blood mercury was reported for each time interval. If the method for total mercury did not change, then data can be compared across time. It also is confusing to mention that data is available for many of the more recent time intervals for children ages 1 and up. It raises the question of why are you not reporting children's data rather than that of women ages 16-49.

Page 21, line 6. It should be mentioned that the "other" category includes ethic groups that traditionally consume more fish per capita than the other defined groups. This leads to high values for this category.

Data tables: Data are shown for women 16-49 and for children 1-5 years old. The data tables show significant differences between "other" and all other groups without any explanation that the probable cause is increased fish consumption. The data tables also show children ages 1-5. It is of interest that the degree of mercury exposure is much less than women ages 16-49, perhaps speculating that there are fewer risks of adverse health effects in children compared to women. If these data tables and those in the previous section include data from children, it is imperative in my opinion to comment on the apparent lower body burden of mercury in children.

Comment: I cannot comment on the quality of the statistical treatment because I lack the expertise in this area. The data tables provide a concise summary of the data comparisons and the significance (for those with the appropriate statistical training, but not for the lay audience and general public or government official)

Reviewer 3:

1) In general, yes. I would like to see the findings of citations #18-20 included in this in some way, in that they suggest that lower dose levels are a cause for concern, which is the primary motivator for public health interventions.

2) I would avoid the use of the term "environmental chemicals," which conveys the idea that mercury and other industrial pollutants are somehow "environmental." In some boxes, the term "contaminants" is used, which is confusing. I would prefer the terms "industrial chemicals and pollutants," or "environmental chemical contaminants," or "environmental contaminants."

3) I would avoid the use of long blocks of text (e.g. p. 17 Summary). This information can be bulleted and presented in clearer forms.

1.5 PBDEs

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Deborah Bennett
- An Li
- Arnold Schecter

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

The comments below are provided with audiences of varying levels of knowledge in mind, and intended to help improve the document so that such audiences, including the general public, can better understand the document. These comments are based on my >10 years of research on PBDEs as an environmental chemist. Due to my background, I would not comment on any statistical method used.

In general, the section "ACE3 Biomonitoring: Polybrominated diphenyl ethers (PBDEs)" was well prepared. Referring to the "Criteria for evaluating indicators" (page 4 of the instruction to reviewers), I feel that the NHANES data base is the most appropriate to use for Indicator PBDE1, due to data consistency, reliability, and transparency.

However, improvements are needed. The comments and suggestions below are arranged by sections (page numbers) of the document. Major comments are labeled as A1, A2, …etc., and minor comments are by page numbers.

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

The text clearly describes the importance to children's health, with a focus on exposures during pregnancy. Below is a list of other references that you may want to review as this would allow for a slight expansion of some of the health effects listed, but it is not critical.

42. Branchi I, Capone F, Alleva E, Costa LG. Polybrominated diphenyl ethers: Neurobehavioral effects following developmental exposure. *Neurotoxicology.* Jun

2003;24(3):449-462.

43. Eriksson P, Jakobsson E, Fredriksson A. Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? *Environ Health Perspect.* Sep 2001;109(9):903-908.

44. Eriksson P, Viberg H, Jakobsson E, Orn U, Fredriksson A. A brominated flame retardant, 2,2 ',4,4 ',5-pentabromodiphenyl ether: Uptake, retention, and induction of neurobehavioral alterations in mice during a critical phase of neonatal brain development. *Toxicological Sciences.* May 2002;67(1):98-103.

45. Viberg H, Mundy W, Eriksson P. Neonatal exposure to decabrominated diphenyl ether (PBDE 209) results in changes in BDNF, CaMKII and GAP-43, biochemical substrates of neuronal survival, growth, and synaptogenesis. *Neurotoxicology.* Jan 2008;29(1):152-159.

48. Kuriyama SN, Wanner A, Fidalgo-Neto AA, Talsness CE, Koerner W, Chahoud I. Developmental exposure to low-dose PBDE-99: Tissue distribution and thyroid hormone levels. *Toxicology.* Dec 2007;242(1-3):80-90.

49. Hallgren S, Darnerud PO. Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats - testing interactions and mechanisms for thyroid hormone effects. *Toxicology.* Aug 2002;177(2-3):227-243.

50. Darnerud PO, Aune M, Larsson L, Hallgren S. Plasma PBDE and thyroxine levels in rats exposed to Bromkal or BDE-47. *Chemosphere.* Apr 2007;67(9):S386-S392.

51. Zhou T, Taylor MM, DeVito MJ, Crofton KA. Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption. *Toxicological Sciences.* Mar 2002;66(1):105-116.

52. Talsness CE, Kuriyama SN, Sterner-Kock A, et al. In utero and lactational exposures to low doses of polybrominated diphenyl ether-47 alter the reproductive system and thyroid gland of female rat offspring. *Environmental Health Perspectives.* Mar 2008;116(3):308-314.

53. Richardson VM, Staskal DF, Ross DG, Diliberto JJ, DeVito MJ, Bimbaum LS. Possible mechanisms of thyroid hormone disruption in mice by BDE 47, a major polybrominated diphenyl ether congener. *Toxicology and Applied Pharmacology.* Feb 2008;226(3):244-250.

54. Chevrier J, Harley KG, Bradman A, Gharbi M, Sjodin A, Eskenazi B. Polybrominated Diphenyl Ether (PBDE) Flame Retardants and Thyroid Hormone during Pregnancy. *Environ Health Perspect.* Oct 2010;118(10):1444-1449.

Additionally, when discussing the exposures, there is a paper that includes early childhood levels that should be included.

18. Rose M, Bennett DH, Bergman A, Fangstrom B, Pessah IN, Hertz-Picciotto I. PBDEs in 2-5 year-old children from California and associations with diet and indoor environment. *Environ Sci Technol.* Apr 1 2010;44(7):2648-2653.

In general, the presentation is clear. There are some things that could be done to make the section clearer. First, it might be useful to list the primary congeners associated with each of the commercial mixtures in the third paragraph to better tie it to which compounds are included in the indicator.

Second, the sentence describing reference 14 is not that clear.

Finally, on line 6 of page 3, one may want to mention dermal exposure as well. I think there is as much evidence for that pathway as for settled dust on food.

Reviewer 2:

Only minor comments and suggestions are given for this section.

P1, L9: Delete "anywhere" because fractional numbers are invalid here.

P1, L10: Change "from 1-10" to "from 1 to 10".

P1, L13: A period "." is missing at the end of the paragraph.

P1, L15: Change "mixtures PBDEs" to "PBDE mixtures".

P1, L15-18: The starting year (in the 1970s) for large scale PBDE manufacturing in the U.S. should be mentioned somewhere in this paragraph.

P2, L8: References 4-10 are cited. The followings could be added:

Wei, H.; Turyk, M.; Cali, S.; Dorevitch, S.; Erdal, S.; Li, A. 2009. Polybrominated Diphenyl Ethers in Dust: Particle Size Fractionation, Evidence of Debromination and Relevance to Human Exposure. *J. Environ. Sci. Health A*., 44(13), 1353-1361.

Stasinska, A.; Heyworth, J.; Reid, A.; Hinwood, A. 2011. A Systematic Review of PBDEs in Dust Comparing Concentrations Across Home, Office and Vehicle Environments and Country. *Epidemiology*, 22(1), S61-S62.

P2, L30-35: For early-life exposure, cord blood, fetal blood and breast milk are mentioned. Why not placental tissues? A set of data on PBDEs in placentas in the U.S. is provided in:

Dassanayake, R.M.A. P. S.; Wei, H.; Chen, R. C. Chen, Li, A. 2009. Optimization of Matrix Solid Phase Dispersion Extraction Procedure for the Analysis of Polybrominated Diphenyl Ethers in Human Placenta. *Analytical Chemistry*, 81(23), 9795-9801. (PMC2794305)

In addition, some data for placenta tissue collected in Canada are also available in:

Doucet et al., 2009, *Environmental Health Perspectives*,117(4), 605-610.
P2, L44: Change "based on measured levels" to "from measured concentrations".

Reviewer 3:

In general, very good.

Areas for improvement:

Leading off with NHANES good but strong and weak points important: No young children included. No persons in military or institutions included. No milk levels included. No target organ levels included. BDE 209, an important PBDE congener, was not measured in any NHANES studies. This is the characteristic congener still in the one commercial mixture still being manufactured or used in the USA.

Question 2 – Indicator Text

Reviewer 1:

Overall, this section is well written and it is easy to understand.

The text should include a reference to the number of samples included in this analysis in the first paragraph discussing NHANES, so the reader does not think indicator is based on 5000 individuals. I think it would be clearer if the specific congeners were matched to the specific commercial mixtures. This would improve the ability to understand the strength of the indicator.

Different PBDE congeners have different levels of toxicity. Unfortunately, the exact relative toxicity between the congeners is not known, making it difficult to provide the appropriate weighted sum. Therefore, I agree that summing the concentrations of the congeners is appropriate; however, I think that some mention that there is likely a different toxicity between congeners and thus a straight sum may not be the best indicator, but given the uncertainties, it is the most appropriate approach, or something to that effect.

It would be nice to list the commercial mixtures associated with each of the measured congeners, either here or overview of PBDEs. I think it would make things clearer.

In the statistical testing section, changes over time are discussed, yet no comparisons are made in the text.

Reviewer 2:

Major comments are provided for the improvement of this section:

B1. Indicator for childhood exposure is not described.
Most of the Indicator text describes the use of EHANES data for women's serum. In fact, there is no mention of the data set for children at all in the Overview on page 4 and numerous other places. The reasons for this are not given in the text.

B2. Justification is needed for using women's data as indicator for children's exposure
ACE's focus is in on children. The ideal indicators are therefore biomonitoring data obtained by analyzing children's biological samples. While the data for children of 12-17 years are a direct

indicator for childhood exposure, serum level of the newborns would be the direct indicator for prenatal exposure. Of course, dataset for newborns may not exist or be too limited in size to be suitable for the purpose of the Indicator, due to practical reasons. This or other reasons for using women's data as a substitute for children's prenatal exposure should be more explicitly stated in the document.

B3. Explanation is needed for using serum rather than other biological samples
There are many types of biological samples which are noninvasive and more easily to obtain than serum. There should be many reasons for using serum rather than urine, hair, saliva, etc. for Indicator PBDE1; and these reasons are not always clear to the general public. Due to the hydrophobicity of PBDEs, measuring biological samples rather than lipid-rich adipose or serum is neither practical due to detection limit nor able to reflect the extent of the bioaccumulation. These and other reasons should be at least briefly stated in the text.

B4. Not including data for BDE-209 may underestimate human exposure to PBDEs.
The lack of data for decabromodiphenyl ether (BDE-209) is a major drawback for Indicator PBDE1. This may cause underestimation and affect the accurate indication and interpretation on children's exposure to environmental PBDEs. Numerous published studies have demonstrated that BDE209 is the dominant congener in house dust (>90% of total PBDEs) which is the major vehicle for PBDE intake by children. In human body, BDE-209 could be debrominated to more bioaccumulative and toxic PBDE congeners or metabolized into hydroxylated PBDEs (OH-PBDEs). Although cross-placenta transport of BDE-209 might be limited due to its large molecular size, its metabolic debromination may produce products which are more transportable (Frederiksen et al. 2010. Environmental Health, 9:32. http://www.ehjournal.net/content/9/1/32).

BDE-209 data are probably not available from the EHANES 2003-2004 dataset, thus inclusion of BDE-209 may have to wait for the next revision of ACE. In this version, however, the reasons for not including BDE-209 should be given, along with some general statements on the possible effect of this drawback. It would be much more beneficial and helpful to the audience of this document, if a quantitative assessment of such effect could be conducted and reported.

B5. Lipid normalization needs caution.
Although no change in this document may be necessary, it should use caution when the PBDE concentration data are normalized based on the lipid content of the biological samples, even though this is a very common practice in data publishing. This is because of the significant inconsistency in lipid measurements, which makes it difficult to compare among published data. For this reason, the U.S. EPA has required that the PBDE concentrations be reported on the basis of wet tissue mass, rather than on the basis of the lipid content (Method 1614, *Brominated diphenyl ethers in water, soil, sediment, and tissue by HRGC/HRMS. Section 17.6.* USEPA 2007. http://www.epa.gov/waterscience/methods/method/files/1614.pdf)

Reviewer 3:

"Body budens" and "nanograms" not defined or explained".

"Demographic groups" are not defined nor illustrated.

"Randomly" not defined

"Relative standard error" not defined, explained.

Question 3 – Indicator Presentation

Reviewer 1:

The first figure is very clear and informative. The "Statistical Note" provided under the fact that Black-non-Hispanic woman have the highest levels is not at all clear. I think most readers would be able to understand a note that provides more information, specifying which groups are statistically significantly different.

In general, Table PBDE1 is clear and informative. However, there is absolutely no idea how large the N is for any of the groups. While I do not think these values need to be in the main indicator text, it may be beneficial to note them in the reference material and make note that the information is in the reference material.

While I agree that it is important to include the information on children (Table PBDE1a), it is not discussed as part of the indicator and is not well integrated into the section. The rational for including this should be stated earlier.

Reviewer 2:

Both major and minor comments are provided for this section.

C1. Poverty lines need specifications of the time and location.
Poverty guideline figures given by U.S. DHH are time and location dependent. In this document, the "poverty level" used for income categorization should therefore be given the year with which the level is associated, as well as the location (e.g. the 48 states in the main land have different poverty line figures than those used for Hawaii and Alaska). Are the poverty level numbers used in this Indicator for 2003-2004 or another time period? Are there any PBDE data collected in, for example, Hawaii and Alaska? If yes, which "poverty level" was used to categorize them based on income? If all the incomes are categorized based on a single set of poverty level figures, I would suggest tabulating these figures in the Method section.

C2. Please be more explicit on the Graph on page 7.
In the Graph on page 7, as well as Data Tables on pages 9 and 10, the terms "< poverty level", "> pervert level", etc could be very confusing to the general public. For example, does "> poverty level" mean poorer or richer with income above the poverty level?
In the Graph on page 7, the highest PBDE level (60 ng/g lipid) is for black non-Hispanic women with family incomes above poverty level. The note below the Graph indicates that this value is generally not statistically significantly different from those for other race/ethnicity and income groups. However, it could be helpful to compare this value with that for the same race/ethnicity group (black non-Hispanic) with income below the poverty level (about 32 ng/g lipid), because the former almost doubles the latter, and because this comparison, if significant, could suggest an important direction of future research on disparity.

P9. The explanation in the 2nd Note on should also be given on page 5, line 27, in the Indicator Text section.

Reviewer 3:

Figures complicated. Why needed? Could more simple displays convey all intended? Or a few sentences?

"Median" not defined. No ranges provided. No important congeners described as such. For example, BDE 47.

No statement about statistical significance of last sentence on page 8.

Page 9: Statistical significance seems missing.

Page 9: This table is complicated and may occupy too much of the limited space for the topic. Better to summarize meaning of many numbers, I believe.

Page 9, lines 23-25 will not be understood by most readers. Explain and maybe use different more simple words.

Page 9: Does the table represent all US women or only those in an NHANES report?

Tables treat all PBDE congeners as though of equal toxicity. We have no evidence for this. A total of those measured may mean nothing or very little. For example, dioxins were first summed. All measured were simply added to one another and the total presented. This is what is being done in this document. There is no explanation that with some chemicals, for example, dioxins, some such as 2,3,7,8-TCDD are very much more toxic than others such as OCDF or OCDD. So a summing of measured congeners may be extremely misleading with respect to toxicity or health consequences.

Pages 15-16 focus exclusively on NHANES. Why is this needed. NHANES is not the only source of the data.

Pages 17-19 more detailed than needed. Why such detail. Wasting space when major points could be made.

Pages 20-28 should be deleted. They are highly technical. Summarize the findings, but stick to important points. The highly technical materials do not belong in this kind of document. If this is meant to be read and understood by various types of scientists, legislators, science reporters, environmental groups, industry scientists, the general public and attorneys the technical details do not belong here.

Question 4 – Context and Utility

Reviewer 1:

For the most part, the strengths and limitations are acknowledged. However, I think it needs to be acknowledged that you are summing congeners without regard to the relative toxicity, as the relative toxicity is not well known.

a) The information will be able to be compared over time. There is no temporal comparison at this point since only one year of data exists.

b) I do not think the indicator can inform discussion on how to improve data. However, I concede that I am not entirely clear on the goals in this regard.

c) I think the indicator will provide an adequate way of assessing temporal trends.

Reviewer 2:

Only minor comments are given for this section:

P15. Row 7, right: Please specify what "NCHS" stands for.

P16. Row 3: Please specify what "QA" stands for.

Reviewer 3:

a) Temporal trends are not characterized. Schecter et al and Sjodin et al have independently characterized marked increase in body burden of PBDEs in the US population during the past decades while dioxins, PCBs and dibenzofurans are declining.

b) University research is not described nor characterized in this document in my opinion. Stockholm research in Sweden began documenting changes in exposure to PBDEs first. Then other agencies, governmental and university based, not only CDC's NHANES, which does do excellent work. But they were not first nor the only ones to characterize important data with respect to PBDEs. In fact, a Swedish PBDE chemist joined CDC to contribute PBDE data in Americans. Various sources will inform discussions.

c) Congener specific measurement of PBDEs, including BDE 209, will provide data on levels. Determining toxicity of each congener will help characterize health risks.

Question 5 – Documentation

Reviewer 1:

There are several shortcomings with the documentation. First, in the data summary table, it is not clear what the missing values result from. Later one can deduce that they were missing lipid values but that should be stated up front.

Table 1 on page 26 clearly has a number of typos, as black non-Hispanic are not included and white non-Hispanic are listed multiple times.

There should be some sort of N values associated with the groups.

In the primary text, there is a group of unknown income, which in some cases appeared to have different income levels. This group is left out of the supporting information.

Reviewer 2:

Both major and minor comments are provided for this section.

E1. Additional data could be provided.
Tables 1 – 6 provide p-values for various comparisons of the medians. These are very helpful. However, many medians being compared are not provided. The Indicator Presentation (Tables PBDE1 and PBDE1a on pages 9 and 10) gives medians by race/ethnicity and income only. No medians are found for, for example, boy and girls, thus the p-values given in the last column in Table 3 have no use, because we won't know from p-values whether boys or girls have higher exposure.

As I mentioned above, the description of the dataset for children 12-17 years of age is so limited in this document, compared with that for women. The reason is not provided.

E2. Could the unadjusted data be provided as well?
As this Indicator represents nationwide children's (not women's) exposure to PBDEs, it is correct to adjust the PBDE concentration medians based on age-specific birthrates. However, in order for this report to be more useful to its audience, I would suggest including the unadjusted data for women without consideration of birthrates in the appendices.

E3. "Black non-Hispanic" is missing.
In Tables 1 to 4 (page 26-28), where is the race/ethnicity group "Black non-Hispanic"? Should "Race2" be "Black non-Hispanic" in Tables 1 and 3, first row? Why the first two rows in Tables 2 and 4 duplicate each other in race columns?

P17. Data Summary Table row 6: The term "missing values" could be confusing to the general public. Something "missing" in colloquial language means being lost due to carelessness or mistakes. Here is a SAS term, thus a brief explanation could be helpful.

P21. L4: What is "indicator B2"?

Reviewer 3:

Many important references are missing. These include but are not limited to the following:

1. Schecter, AJ, Pavuk, M., Paepke, O. et al. 2003 Polybrominated Diphenyl ethers in U.S. mothers' milk. Environmental Health Perspectives, 111(14), 1723-1729.

This paper was the first to document that all US persons, in this case women, were contaminated with PBDEs; that the levels were orders of magnitude higher than European levels; and that intake by nursing infants of PBDEs was extremely high.

2. Schecter, A.J., Paepke, O, Tung, K.C. et al. Polyborminated Diphenyl Ethers Contamination of US food. Environmental Sciences and Technology, 38(20), 5306-5311.

This was the first description from a market basket survey of PBDE congeners in U.S. food and showed high levels of various PBDE congeners in meat, fish and dairy products, thus documenting one source of PBDE body burden in humans.

3. Schecter, A.J., Paepke, Ol, Tung, K.C., et al., 2005. Polybrominated diphenyl ether (PBDE) flame retardants in the US population: Current levels, temporal trends, and comparisons with dioixns,

dibenzofurans and polychlorinated biphenyls. Journal of Occupatinal and Environmental Medicine 47(3): 199-211.

This was among the first publications documenting marked increase in US human body burden of PBDEs while dioxins, dibenzofurans and PCBs were markedly declining.

4. Schecter, A., Paeplke, O., Tung, K.C. et al. 2006. Changs in Polybrominatedf diphenyl ether (PBDE) levels in cooked food. Toxicological and Environmental Chemistry 88(2): 207-211.

This documented, for the first time to the best of my knowledge, that cooking, broiling, and dripping away fat, could decrease PBDEs in food.

1.6 PCBs

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Lucio Costa
- Susan Jobling
- Arnold Schecter

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

The introduction presents a short, but comprehensive, overview of PCBs. One aspect that may deserve an additional sentence is the presence of non-dioxin like PCBs and dioxin-like PCBs, which may have substantially different pattern of toxicity.

Reviewer 2:

The topic text clearly describes the topic and its importance. Missing desirables include levels of PCBs that would be considered harmful or worrisome in human tissue, so the reader can put the following text into context.

The determination of critical windows of susceptibility to environmental chemical exposures and health has become a major public health focus. Early age at exposure is a really important determinant in subsequent health effects due to environmental chemical exposures. This fact needs emphasis.

Particular routes of exposure need discussion: food supply (fish, dairy, hamburger, and poultry being the most contaminated) and our bodies. Some research also links PCBs to increased rates of type 2 diabetes. This is not described.

Because the effects of these contaminants are additive, it is necessary to take into account the cumulative exposure to organohalogen contaminants such as PCBs during risk assessment.

Recent pharmacokinetic (PBPK) models show that that co-exposure to PCB congeners increased the lactational transfer of methylmercury to the offspring of maternally exposed mice. PCB congeners may increase the lactational transfer of MeHg by escalating albumin levels in maternal blood. This should be mentioned.

Reviewer 3:

The initial pages are reasonably done but could use improvement as illustrated below.

Page 1, lines, 3 and 4: produced "commercially and used"

P1, l 9: Also distributed in humans, not only found in the environment.

P 1, ls 14-17: The literature also describes respiratory secretions and altered functions, eye pathology, skin effects, and cancer.

Page 1: l 9Superfund is not defined.

Page 1: The text seems to omit laboratory animals and wildlife; biomonitoring and health.

P 2, l16-18: Omits other depot sources perhaps of more direct or obvious importance, for example, PCBs in sediment as in the Hudson River of NY.

Biomonitoring has also shown elevation in children's blood levels, as Schecter and Wolff showed in children playing with PCB contaminated materials.

GE has data showing some of their PCB workers with very high PCB levels. It is believed that workers sometimes brought home contaminated clothing and contaminated some in the home from various studies of PCBs, dioxins and PCDFs which has sometimes contaminated wives with dioxins and PCDFs and I believe also PCBs. Since this is the case it is probable children were contaminated by clothing workers wore and milk produced by contaminated spouses.

This document ignores the male sex without any comment. The reasons are not stated. Is this scientifically sound?

Question 2 – Indicator Text

Reviewer 1:

This section contains several interesting and important information; however, additional details may be added. The four PCB congeners are said to have been chosen because of their higher levels in the environment. Are these all non-dioxin-like PCBs or else?

Why Mexican-American were chosen over other Hispanics is not clear.

It would also be useful to define the poverty level.

Reviewer 2:

The text provides sufficient information about the data set and the indicator calculation to enable understanding. This is very clear.

Reviewer 3:

The document seems to rely on NHANES almost exclusively here and in many other areas. This is an important study or series of studies but not the only study of importance.

The text does not review work prior to NHANES and at the same time as NHANES methods of measuring PCBs in blood, milk or adipose tissue and the results.

It was customary until very recently to not perform congener specific testing but present one number which was based on relation to a commercial PCB mixture. This usually was in parts per billion or ppb wet weight or sometime lipid based. Mary Wolff was a strong proponent of this method of chemical analysis and reporting.

Frequently approximately 5-10 ppb was reported as US adult general population median or mean level of PCBs. Most older literature includes biomonitoring done and reported in this fashion.

P4, L 14: “Body burden” not defined or explained.

P4, l 30: “Ethnicity and race” not defined nor is it explained how NHANES estimated race or ethnicity of a person in the survey.

P4, l 41: “Poverty level” not defined nor illustrated.

P5, l 7: “Statistically significant” not defined nor contrasted with clinically or biologically significant.

P5, L10: Perhaps “by chance” might be easier to understand than “randomly”.

The document should read to be understood by the educators, government officials and concerned parents mentioned as part of the intended audience.

Question 3 – Indicator Presentation

Reviewer 1:

Data are presented in a graph and a Table. An additional Table shows the 95% data. The bullet-points provide a snapshot summary of the data.

Reviewer 2:

Discussion of whether maternal serum is the best indicator is needed. Three types of tissue samples-umbilical cord (UC), umbilical cord serum (CS), and maternal serum (MS)-have often been used to assess fetal exposure to chemicals. Some studies suggest that umbilical cord serum is the best sample to assess fetal contamination status of persistent chemicals.

Reviewer 3:

Page 6: Complicated graph. Why so many comparisons in the graph.

Why is no other data than NHANES also included so women under 16 years or over 49 years are included?

Is "race" meaningful and how does NHANES determine it?

Is "ethnic group" meaningful and how does NHANES determine it.

The above two are subject to intense debate which should not be ignored in this important document.

5th, 10th, 25th, 75th, 90th and 95 percentiles would be of interest here and useful to the readers I recommend adding them.

Explanations are not offered for the results: Is one possible explanation of lower levels in Mexican women?

Again, males are not included which I believe to be a mistake.

Page 8, Lines 25, 26: "Standard error" and "relative standard error" are not defined nor explained.

P9, l 15 and elsewhere: I do not understand, nor do I expect the typical reader to understand why a correction for birth rates for women is needed in a biomonitoring discussion.

Question 4 – Context and Utility

Reviewer 1:

It is unclear what data on "poverty details" add to the overall "picture". The data would be more useful if some additional comments/interpretations were provided. In particular, the levels in Mexican-Americans are about 50% lower than Caucasians and African Americans. Is there any possible explanation, interpretation for this? Overall, poor Mexican-Americans are associated with the lowest blood PCB levels. This would need some comments.

Reviewer 2:

The indicator is quantifiable and relevant to the environment and children in the USA.

The indicator can be used to inform discussions among policy makers and the public about to improve data

The indicator can potentially be used to track and understand the potential impacts of PCBs on children's health and to identify ways in which to minimize these impacts. However, epidemiologic weight-of-evidence reviews to support regulatory decision making regarding the association between PCB chemical exposures (and chemical exposures in general) and *neurodevelopmental* outcomes in children are often complicated by lack of consistency across studies. Our ability to conduct weight-of-evidence assessments of the epidemiologic literature on neurotoxicants such as PCBs is at the moment limited, even in the presence of multiple studies, because the available study methods, data analysis, and reporting lack comparability. Consensus standards for the conduct, analysis, and reporting of epidemiologic studies in general, and for those evaluating the effects of potential neurotoxic exposures in particular are needed.

Reviewer 3:

Obvious examples of ways to improve the data would be to have NHANES collect data from birth on and to include institutionalized and military population estimates as well.

Another would be to use data in addition to NHANES if from peer reviewed scientific documents or other government reports.

Other comments have been listed prior to this section.

Question 5 – Documentation

Reviewer 1:

The methodology is described in great details. Some aspects (e.g. sections on Overview of data files, and Equations) are very technical, and of limited usefulness for the generic reader.

Reviewer 2:

The documentation is complete and transparent.

Reviewer 3:

A glaring omission is that of omitting the WHO 2005 dioxin TEF documentation. The DL PCBs are mentioned in the text without a reference.

No toxicology data and no wildlife data which could help interpret meaning of PCB potential health effects are cited.

Little of Yusho rice oil poisoning with PCBs and PBDEs is mentioned. This has been known as the first human PCB and then PCB plus dibenzofuran human poisoning known. This has been summarized by Masuda in Dioxins and Health, 2nd Ed, Eds A. Schecter and T. Gasiewicz, Wiley, 2003

Ref 14 has an incomplete citation and needs to be corrected.

"Metadata" is not defined nor explained

I do not understand why so much space has been taken up with methods especially if they will not be published but only available on the ACE website. Perhaps this is reasonable. But much is presented without orienting the reader about the technical details presented. Those familiar with statistical manipulations and NHANES may understand this material but I doubt if the lay readers will follow this without explanation which might not be that difficult to add.

1.7 Perchlorate

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Dana Barr
- Kurunthachalam Kannan
- Vlasta Molak

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

This document presents the draft text, indicator and documentation for the topic on "perchlorate" to be published in ACE3, in the Biomonitoring section. Perchlorate is an important environmental contaminant and children are exposed to perchlorate on a daily basis. Perchlorate can disrupt thyroid hormone homeostasis and deficits in maternal thyroid hormone during early pregnancy can lead to neurodevelopment effects in infants and children. Overall, the draft is well written, although several areas need some improvements in clarity. Following are the comments on specific comments for the charge questions.

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

General comments on ACE introductory information:
The term "concrete, quantifiable measures" seems to infer that there is no uncertainty in the interpretation of these data. Temporal variability, analytic variability, creatinine correction issues, diurnal variability and sampling of population dense areas are introduce some bias in the interpretation. Somewhere in the report these issues should be succinctly addressed and not mired in the small print as they are in CDC's National Report on Human Exposure to Environmental Chemicals. For example, the sampling by design limits the representation from less population-rich areas such as the West that may be "hot-spots" for exposure to perchlorate, for example, from jet fuel. So while these data are representative, they may not identify particularly unusual exposures that may occur in certain areas. Limitations in interpreting biomonitoring data should be given…. Not simply the standard language that "just because you have a chemical in your body it doesn't mean disease" type of limitation statement but the true complexities in trying to present these data in some form of interpretable framework.

Definition of body burden should be included in the glossary of terms. Body burden is NOT equivalent to a biomonitoring measurement and should not be used interchangeably.

Further define "exposure" in the glossary. Exposure does not necessarily mean the chemical has entered the body. Biomonitoring data can help evaluate exposure but are not equal to exposure.

Should stick to facts in glossary of terms. Definition of benzene for example is factual but to define "dioxins" as a "group of harmful chemicals" is not strictly factual. Furthermore, cadmium is a known renal toxicant and that is not indicated in the glossary. Methyl mercury. Most mercury (~90%) found in living organisms is in this form. Organophosphorus pesticides, not organophosphate pesticides. They are closely related in structure but not toxicity. Should clarify. Again, classifying PCBs as "toxic" is not strictly factual. Toxic in relation to what other chemicals? Organophosphorus insecticides are not referred to as toxic in the glossary although they have a real acute toxicity that can cause death. "Volatile Organic Pollutants" are more widely known as "Volatile Organic Compounds" or VOCs.

Deciliter. Should also add 100 milliliters.

Body burden. Body burdens can be calculated from blood measurements with supplementary toxicokinetic information. A body burden measurement and a biomonitoring measurement are NOT equivalent. This section should be rewritten to refer to biomonitoring measurements only.

The front matter is transparent but many terms are incorrectly or non-factually defined.

The topic information adequately links the topic to exposure but does a less successful job in relating it to health.

The language seems to simplistic even for lay persons.

Reviewer 2:

The topic text is well presented. The scope of the document and significance of perchlorate as a contaminant in children are logically described. However, some statements are not precise and vague and need to be adequately clarified. For example, line 8 of page 1 mentions that "some food crops produced in the southwestern United States" contain perchlorate. Although the statement is not wrong, it appears as if only those food crops produced in the southwest U.S. contain perchlorate, which is not true. Contamination of foods with perchlorate is widespread. I would suggest rephrasing the line 8 of page 1 as "……..surface water and found in foods collected from the United States" with reference to Murray et al. (ref#14).

Additional aspects to be included:
Page 1, line 13: because line 18 needs to be changed to reflect a general statement on contamination in foods, the lines 12-13 should be rewritten as "……..has been detected in human breast milk, urine, blood, and saliva". This makes it more meaningful because line 8 would focus on sources (water and food) and line 13 would focus on biomonitoring studies.

I would add two references for blood and saliva biomonitoring results for the United States. On line 13, include the following two references:

(1) Oldi, J.F. and Kannan, K. (2009). Analysis of perchlorate in human saliva by liquid chromatography-tandem mass spectrometry. Environmental Science and Technology, 43, 142-147

(2) Oldi, J.F. and Kannan, K. (2009). Perchlorate in human blood serum and plasma: Relationship to concentrations in saliva. Chemosphere, 77, 43-47.

Page 1, line 35: A reference is needed for the statement that deficits in maternal thyroid hormone can reduce childhood IQ.

Mention and report of actual biomonitoring data on perchorate in children will enhance the significance of the topic text. One study by Blount et al. (reference #25) has analyzed perchlorate in newborns and this should be explicitly mentioned in the topic text. A convincing evidence of exposure of newborns to perchlorate is needed to enhance the significance.

Reviewer 3:

The text is rather short and may be expanded to explain in more detail a correlation of exposure to perchlorate and its concentration in urine. While there are adequate explanations why exposures to perchlorate in pregnant woman may affect the thyroid function in children, this issue needs to be expanded to indicate how the urine concentrations of perchlorate in a pregnant women correlate with possible exposures of fetus to this compound.

Also, the rationale for measuring perchlorate in children of ages 0-7 (0-6 and 7-17) needs to be better explained and studies that are quoted in EPA Health Advisory (on line) could be cited. There seems to be a large difference between children 0-7 and children 0-17 in urinary concentrations of perchlorate, which may be explained by the difference in creatinine excretions between different development stages of growth. The literature on creatinine output as well as perchlorate excretion needs to be cited (from EPA HA).

Question 2 – Indicator Text

Reviewer 1:

General comments on Perchlorate Biomonitoring section:
Under perchlorate urine measurement, "perchlorate is metabolized" is stated but perchlorate leaves the body unchanged. Perhaps it is more accurate to state that "perchlorate passes quickly through the body unchanged and is excreted in urine."

The last word in the Perchlorate urine measurement section states that perchlorate exposure is "relatively continuous." This cannot be determined with cross-sectional biomonitoring measurements. If longitudinal studies have suggested this, it should state so. This should be clarified.

Creatinine adjustment. This section leaves out the important information that creatinine excretion is dependent upon muscle mass thus children and the elderly will have much lower excretion rates than adults. Females will excrete less than men. I will suggest later that you eliminate creatinine adjustment because I firmly believe that the findings with children are purely artifact and not real. However, if you leave this section, you need to state clearly that this makes comparing child and

adult concentrations difficult and will tend to make child concentrations appear falsely higher (typically about 2 times higher as their creatinine excretion is about ½ of that of adults).

Page 4, second paragraph. "Urinary creatinine concentrations "can" vary…" The DO vary SIGNIFICANTLY with the variables listed.

Creatinine correction does NOT improve the comparability of urinary chemical measurements across populations when the populations differ in age, sex, race/ethnicity.

Temporal trends. NCHS does indicate that 3-cycles are necessary to address "trends" (although they abhor the use of that word); however, significant differences in the two cycles can and should be evaluated.

Page 4, last paragraph. One does not "capture exposure" but "assesses exposure" using biomonitoring data.

Page 5, last paragraph, line 23. Urinary concentrations or levels are NOT "exposure levels." This should be changed.

What was the minimum cell number requirement for statistical evaluation?

Should note statistical significance on graphs.

Was there a poverty-creatinine interaction term?

Non-Hispanic blacks have higher creatinine concentrations than other race/ethnicities. Did this add to their lower creatinine-adjusted perchlorate levels (artifactually?)?

I firmly believe that the final finding is not real but an artifact of creatinine correction.

Tables. Should define NA.

I was disappointed to see the environmental data separated from the biological data. Without the former, this looks like a regurgitation of CDC's report and uses similarly medicinal language that fails to make any interesting assertions or conclusions about the data.

I liked the use of adjustment of age-specific natality. Great concept.

I appreciated the presentation of the statistics for transparency purposes. However, the remainder of the document is almost overly simplified then these complicated statistics are presented. It seems like there should be a nice common ground somewhere in between.

Does the time lag in date of collection and measurement of data affect the results? Similarly, does time of day of collection affect the results?

Reviewer 2:

Information on the dataset:
Adequate information has been provided about the dataset. However, a few key items are missing. For example, readers will be curious to find out about the number of samples representing each of

the population groups mentioned. This information can be found in appendix or can be deduced from the data summary table on page 19. However, this information will not be directly available in the main text of ACE3 and will leave the readers in quandary. I suggest that on Page 4, line 24 to insert a sentence on the number of samples analyzed for perchlorate (in total) for the women ages 16-49 years during the two time periods of NHANES represented in this document. This information may be introduced in Tables PER1, Per1a, Per1b and Per1c in the main body of the table or as a footnote/legend.

Page 4, lines 24-27: median is described here. It is also important to mention about the 95th percentile, because values for 95th percentile are discussed and described in tables and text. For non-experts, 95th percentile is hard to understand and may even be interpreted as 95 percent of samples had that level described as 95th percentile.

Page 4, line 34: Some explanation regarding "poverty level" is needed. Again, details are given on page 20 and 21, but this information is not directly available for readers. At least a sentence or two indicate what "poverty level" means will help clarify this term.

Page 4, line 41: "NHANES survey" should be NHANES program. The word 'survey' is embedded in NHANES and 'NHANES survey' is verbiage.

Reviewer 3:

The overview of the indicator text needs to include the relevance of the urinary concentration to possible exposures in utero. If there are no such studies available the rationale needs to be indicated why such urinary measurements are important.

Also, the studies in both animals and humans that show some possible adverse effects need to be better incorporated.

Also, it would be good to have a more extensive discussion about validity of normalizing the perchorate using creatinine. Since the muscle metabolism may be different in growing children, this creatinine output per liter of urine may be different from those in adult women. Additionally, pregnant women may have a different creatinine output then non-pregnant women.

All those issues need to be dealt with in more depth. Also, since differences are observed between white and black populations, it would be relevant to see if there are racial differences in creatinine excretions in urine.

Question 3 – Indicator Presentation

Reviewer 1:

Should note statistical significance on graphs.

Tables. Should define NA.

Color scheme was not particularly appealing.

Reviewer 2:

The figures and tables are clear and understandable. One way the presentation of data could be improved is by comparing the results with the overall general populations (to know if women at child bearing age are exposed to elevated levels relative to the general population).

Benchmarks are not available and public may be in quandary.

I would add the information on the number of samples for each categories in tables or figures (i.e., n=???).

Reviewer 3:

Indicator presentation if fine standard bar graphs. Data Tables however would be more meaningful if they also included mean values (with standard error) rather than only median values. Inclusion of the standard error would give a clearer indication of the individual variation of the urine concentrations of perchlorate.

Also, findings that perchlorate is lower in black women than in other women may need some discussion. It appears that the (all races/ethnicities) women of above poverty level have higher concentration of perchlorate then women under the poverty level, which is very interesting, since with more environmental pollutant indicators are higher in poor people then in rich people. This difference may be explained by including larger number of black women who have lower perchlorate concentrations in urine, or perhaps the difference lies in the normative factor, cretinine.

Question 4 – Context and Utility

Reviewer 1:

The limitations of this report are not worded strongly enough.

It is not clear how this report differs too much from CDC's existing report on biomonitoring data.

It would be more valuable to integrate environmental information in with the biomonitoring data.

Reviewer 2:

Some information regarding actual biomonitoring data from infants and children is useful. Also, an indication of why exposures in children are higher than in adults is useful. There are biomonitoring studies involving the analysis of perchlorate in children's blood and such references should be included. Please see:

Zhang, T., Wu, Q., Sun, H.W., Rao, J. and Kannan, K. (2010). Perchlorate and Iodide in Whole Blood Samples from Infants, Children, and Adults in China. Environmental Science and Technology, 44, 6947-6953.

Reviewer 3:

It is not evident from the document why perchlorate was chosen as an indicator for biomonitoring in women of potential birth giving age, and in children rather than some other environmental pollutant which could also cause adverse effects. This choice of perchlorte as an indicator needs to be better explained. The relevant literature is in the EPA Health Advisory draft.

The utility of such indicator as well as correlation of the urine concentration of the perchlorate with the blood levels in uterus may be relevant, since the statement is that perchlorate interferes with iodine absorption and thyroid functioning, resulting in possible adverse neurological development effects.

Question 5 – Documentation

Reviewer 1:

Yes, the transparency is to be applauded EXCEPT with the creatinine correction issue. I still feel like this is a faulty finding related to child and adult differences.

Reviewer 2:

The metadata tables are useful and complete. The documentation is complete and transparent. Some information regarding the analytical technique employed will be helpful (such as IC-MS/MS or LC-MS/MS), in the "methods' text on page 18.

Page 19, Limit of detection is given in ug/L, but the data in the text are reported as ug/g. This needs to be clarified.

General comment: One of the major issues with the document is that is just describes data on urinary perchlorate levels in women at child bearing age. For the readers it is hard to interpret exactly what does that mean. A comparison of this data to the general US population from the NHANES data can be helpful to show if women at childbearing age are exposed at elevated levels of perchlorate or not. A mention of this in the text would help. In other words, some discussion regarding the implications/significance of the data presented in this document is needed.

Reviewer 3:

[No Comment Provided by the Reviewer]

1.8 Perfluorochemicals

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Judy LaKind
- Barry Ryan
- Mike Wilson

General Comments (If Any)

Reviewer 1:

As someone who has worked on an indicators report such as this one, I fully understand and appreciate the difficulty in what EPA is trying to achieve and commend EPA for taking this on! For this type of report, in my view the most difficult aspect is attempting to make each section useful for a multitude of audiences. This difficulty is compounded for the PFCs indicator (which is the only one I reviewed) because of the data gaps and contradictory results in the literature. In order to make this indicator useful, my major recommendations are: (1) to better capture the complexities and data gaps in the literature, in part by including more information on toxicological studies and in part by not conflating the four chemicals under discussion; (2) presenting the NHANES data without birth-rate adjusted years – this does not really provide more insight into the topic and will be impossible for most readers to understand; and (3) to have separate short statements for health care providers and parents (the former who have little time to read this type of report and the latter for whom this report is likely to be too technical). These could take the form of "Take home messages to the health care provider on PFCs" and "Take home messages to parents on PFCs."

Reviewer 2:

None

Reviewer 3:

I base my "content" assessment on the *utility* of the information as presented in the document, from the perspective of the scientific community, the public, and policy makers. I base my "organization" assessment on the presentation and readability of the information.

Question 1 – Topic Text

Reviewer 1:

Q. Does the topic text appropriately and clearly describe the topic and its importance for children's environmental health?

A. There are instances where the text does not seem to capture what is in the literature. I have given specific examples below. This area of research is in a relatively early stage and several studies have reported conflicting results, which is not unusual. This is not really reflected in the current text.

Q. Are there additional aspects of the topic's importance for children's environmental health that should be included?

A. It is common for environmental epidemiology studies to give conflicting results. While this information should be included in the chapter, it would be useful – especially for researchers – to read about the toxicological research.

Q. Is the relevant literature appropriately summarized? Are there other important references that should be added?

A. Overall comment on this section: The indicators include data on four PFCs, but most of the cited publications focused on PFOA and PFOS. It would reasonable to let the reader know that the descriptions in this summary mainly describe two of the four compounds and that relatively little is known about the others. Where data are available for the other two, this should be noted (as described below).

Pg 1, line 10: Estimates of persistence in humans appear to be based on one occupational study with an N of 26. Rather than stating that "most tak[e] years to be cleared from the body", the uncertainty surrounding this topic should be described. Also, Olsen et al. seem to have focused on two of the PFCs, so it is not accurate to state that "most" of the PFCs take years to clear. It would be more accurate to say that we have extremely limited data for some and no data for others, but that the extant data (in combination with physico-chemical properties of the compound) suggest long half-lives.

Similarly on pg 1, line 26, environmental persistence is noted but no reference given. A quick literature search revealed little data on this topic. HSBD provided some information on PFOS and PFOA, but much of it is based on modeling. I found even less information on the other chemicals discussed in this section. Again, I think it is important to describe the data gaps in this important area rather than making a definitive statement based on minimal information.

Pg 1, lines 31-32: The two studies mentioned are modeling studies using food data from a handful of publications. In the case of PBDEs, it was assumed that food was a (or the) major exposure route because of assumed similarities to other POPs. Research ultimately pointed to dust as a major contributor to exposure. Is EPA really confident that the current PFC database on exposure sources supports this statement? I would recommend making clear the uncertainties.

Pg 1, line 38: The following references can be added:

Llorca M, Farré M, Picó Y, Teijón ML, Alvarez JG, Barceló D. Infant exposure of perfluorinated compounds: levels in breast milk and commercial baby food. Environ Int. 2010 36(6):584-92.

Thomsen C, Haug LS, Stigum H, Frøshaug M, Broadwell SL, Becher G._Changes in concentrations of perfluorinated compounds, polybrominated diphenyl ethers, and polychlorinated biphenyls in Norwegian breast-milk during twelve months of lactation. Environ Sci Technol. 2010 44(24):9550-6.

Pg 1, line 39: Breast milk may in fact be a key source of exposure. This is likely to be of interest to the public and health care providers. Is there a reason why EPA does not provide context? For example, Llorca et al. (see above) state that "…ingestion rates of PFOS and PFOA, with exception of one breast milk sample did not exceed the tolerable daily intake (TDI) recommended by the EFSA." This is a non-US result and EPA may question their results (and again, it is just one study), but at least it gives some perspective on the implications of exposure. Why leave it out?

Pg 1, line 41: Why would children be more exposed to "certain" PFCs in dust? Which ones? Why not all?

Pg 2, line 3: Could add this:

Toms LM, Calafat AM, Kato K, Thompson J, Harden F, Hobson P, Sjödin A, Mueller JF.Polyfluoroalkyl chemicals in pooled blood serum from infants, children, and adults in Australia. Environ Sci Technol. 2009 Jun 1;43(11):4194-9.

Pg 2, lines 9-10: Why not note from the same study that "PFOA was detected only in maternal samples (range, < 0.5 to 2.3 ng/mL, 4 of 15)." In contrast, in the Baltimore study, both PFOS and PFOA were detected in cord blood. Again, doesn't this help provide context to the reader? It seems from the literature cited that it is not useful to lump all PFCs together, so being more precise about what chemicals have been studied and what was found for each chemical is important. It also helps to provide information on variability and uncertainty.

Pg 2, lines 12-13: "A growing number…" Based the publications cited in this paragraph, it appears that there were four studies with positive associations, although two of these papers seem to refer to the same cohort. One with an N of 239 found several positive associations, but not with birth length. Two of the cites are from the same cohort (N = 1400) and they concluded "These findings suggest that fetal exposure to PFOA but not PFOS during organ development may affect the growth of organs and the skeleton" and "We observed no adverse effects for maternal PFOS or PFOA levels on small for gestational age." The last paper cited (N = 428) found a negative association with PFOS (but not PFOA) and birth weight. Two other studies were seemingly dismissed as "smaller studies" but the first had an N of 252 (similar to the first paper referenced in this paragraph). This paper, which found that "maternal PFA exposure has no substantial effect on fetal weight and length of gestation at the concentrations observed in this population," is quite interesting because the authors actually measured PFCs other than PFOS and PFOA. The second "smaller" study indeed had a smaller N (101) but is also interesting as other PFCs in addition to PFOA and PFOS were measured.

With language like that used on lines 12-13, it feels as though EPA wants to present the data through a prism unsupported by the actual papers. I would suggest simply summarizing the available studies – perhaps in a table – with chemicals measured, N, endpoints assessed, and outcome and let the reader evaluate the state of the science him/herself.

Pg 2, lines 26-29: Similar issue here. The first paper cited in this section found the following: "Analyses of all locations showed no associations with TSH or T4 and PFOA. A negative association was observed for free T4 and positive association for T3; however, the findings were well within these assays' normal reference ranges." The second found that "PFOS concentrations were negatively associated with TSH, tT(3,) and TBG and positively with fT(4) concentrations." The last study cited had some interesting complexities: "In fully adjusted logistic models, women with PFOA >or= 5.7 ng/mL [fourth (highest) population quartile] were more likely to report current treated thyroid disease [odds ratio (OR) = 2.24; 95% confidence interval (CI), 1.38-3.65; p = 0.002] compared with PFOA <or= 4.0 ng/mL (quartiles 1 and 2); we found a **near significant** similar trend

in men (OR = 2.12; 95% CI, 0.93-4.82; p = 0.073). For PFOS, in men we found a similar association for those with PFOS >or= 36.8 ng/mL (quartile 4) versus <or= 25.5 ng/mL (quartiles 1 and 2: OR for treated disease = 2.68; 95% CI, 1.03-6.98; p = 0.043); in **women this association was not significant**. (emphasis mine)"

The information in these studies is more complex (and interesting) than it would seem based on reading EPA's synopsis; the complexities and contradictions as well as the data gaps are not captured in the summary given by EPA in these lines.

Pg 2, line 40: "the developing fetus is likely to be sensitive to maternal levels of cholesterol and triglycerides…" Is this EPA speculation or do the cited papers support this statement? If the latter, why include the word "likely"?

Pg 2, line 42: Is human evidence lacking because studies have not been conducted or because they have been conducted but the findings have been negative?

Q. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

A. As EPA is aware, it is extremely difficult to craft text that works well for all of the audiences listed above. As the text is currently written, it does not capture the complexities and data gaps in the literature that would be important to researchers. At the same time, I am not sure what the take-home message is supposed to be for doctors, nurses, parents and educators. I recommend inclusion of a table summarizing the key details of the available literature (as noted above) for researchers and government officials. For others, what it is that EPA is trying to say about these compounds and children's health? Can modeled intakes be compared to EPA's reference dose? If a doctor were to read this, what is the key point that he/she would want to be able to tell parents? Maybe a box is needed for each biomonitoring indicator with a "note to parents" and a "note to doctors" with the take-home message for each.

Reviewer 2:

The topic text offers a concise, albeit brief, introduction to the primary sources of selected perfluorochemicals in the environment. The text is quite brief on the chemical properties and might stand a bit of expansion in that area.

There is adequate description of current trends in production and distribution in the environment. As pointed out in the text, broad-based exposures are not well understood, but specific-source exposures are under investigation currently (See the Steenland 2009 reference.) A more recent reference offers insight into distribution in environments subject to local-source contamination:

Hyeong-Moo Shin, Veronica M. Vieira, P. Barry Ryan, Russell Detwiler, Brett Sanders, Kyle Steenland and Scott M. Bartell. Environmental Fate and Transport Modeling for Perfluorooctanoic Acid Emitted from the Washington Works Facility in West Virginia. Accepted for Publication in: Environmental Science & Technology January 4, 2011 dx.doi.org/10.1021/es102769t Publication Date (Web): January 12, 2011

The text also offers an introduction to health effects associated with exposure to these compounds. The literature is beginning to expand rapidly in this area with several studies underway.

Nevertheless, the information presented is indicative of potential exposure-related health outcomes associated with these compounds. There are a series of studies nearing completion that may offer further insight into the relationship between exposure and effect for these compounds (See http://www.c8sciencepanel.org). A recent study, (J Clin Endocrinol Metab. 2011 Mar 16. [Epub ahead of print] Implications of Early Menopause in Women Exposed to Perfluorocarbons. Knox SS, Jackson T, Javins B, Frisbee SJ, Shankar A, Ducatman AM.), has suggested an association between exposure to PFOA and PFOS and the early onset of menopause, but others have analyzed the same data and see no such effect.

Reviewer 3:

Content

1) Given how early the science evidence is on PFCs (relative to lead, for example), one sentence is needed to explain that while the evidence is still emerging for the links between PFC exposure and disease, the outcomes likely associated with PFC exposure (e.g., low birth weight, high cholesterol, thyroid hormone disruption) are also associated with exposure to other synthetic chemicals and pollutants, which increases the significance of even small alterations that may seem insignificant in isolation, but which can have serious population-level effects when combined with small alterations caused by other exposures.

2) That is, the apparent thyroid hormone alterations associated with PFC exposure may be more significant given known, concurrent exposure to other chemicals that affect thyroid homeostasis, such as PCBs, PBDEs, TBBPA, perchlorate, several pesticides, etc.

Organization

1) There is excellent information in this section, but subheadings would help readers navigate the information (like the ones that are used in the indicator text). Subsections could be delineated by of the following headings:

Page	Line	Text for a subheading
1	2	How are PFCs used?
1	17	What action has been taken on PFCs?
1	30	How are people exposed?
2	11	What are the possible health effects?

2) At the outset of the health effects section (p. 2 line 12), a summary statement of the relevance of early developmental exposures would increase the reader's ability to understand implications of this information. It is not readily apparent to most readers why low birth weight is significant for children's health (and public health more generally) given the implications of low birth weight for risks of common disorders such as hypertension.

References

Incomplete references:

Number 9 (Egeghy P) – journal issue, date and pages are missing.

Number 53 (Melzer D)—journal issue, date and pages are missing

Number 55 (Nelson JW)—correct article date is 2010 not 2009.

Additional references that should be included:

Woodruff TJ, Zota AR, Schwartz JM. 2011. Environmental Chemicals in Pregnant Women in the US: NHANES 2003-2004. Environ Health Perspect. doi:10.1289/ehp.1002727

Miller MD, Crofton KM, Rice DC, Zoeller RT. 2009. Thyroid-Disrupting Chemicals: Interpreting Upstream Biomarkers of Adverse Outcomes. Environ Health Perspect. 117:1033-1041. doi:10.1289/ehp.0800247

Line edits:

Page	Line	Text
1	3	Strike "manmade", and insert "*synthetic*"
1	9	Insert italicized word: "…PFCs are *highly* persistent…"
1	12	What is the production volume? (For the relevant TSCA inventory reporting year)
1	31	Need a clearer overall statement of exposure routes at the opening of this section.
1	37	Insert italicized text: "…have been found *at high levels* in drinking water…"
2	9	Strike "widespread presence", and insert "*ubiquitous*" based on the Woodruff et al. (2011) analysis of PFCs in pregnant women (99%) and women of childbearing age (100%) in NHANES 2003-2004.
2	29	Potential impacts of thyroid hormone disruption during pregnancy are much more extensive than discussed here. See additional reference above (Miller, MD et al., 2009).
2	35	Describing animal and human data as "conflicting" suggests the data are contradictory. In actuality, the lipid levels change (in opposite directions in humans and experimental animals) is most likely explained by the physiological differences in the mechanisms involving peroxisome proliferation. This could be more accurately explained in the text: "… although *physiological differences between humans and experimental animals cause lipid levels to fluctuate in opposite directions*; … *In animal studies involving various species…"*

Question 2 – Indicator Text

Reviewer 1:

Q. Does the indicator text provide sufficient information about the data set and the indicator calculation to enable an understanding of the indicator?

A. Specific comments here:

Pg 4, overview: "blood levels during pregnancy have been associated with adverse children's health outcomes." This is not a particularly helpful statement. What blood levels and what health outcomes? As noted above, the literature is fairly sparse and contradictory. There is nothing wrong

with being clear about that here. The statement might be stronger if toxicological information was provided in the previous section.

Pg 4, lines 17-19: "The focus is on women…" Is this statement really correct or is it the case that there is simply a lack of studies on adolescents (with few exceptions, such as Fei C, Olsen J. Prenatal Exposure to Perfluorinated Chemicals and Behavioral or Coordination Problems at Age 7. Environ Health Perspect. 2010 Nov 9. [Epub ahead of print])? The chapter cited a study on pooled measurements in children – this could also have been used as an indicator. Since EPA cannot/doesn't try to relate blood levels to specific risks, but more as an indicator of exposure, why not include US data from children? At the very least, NHANES data for 12-19 year olds could be included.

Pg 4, line 30: This statement on persistence again argues for inclusion of NHANES data on 12-19 year olds.

Pg 5, line 40: shouldn't this read "*significant* difference"? Same comment for Pg 6 line 1. Pg 6, lines 2-4: Of course this sentence is correct, but its placement is odd. The reader will have just struggled through 6 pages of information on why PFCs are such an important children's health indicator, and then will read that exposure levels over time don't suggest interpretation regarding health implications. Certainly if I were a physician or parent reading this I would have no idea why EPA gave me this material. I would further question why EPA then goes on to provide extensive analyses of the NHANES data at the end of the chapter. Why not have a summary statement at the beginning of the chapter (and maybe for each indicator chapter on biomonitoring) noting that biomonitoring gives useful information on population trends, etc but at that at this point – for most chemicals – the health significance of these numbers is unclear.

Pg 7: The text leading up to this point does not prepare the reader for seeing data on the four individual PFCs.

Q. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

A. I have already commented on this above. I do think that the Indicators section will be impossible for most non-researchers to read.

Reviewer 2:

The indicator text begins very abruptly with only the slimmest of introduction in a text box. I believe that the reasoning behind selecting this indicator should be more developed. It may be that this is the only indicator that provides useful information, but there is no reason to assume so given the text. The report dives into NHANES immediately without any description of why or wherefore. Are only NHEANES data being used in this indicator? If so, why? Is it for statistical representativeness? If the latter is true, then the reader needs to be convinced that the NHANES participant selection is what is appropriate.

Who is the audience here? The style of this section is hard to get a handle on. It goes up and down in level. There is a discussion of birth-rate adjusted data in Lines 9ff on Page 5, which I believe is at an appropriate level. But on Lines 15 -17 on the same page, there is a description of what a median is. I do not want to be elitist, but there is need to assume that the reader either has no knowledge

and everything must be explained, or that minimal understanding of the basics is assumed. Pick one and write accordingly. I have no objection to the text on Lines 15-17; given the supposed audience, it may be appropriate to develop from the ground up but consistency is important. On the other hand, the presentation of the Indicator in graphical and tabular form on Pages 7ff makes the assumption that the reader will be able to glean essential information from this sort of presentation, which assumes experience with data presented in these ways (See below.)

I have some wording problems in this section as well. Can we replace "womb" on Page 4, Line 19 with "uterus" or better yet with "in utero." If Nirvana can title an album as such, I think we as scientists can use the term correctly.

Under Perfluorinated Compounds. The word "respectively" should be inserted after "women" in Page 4, Line 27.

Reviewer 3:

Organization

The following are suggested line edits. Broader comments on the indicator are in the following section in response to question 3.

Page	Line	Text
4	3	See comment below (question 3) on utility of addressing only the *change* in blood PFC concentration over time.
4	12	Strike "environmental chemicals"—this designation implies that the chemicals in question are intended to be (or inevitably occur) in the environment.
		Change to "synthetic chemicals and pollutants," or even "chemical contaminants".
5	13	This section should include information that allows the reader to understand the significance of these levels; e.g., how many women have blood PFC concentrations at the 95th percentile? How many at the median level? As discussed below, the public health significance of this indicator is missed if the only information presented is the blood levels and change in those levels over time.
5	36	Description of statistical significance is difficult to understand. Rewrite as follows: Strike "not only" in the first sentence. Change to "…depends *on the numerical difference in the value of an indicator between two groups, as well as the amount of variability among the values within one group, and the total number of measurements in the survey, among other aspects of survey design. This total number of observations determines the power of a survey, or its ability to detect an actual difference between two groups."*
5	40-41	"…to detect [strike 'a'] *that* difference when *a large number of* samples have been *tested* in those groups…"
6	1	"…within each group, then [strike 'a'] *the* difference…"
6	4-5	"…does not [strike 'necessarily suggest any interpretation regarding the'] *address any potential* health implications."

Question 3 – Indicator Presentation

Reviewer 1:

Q. Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data?

A. The approach of using birth-rate adjusted years complicates this topic unnecessarily. It will be difficult enough for most people to understand what to make of the biomonitoring data without adding this layer of complexity. Also, as PFCs are considered persistent, NHANES data on the 12-19 year olds should be included (as well as the pooled data on children). The levels in the 12-19 year olds will capture – at least in part- information on early exposures and EPA will be able to use these data to assess trends with future National Exposure Reports.

Q. Are there ways in which the presentation and description of the indicator values could be improved?

A.
1. Leave out the birth-adjusted years data and present the biomonitoring data on its own.

2. Include 12-19 year olds.

3. Consider leaving out Table PFC1b, c. What will people do with this information? Researchers would likely use the NHANES database itself to explore this issue – for others, these numbers will likely be meaningless.

4. Mention prior to a footnote on pg 21 that data from 2001-2002 were not included.

5. In the table on pg 23, define in a footnote what is meant by "missing data."

6. Reconsider stratifying by income – how can these data be interpreted by the reader? Why not instead consider examining diet type or other factors from the questionnaire that might be explanatory. Just because an assessment *can* be done, it doesn't mean it *should* be done!

7. Pg 31, line 19. The issue of multiple comparisons is contentious (see, for example, Neurotoxicol Teratol. 2005 27(3):395-406. Methodological issues in research on developmental exposure to neurotoxic agents. Jacobson JL, Jacobson SW.) . This decision should be supported in the text.

Q. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)? Please comment on the appropriateness of the comparisons made in the indicator(s) and whether other comparison populations and/or benchmarks may be informative to the public.

A. See above.

Reviewer 2:

My response to this question has two answers, neither of which puts this presentation in a good light. Individuals reading this document are going to one of two types: persons familiar with graphical and tabular representations of data; and, those who are not.

For those familiar with the data presentation, it is crystal clear and may, in fact, be redundant-certainly in the case of The Indicator PFC1 figure and Table PFC1. These two display exactly the same information. Later tables supply new information, which may or may not be better displayed using figures. There is not anything intrinsically bad about the redundancy of presentation. One may well argue that there should be both graphical and tabular presentations for all of the data. The visual image of the data gives a quick overview of important and relevant information, e.g., relative amounts of the various PFCs and temporal trends in their values. Tabular data gives more information on the quantitative values associated with the figures precluding the need to "read off the chart" to get a value.

For those not familiar with data presented in this way, the text will offer more insight than the figures or tables. The text as presented may require a bit of introduction but, to my mind, gives the story that most who fall into this category may find useful.

Reviewer 3:

Content

1) The primary focus of the indicator text, graph, bullets and tables is the decline in serum levels of PFOA and PFOS; the lower levels of PFHxs and PFNA levels compared to PFOA and PFOS, and the slight increase in PFNA levels over time. The text does not address the number and percent of the population affected and any indication of the relationship between the levels found in NHANES and the exposure levels associated with health effects in the literature. The reader is left with the questions: Why the difference? Do they have different applications? Are they absorbed or metabolized differently?

2) The text gives strong preference for this information (change in PFC levels over time) by highlighting it as the only data represented graphically in the section. More questions are raised by this information than are answered. While this reflects the limited state of knowledge on PFCs relative to other longer-studied chemicals, there is more that could be said here. Other aspects of this indicator are potentially much more relevant for understanding the public health implications and the policy responses than the change in PFC levels over time. These include, for example:

How many women (and how many pregnancies) would this affect? What percent of the population? *Relative levels over time do not communicate the extent of the potential public health impacts.*

Woodruff et al. (2011) present data on median and 95th percentile concentrations of PFCs in pregnant women included in the NHANES 2003-2004 survey. They report PFCs detected in 99% of pregnant women in the subset and 100% of non-pregnant women. This information as presented by Woodruff et al has greater public health utility than a description of how those levels have changed over time.

How do the measured serum levels compare with levels associated with health effects (e.g., How many women would have blood concentrations that fall at or above those levels)? This is more

complex than for chemicals with established RfDs, but anything that could convey this information would vastly increase the utility of the indicator.

The differential in median concentrations by race and income is significant for understanding the source of exposure, identifying high risk populations, and targeting interventions. These data should be presented more prominently. Titles for the bulleted sections would help, such as "Poverty is associated with higher blood levels of PFCs" (p.8, line 5), and "White non-Hispanic race is associated with higher blood levels of PFCs" (p.8, line 15).

3) Regarding the age-adjustment: is the relevance of this weighting affected by the long persistence and bioaccumulation of this class of compounds? It would be helpful for the reader to relate the outcome of this weighting to the serum PFC concentrations actually found in pregnant women in the Woodruff et al analysis, for example.

Question 4 – Context and Utility

Reviewer 1:

Q. For each indicator, please comment on whether the text appropriately and objectively reflects the strengths and limitations of existing knowledge regarding relationships between environmental conditions and children's health that are relevant to the topic.

A. [No comment given by the reviewer]

Q. For each indicator, please comment its utility and appropriateness addressing the three principal objectives of ACE:

a) To presents concrete, quantifiable indicators of key factors relevant to the environment and children in the United States. These indicators are designed to offer a basis for understanding time trends for some factors and for further investigation of others.

A. This is addressed in my previous comments.

b) To inform discussions among policymakers and the public about how to improve federal data on children and the environment.

A. By highlighting the data gaps, policy makers should understand the need to provide funding for research on these chemicals.

c) To provide indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children.

A. It is important to track levels of persistent chemicals and PFCs are a useful part of the report. For policy makers and the public, some kind of context related to health would be helpful. The only paper I located that could help was this one:

Environ Int. 2010 Aug;36(6):584-92. Infant exposure of perfluorinated compounds: levels in breast milk and commercial baby food. Llorca M, Farré M, Picó Y, Teijón ML, Alvarez JG, Barceló D.

In this study, an analytical method to determine six perfluorinated compounds (PFCs) based on alkaline digestion and solid phase extraction (SPE) followed by liquid chromatography-quadrupole-linear ion trap mass spectrometry (LC-QqLIT-MS) was validated for the analysis of human breast milk, milk infant formulas and cereals baby food. The average recoveries of the different matrices were in general higher than 70% with a relative standard deviation (RSD) lower than 21% and method limits of detection (MLOD) ranging from 1.2 to 362 ng/L for the different compounds and matrices. The method was applied to investigate the occurrence of PFCs in 20 samples of human breast milk, and 5 samples of infant formulas and cereal baby food (3 brands of commercial milk infant formulas and 2 brands of cereals baby food). Breast milk samples were collected in 2008 from donors living in Barcelona city (Spain) on the 40 days postpartum. Perfluorooctanesulfonate (PFOS) and perfluoro-7-methyloctanoic acid (i,p-PFNA) were predominant being present in the 95% of breast milk samples. Perfluorooctanoic acid (PFOA) was quantified in 8 of the 20 breast milk samples at concentrations in the range of 21-907 ng/L. Commercial formulas and food were purchased also in 2009 from a retail store. The six PFCs were detected in all brands of milk infant formulas and cereals baby food analyzed, being perfluorodecanoic acid (PFDA), PFOS, PFOA and i,p-PFNA the compounds detected in higher concentrations (up to 1289 ng/kg). PFCs presence can be associated to possible migration from packaging and containers during production processes. Finally, based on estimated body weight and newborn intake, PFOS and PFOA daily intakes and risk indexes (RI) were estimated for the firsts 6 month of life. We found that ingestion rates of PFOS and PFOA, with exception of one breast milk sample did not exceed the tolerable daily intake (TDI) recommended by the EFSA. However, more research is needed in order to assess possible risk associated to PFCs contamination during early stages of life.

Reviewer 2:

Note: There is only one indicator for this class of compounds.

This question is difficult to address with respect to PFCs because so little is known about the health effects associated with exposure to these compounds. The data presented give context to any results observed for an individual or community. They allow putting a given set of observations on a scale with the rest of the United States, for example. However, the key factors influencing exposure, above and beyond living adjacent to a known source, are not known, as was pointed out in the text itself. Personal habits, dietary sources, etc., are thought to influence exposure and thus the value for this marker, but so little is known that it is hard to address the topic.

Despite these caveats, I believe the document has done as good a job as can be done regarding putting the serum levels in context. Levels across the United States and across demographic categories give the context readers need to at least place themselves in a distribution. As more data become available from laboratory and epidemiologic studies, then the context can be broadened to include health-related outcomes. We simply cannot do so now.

Reviewer 3:

Content

1) It is excellent that ACE3 will include an indicator for PFC exposure. The high production volumes, high environmental persistence and bioaccumulation of this class of chemicals, combined with evidence of potential health implications associated with exposure; merit its inclusion in the ACE3. Furthermore, the focus on exposure to women of childbearing age, as an indicator of risk to

children's health, communicates an essential tenet of environmental health that requires continued attention—that exposures early in development can have significant and unpredicted effects later in childhood or adulthood.

2) The PFC indicator will be highly useful in this respect, but it needs significant additional information to successfully communicate the *implications* of the information. The current version of this indicator focuses almost exclusively on the change in blood serum concentration over time, without addressing the larger point of how many women—and children during development—are exposed to multiple PFCs. The only conclusion that is readily evident from this presentation of the information is that the median concentrations of PFOS and PFOA have declined since 1999, remained stable for PFHxS, and increased slightly for PFNA.

3) For the indicator to accomplish the three goals of ACE, a discussion should include the information discussed above (bullet points under question 3), as well as points such as: Why these declines may have occurred (a phase-out of PFOS?), what that means; e.g., is PFOS being replaced by another chemical that is not being monitored? Is the decline consistent with decreasing levels in the environment?

Question 5 – Documentation

Reviewer 1:

Q. Is the documentation complete and transparent?

A. Additional references are provided in these comments. Using birth-rate adjusted data makes the indicator less transparent.

Reviewer 2:

Subject to the caveats outlined in the earlier sections, I believe the document properly reflects current understanding and does so in a fairly complete and transparent manner.

Reviewer 3:

1) With the exception of the incomplete references flagged above, the documentation is complete and the methods are transparent. The only aspect that isn't represented is regarding the literature review and whether there were consistent search terms used or inclusion/exclusion criteria for studies, but that may well be beyond the scope of this document.

1.9 Phthalates

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Jennifer Adibi
- Susan Duty
- Susan Jobling

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

The topic does appropriately address the topic and its importance for children's environmental health. Additional findings that could be mentioned include:

Prenatal DEHP exposure was found to be associated with longer gestation and a higher risk of delivery by C-section (Adibi et al. AJE. 2009). This was a population of predominantly white U.S. women with a high degree of education. The same exposures were associated with shorter gestation in a population of low-income, African and Dominican American women in New York City (Whyatt et al. Pediatrics. 2009). This suggests that people may respond differently to phthalate exposure, given the same exposures, depending on other factors such as stress, nutrition, socio-economic status, or co-exposures. This is an important message to the public since we know all people are exposed at relatively similar levels; yet not all people have the same outcome or are affected in the same way.

We also published a report showing that prenatal exposure was associated with placental gene expression in a cohort of women in New York City (Adibi et al. EHP 2010). I believe that this is only study to date that has measured a fetal biomarker with direct relevance to the prenatal period, and shown its correlation to phthalates.

It is important to state in this section that all of the findings described here on effects in humans are taken from observational studies where we can only measure correlations. We cannot measure

cause and effect, nor can we remove all of the sources of bias. Human studies are very important to reveal relationships that may have a true biologic basis, but findings must be confirmed in multiple populations and/or in an experimental system.

Specific comments include:

Page 1. Line 18: In order to understand the CPSIA Act as a significant reduction in children's exposure, can the authors state what the average percent (by weight, volume) of toys and childcare products was before the act was passed?

Page 2. Line 4: I suspect that exposures of children and women of childbearing age to phthalates through medical devices are relatively rare and restricted to those with chronic disease or acute injury.

Page 2. Line 32: Are authors sure that the statement, "… exposure levels much higher than what the general population may be exposed to…" is true? Or maybe you could define what much higher means, 1,2,3 order(s) of magnitude?

Reviewer 2:

I think the topic text does appropriately describe the topic. I think the language is appropriate for a professional reader but not for concerned parents. The technical language is too high for that although there are several definitions of terms that are very helpful in bringing the message down to the well-educated lay-person level. Not sure I would change the text though since the audience for this document I think really is the professional?

I found several discrepancies between what the text stated and what was contained in the reference that was listed for that text. For example, page 1, line 27, the references 10-12 should go after the word 'ingestion' not where it is currently located on line 28. Also on line 28 page 1, the reference '9' should go after personal care products and there should be a reference for 'inhalation' exposures as well(perhaps reference 14?)

Again on line 44 the reference '9' listed after lotions refers to a paper describing personal care product use in men (cologne, after shave, etc) but not nail polish. The reference for the nail polish text should be:

Rachel Kwapniewski, Sarah Kozaczka, Russ Hauser, Manori J. Silva, Antonia M. Calafat, Susan M. Duty. Occupational exposure to dibutyl phthalate among manicurists. Journal of Occupational and Environmental Medicine 50(6): 705-718.

On page 2 line 18, the cited reference #18 refers to NHANES data descriptive survey. It does not address consumer products, detergents, soaps etc. The study reports phthalate levels by age, gender, ethnicity/race, time of day of collection but that is all. Will need to cite the more appropriate primary sources for this information (?ref #4??)

Also on page 1 line 15, the cited reference '8' is not a study measuring phthalate leaching from plastics but rather a study of phthalates and infant health, basically a literature review. Should you not cite the primary source for the study that determined phthalates can leach?? That would be: Nassberger et al., 1987 Exposure of patients to phthalates from polyvinyl chloride tubes and bags during dialysis. Nehron 45, 286-290.

Otherwise if referring to secondary sources I would stick with the ATSDR documents.

Another example of using reference 8 is on page 1 line 33. This particular review paper made this statement in the introduction but it was unsubstantiated by any reference. Not sure if there is a primary reference for that? Although it seems logical, I really don't think we should be making unsubstantiated exposure statements in this public document.

I only noticed these discrepancies but imagine there are several other incidences of this. Should I be looking at every reference to detect these discrepancies or is that an editorial function later? I am very mindful of these discrepancies, because as a student I was always using the reference lists as an extremely important tool to guide my research. I was taught to always get the primary source since secondary sources can inadvertently misrepresent findings. I was occasionally frustrated when a statement that I thought would lead me to a primary source, kept looping me back to summary documents that were often unsubstantiated.

Other examples of the cited reference not clearly being a primary source for the text cited include:

Page 1 line 39 reference 10

Page 2 line 20 references 21, 22

Page 4 line 7 reference #61 does not relate to what is discussed in the text. #61 refers to a study by Colon, which I believe is not scientifically credible since they measured phthalates in serum and not the metabolite in urine and also did not account for natural phytoestrogen in soymilk which apparently is commonly fed to young children in Puerto Rico. So because of its questionable credibility and the fact it does not relate to the text it follows, it should be removed.

Reviewer 3:

Possible human health effects of phthalate plasticizers have been intensely discussed very recently. Di(2-ethylhexyl) phthalate (DEHP), the phthalate acid ester with the largest production volume worldwide, has been substituted by new compounds like Diisononyl 1,2-cyclohexanedicarboxylic acid (DINCH) or Di(2-ethylhexyl) terephthalate (DEHT) in many applications. There are numerous reports about concentration levels of phthalates in indoor environments, but data on concentrations of these alternative plasticizers are not available yet and they need to be . Some mention of this needs to be made in the text.

Recent findings from animal studies suggest that a cumulative risk assessment for phthalates is warranted, and a cumulative exposure assessment to phthalates via human biomonitoring would be a major step into this direction. This is not mentioned and should be.

Finally, the text indicates that from an epidemiological perspective one can correlate various multiple health outcomes with phthalate exposure. This could be because it is indeed the case, but it could also be because phthalates are so ubiquitous that their concentrations co-vary with many other contaminant groups that may play a role in the manifestation of the disease outcomes. For example, Urinary high-molecular-weight phthalate and serum tobacco smoke metabolite concentrations are positively associated with bisphenol-A concentrations so linking exact cause and effect must be done with caution.

Question 2 – Indicator Text

Reviewer 1:

Yes, the indicator text provides sufficient information. I have some methodologic questions:

The NHANES sample of women of reproductive age also includes pregnant women. The numbers are small but they are there and the authors may want to consider removing them or treating their values differently.

I agree that creatinine adjustment is potentially important. However, when the authors are dealing with a large sample as in this case, the within-person variability in the exposure measure is usually dwarfed by the between-person variability. Depending on the degree of within-person variability, we usually assume you need a N of 50 or 100 to minimize the effects of within-person variability. Given the great potential for creating more unwanted variability in your exposure measure (as you state on page 6, lines 37-38) by adjusting for creatinine, authors may want to compare estimates with and without adjustment.

We published a paper where we showed that creatinine adjustment actually increased variability in our phthalate measures taken longitudinally over the last trimester of pregnancy (Adibi et al 2008. EHP). Specific gravity adjustment which is unbiased, decreased the within-person variability as desired. I know specific gravity is not available for NHANES, but no adjustment may be preferable to creatinine.

I am confused as to why authors are using the median to characterize group differences in phthalate exposures, and not geometric means. The geometric mean has been the convention established by the investigators at the CDC. The actual point estimate for the geometric mean and the median are similar. However, you can calculate confidence intervals for the geometric mean, which provides a nice way to look at variability, and also to compare groups. If there is no overlap in their confidence intervals, then they are significantly different and you can see if the difference is marginal, small, or large. To people in the field as well as to non-scientists it would be more intuitive to think about group means and variability around the mean than to think of medians and relative standard errors and percentile differences. I am happy to provide the SAS/Sudaan code that I used to do this with NHANES phthalate data.

I agree after looking at the tables that there might be a multiple comparison problem, as authors state (page 7, line 37). Authors might present the raw p-values as well as the Bonferroni adjusted p-values.

Specific comments:

Page 7, line 4: change “distribution of children’s prenatal” to “distribution of prenatal”

Page 8, line3: This last sentence is not clear. Clearly statistical significance is important in the interpretation or else authors would have not gone through the trouble to calculate it. Authors should not report differences that are not statistically significant. It muddles the water and this is why we have NHANES…to measure associations with statistical certainty given the sample size and weighting to make it representative of the U.S. population.

Reviewer 2:

I would rewrite the first sentence under 'overview' to make it clearer which indicator refers to adults and which to children. For example: Indicator PHTL1 presents concentrations of phthalate metabolites in the urine of U.S. women ages 16-19 while PHTL2 presents concentrations of phthalate metabolites in the urine of U.S. children ages 6-17 years. This would make it consistent with your other statements in the 4th line of that same paragraph.

I did find the discussion about birthrate adjustment straightforward here but in the methods section I got confused again.

Under statistical testing page 7 line 35 and 39, I think changing 'randomly' to 'by chance' would be easier for the non-statistician to understand. (Also should change the work 'chance' on line 34 (after the word '5%') to 'probability'.

Page 8 line 3-5 seems not as clear as language used in the CDC. I think this would be better: 'the measurement of an environmental chemical in a person's blood or urine is an indication of exposure; it does not by itself mean that the chemical causes disease of adverse effects.'

Similar concerns about the references cited as I mentioned in above section. Citation references are often from secondary sources and not the primary source that actually researched the issue being discussed. A pharmacokinetic or pharmacodynamics article should be cited on page 6 line 11 instead of reference 10 which uses the pharmacokinetic data to make their assumptions and calculations.

Other citations that seem to lead to secondary sources and not primary source;
Page 6: line 12 references 10, 66, line 14 reference 67, Line 18 is missing the reference which should be the CDC #62 ref

Reviewer 3:

The focus on urinary metabolites is appropriate and also on women of child bearing age and children

For both indicators the text provides adequate information about the data set and the calculation to enable a basic understanding of the indicator.

One minor comment is that I would explain (page 39) what "no adjustment is made for multiple comparisons" means. Of course there are merits in making these types of adjustments and merits in not doing so but it should be made clear to the reader what this means and why.

Question 3 – Indicator Presentation

Reviewer 1:

There are better ways to show a time trend than by a bar chart. Bar charts are more appropriate when you are representing a frequency or distribution as opposed to a single data point. I would suggest plotting the geometric means of the phthalate metabolites (y axis) by the years surveyed (x axis). You could depict the confidence interval around the mean with error bars. Or if you want to

show the median, also you could do box plots with the median, 25th and 27th percentiles. You could draw a line between the means or medians. The geometric mean has become the convention in the literature for characterizing NHANES environmental chemical data, and especially for comparing subpopulations and different populations.

Again, the data tables need to show the variability in the distributions in some form. Showing a single data point from a distribution that is highly skewed is not informative. I have never heard of the relative standard error. You should include a sentence or two to explain what it is, and why it is expressed as a percentage of?

MEHP is not as reliably measured as other DEHP metabolites as evidenced by its low intraclass correlation. This might be due to analytic limitations, but most likely it is due to the high lipophilicity of this metabolite compared to others. The large variability might be important in terms of what is happening in the population. I am not sure why authors do not include an estimate for 2005-2006 in Table PHTL1a.

Analytic drift over time, batch effects, modifications of the analytic method, or improvement in instrumentation over time could also be contributing to these trends. I have worked with the CDC laboratory that conducts these analyses and noticed statistically significant batch effects. Is there any documentation from the lab as to how they adjust for this that you could mention? Given that the differences are small; this could explain some of the variability. Also in the documentation, you show that the limits of detection change significantly over the years, as does the percentage below detection (especially for 2001-2001). This should be addressed somewhere in the text as a source of variability in biomonitoring data over time.

It is important to show sample sizes somewhere in the Figures or in the Tables.

Specific comments:

What do the white lines on the bar graphs represent?

The y axis should be labeled "median concentrations," or else just rely on the title and don't label the y axis.

Page 10,line 1: Does this mean you had a skewed distribution? I am not sure what the difference between the median and 95th percentile communicates in terms of risks to children's health?

Page 10, line 7: For the benefit of the reader who understands statistics, authors should describe in one line how you used medians to test significance and assess variability.

Page 10, line 16 (also page 11, line 9): authors should make a decision to control for demographic variables across all metabolites, or not at all. Given that these comparisons across metabolites are carried out in the same group, all covariates should be held constant across metabolites even if they are not significant.

Page 12, line 3: Authors should be consistent. If you are setting statistical significance at p<=0.05 as your main criterion for a true difference, then only differences that meet that cut-off are different.

Table PHTL1b: This information would be more easily conveyed in a figure than in a Table. Geometric means and confidence interval would be preferable, or medians with 25th and 27th percentile.

Page 17, line 10: In a population level study of this magnitude (hard to judge because authors do not report sample sizes), the within subject variability should not be a big issue with the exception of subpopulations with large physiologic variability, i.e. pregnant women. In the large sample setting, the between-person variability generally overwhelms the within-person variability.

Reviewer 2:

Bar chart on page 9 and page 11:
Bar charts are appropriate descriptive graph for nominal level data where proportions are reported. The appropriate graph for continuous scale-level data should be the line graph.
I think it would be much clearer to have the x axis be NHANES survey year, the y axis the same (concentration of indicators) and a separate line graph for each metabolite over time. Each of the 3 metabolites could be in a different color and with different point estimate indicators (triangles, squares, circles etc). Not only would this keep the presentation true to current notions of how statistical data should be showcased, I think the visual display will be more compelling. You will see the changes over time much easier and the metabolites have such different scales of measure that the line graphs won't overlap and so the reader can easily see that DEHP metabolites are higher in urine than DBP and DBP is higher than BBzP metabolites.

Also a footnote to determine if these are crude or adjusted models would be helpful in both graphs.
Page 9 line 12 and page 11 line 6: I assume these were time trend analysis in linear regression? Should it be explicitly stated??? In other words you did not just look at year one and compare to the last year, you looked for a linear trend over time correct?

Page 10, line 3: might want to clarify why the ranges were from 10-12. The range seems to depend on the year of the survey (ie in one year DEHP metabolites we 10 times higher, another year it was 12 times higher). What would also be interesting is if the 95th percentile is increasing linearly each year too or are they higher one year, lower the next and higher again?

Page10 lines 16-20: using the word 'only' in line 16 seems to try minimize the importance of this finding between income and DEHP when in fact it is showing that the relationship is robust when known associations between group concentrations are taken into account. I found more support for DEHP than I do for BBzP since the association became nonsignificant once these differences were adjusted for.

Data tables:
PHTL1 page 13: Titles, headings and subheadings are clear and easy to understand
Abbreviations missing from notes section. I would prefer to see the sample sizes in the column headers (ie) N=642 for 1999-2000. I know it is in tables further back, but those later tables are very dense and likely not going to be read by the concerned parent or educator. I think having a sense of the sample size in these tables is important. If there happens to be a lot of missing for each metabolite, then a symbol can refer the reader to a footnote describing how many were missing for each analyte.

The footnote ii for this table: should you add the bolded words 'combined **sum of** urinary levels of MnBP and MiBP…?

PHTL1a page 14
Same comments as above plus:

Line 20-23: couldn't it just as easily underestimate high end exposures?

Table PHTL1b page 15
Not sure why data is restricted to 2003-2006. No where in the text prior or in these bullets does it describe why (same comment for table PHTL2b and c). Again I would like to see the sample size listed for each of the groups in the column headers

Not sure how you got these values in the PHTL1b? Did you take an' average of the average' metabolite concentrations across the survey years?? Or did you take the average of all the values of all the survey samples over the entire time period? For example: 'all incomes' column, 'all races' row under DEHP is the same value as if I added the 3 DEHP values in table PHTL1 and divided by 3. This would minimize the influence of sample size differences in each survey. I wouldn't think I would get the exact same value if I took an average of the entire sample without breaking down by survey year, would I? Then for BBzP, I don't get the same value as I would if I averaged the values in table PHTL1 so I am confused how you obtained these values.

In this table I would like the sample sizes in row and column headers.

Table PHTL2 and 2a
Just add sample size to column headers.

Also the note on page 17, line 12: the reference #72 doesn't seem to reflect the title of the article?

That article is on perchlorate?

Table PHTL2b
Again why only 2003-2006?

Sample sizes in column and row headers.

BBzP row header format is fouled up.

Table PHTL2c
Why 2003-2006 (and not 1999)?

Sample sizes in column and row headers.

Comparison groups;
I agree with race/ethnicity, income and survey year.

I would have liked to see a breakdown by age group categories. There is so little known about children I would like to see metabolite breakdown by developmentally appropriate age groups (pedi is not my specialty to I don't know what those groups should be? Perhaps elementary school, middle school and high school ages?)

Also would weight categories offer any interesting comparisons in light of the childhood obesity epidemic? Phthalates are not lipophilic and should not bioaccumulate, but could phthalates themselves because of endocrine action be associated with weight gain in children?

Reviewer 3:

The presentation of each indicator is fine and needs no further description, at least in my opinion

Question 4 – Context and Utility

Reviewer 1:

PHTL1 and PHTL2 (responses are the same for both indicators)
Why are the authors interested in time trends specifically? Can they help determine if regulations are working? If women and children are becoming more informed and reducing their exposures? Phthalate-induced health risks are increasing or decreasing? Authors should somehow connect the issues raised in the indicator text with the data presentation.

It would be interesting to answer the question if exposures are changing and then specifically in which subsets of the population. However, it seems that the point of the document is to portray phthalates as a health risk to children. There could to be a clearer connection between why differences by time and demographic group matter to health. Are some groups below or above a threshold for potentially harmful exposures? Are some of the health endpoints described in the initial text more prevalent in some of these groups, or increasing or decreasing with time which might indicate a phthalate relationship? It seems the point of all the data presentation is show that everyone is exposed, there is not much change over time, and some groups are more or less exposed. It would be good to make clearer connections between the data and the prenatal and childhood health risks.

No, I don't think this analysis does justice to the NHANES database as a tool to inform decision-makers. The questions being asked should be more specific and more directly related to human health. The data should be presented in a more comprehendible format.

No. If I wanted to compare phthalate exposures in any given population to NHANES, I would probably not compare medians. I do not see any way to use this document to better understand exposure risks, or to make decisions about how to minimize risks. The information is not specific enough nor does it point to specific sources of exposure. The initial text by itself does an adequate job of introducing phthalates, source categories, routes of exposures, putative health risks, and general state of our knowledge on this topic.

Reviewer 2:

Yes it meets this objective

I am not sure the untutored politician would be able to get the nuances in this document. I am sure they all have scientific advisors though and this document would certainly help put the issue of environmental exposures into perspective.

The time trends will be particularly helpful as legislation and public opinion sway manufacturers to remove phthalates from commercial products.

Reviewer 3:

Does this provide a basis for assessing and understanding time trends?

Phthalates are metabolized and eliminated in urine within hours after exposure. Several reports suggest that concentrations of phthalate metabolites in a spot urine sample can provide a reliable estimation of exposure to phthalates for up to several months, but recent studies indicate that MEP and MEHHP urinary concentrations varied considerably during 1 week, and the main contributors to the total variance differed also. The nature of the exposure (diet vs. other lifestyle factors) and timing of urine sampling to evaluate exposure to phthalates should be considered. When collecting multiple spot urine samples, changing the time of collection may provide the most complete approach to assess exposure to diverse phthalates. This obviously wasn't done but should be mentioned as part of the discussion of the utility of the measurements

To inform discussions about how to improve federal data on children and the environment?

As already mentioned, DINCH and DEHT should be mentioned as future compounds important to monitor.

Indicators of potential impacts on childrens health ?

What is missing is some idea of what levels should we be worried about. This is what every politician and concerned parent, for example wants to know. Otherwise we are just looking at numbers without much meaning.

Question 5 – Documentation

Reviewer 1:

The documentation is quite extensive and could be shortened. For example, the birthrate adjustment is explained numerous times.

Specific comments:

pre-natal should be changed to prenatal

Tables 1. Can authors present contrasts or something to indicate the direction and magnitude of the difference between the two groups? I think it is difficult to expect the reader to cross-reference tables.

The "other" category shows significant differences in income. Can the authors comment on how to interpret this? Which groups were in the other category, or might this be a misclassification of race/ethnicity?

Table 3,6. It is not clear what the comparison is in this table. Could it be stated more simply?

Seeing the vast number of comparisons in these tables definitely raises concern about multiple comparisons. Authors could adjust the raw p-values and report the findings in both cases.

Reviewer 2:

Method section. This is the section I had the most confusion with especially around the weighting. I do get the concept but the example with all the code was quite confusing. Perhaps if I had the data and could play with it, it would become clear to me.

Data summary page 28
Is the value '23' found in year 2001-2002 under MBP, percentage below LOD incorrect?? It is so different from all other years as to look suspicious.

Same question on page 29 under 2001-2002, for %below LOD for MEOHP. The value '6' seems out of proportion to all other years

Same questions for PHTHL2 table on pages 29. the value '17' appears suspicious under MBP % below LOD.

Also the format of the row heading for MBzP is off.

What was going on with MBP in 2001-2002?

Page 32: the creatinine adjustment equation seems odd. Why (0.01* creatinine) in the denominator rather than just creatinine?? Is it because of the unit of measure?

Page 33, line 13. Do you mean you readjust the phthalate metabolite levels BEFORE any analysis is conducted??

Page 33 line 22. I thought a formula would be helpful here, not the narrative formula. I couldn't tell if 'and' meant 'plus' and 'product' meant 'multiply'. Or at the least, I think a reference to the example on page 35 would help.

Page 33 line 31: should 'family units' be 'poverty level'?? Not sure what you are saying.

Page 35 lines 17-21. Sorry, lost me.

Page 36: sorry lost me with the i^{th} and j^{th} notations. Brought back statistical nightmares☺ I mean I basically get it and if I was in the 'zone' again, I'm sure it would make much more sense. I guess I think the SAS commands (or SPSS commands) would be easier to understand than the actual equations.

Page 40
Table 1. Again why 2003-2006 instead of starting in 1999?

Not sure I see the utility of the amazingly busy tables on pages 40-46. Without sample sizes for each comparison it makes it hard to assess the credibility of the comparisons. Could be tons of spurious associations just because of the multiple testing issue

Reviewer 3:

The documentation appears transparent and complete. There are no problems here

2.0 ENVIRONMENTS AND CONTAMINANTS

2.1 Climate Change

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Kirsten Malecki
- Vlasta Molak
- Perry Sheffield

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

Overall, the topic text is clear and well written, however, I was hoping for the link/importance to children's environmental health to come earlier. The description of climate change and overview of potential impacts were concise, well written and fairly comprehensive. One area that could perhaps use a little more attention but for which there is less literature is around the issue of GI illness and heavy rainfall events. Gorelic et. al, 2010 did an analysis in Milwaukee County looking at GI illness and rainfall. In the upper mid-west rainfall events are estimated to be increasing in frequency and intensity as a result of climate change, this would be an important paper to include.

More specific comments:
Page 1 line 11- first sentence is a good segue – but you don't provide any examples, I would suggest moving text from page 2 starting with line 44 up to this section or starting a new paragraph focusing on why this is an important children's environmental health topic following the second paragraph this will provide some additional context for each of the specific areas of concern described next.

Paragraphs 5 and 6 both do a good job of emphasizing the link to children's health in the final sentence, this is not the same for paragraph 7 – lines 14-23 page 2. I would recommend talking about children's susceptibility because of their immune systems, as well as their increased time

outdoors, patterns of play in sprawling suburban areas encroaching on forests that increase their potential for exposures.

Similarly – prgh 8 lines 25-29 pg 2 talks about increasing allergens but does not link back to significance in kids--- has there been an increase in allergen related asthma exacerbations in summer months?(I know there hasn't been but perhaps this needs further explanation etc. and at least some mention to put this background into context….

Paragraph 9 lines 34- pg. 2 – I think we need to provide some link to why these changes will impact children….why do we care about pesticide use and increases --- e.g. this would be a place to link back to other sections e.g. childhood cancer and neurological impacts on kids…line 35 – kids are more susceptible to heavy rainfall and GI illness – similarly – we care about increased persistent chemicals in kids because of reproductive impacts on the next generation. All of these associations/links to children's health have been made but they are not clear in the context of this text.

Finally- I think this section needs to conclude with some description of given all the potential indicators to choose from – why this one? You indicate there are a number of other metrics but then don't justify the representativeness/robustness of the indicator chosen – why air and not water? Why not another air quality related indicator? How is this indicator related to the other air quality measures in the report etc.

Also page 3 line 8 – how is "unusually high" defined? You do this on the next page, but some redundancy may be OK.

Page 5 – line 7-9 this sentence should be in the topic area and be part of the intro---

Reviewer 2:

The text is well researched and well written. It clearly describes the importance of climate change on children health and explained various problems that can result from the increased temperature. The relevant literature is appropriately summarized. However, since the major effect resulting from high environmental temperature are heat exhaustion and heat stroke, those topics need to be described in more detail, especially in regards to disease vs. temperatures and humidity. Therefore I recommend that such a curve of health effects vs. temperature (and humidity) be presented and topics of effects of temperature (and humidity) on heat exhaustion and heat stroke in children are discussed. One can easily find a literature on this topic by searching Internet. Alternatively, one can also use data on reported emergency room and/or clinic visits of children who had experienced adverse effects of high summer temperatures in the last 30 years. This would be actual data rather than some theoretical possibility, and thus more accurately describe the adverse effects of global climate change on children in USA and possible indications of trends in children health.

Reviewer 3:

The topic text provides a clear introduction appropriate for a wide audience. This reviewer has some suggestions regarding additional aspects worth noting and edits.

1) In addition to the currently listed health effects (3rd paragraph on page 1) that could result from heat exposure, less specific effects such as dehydration and subsequent electrolyte imbalance are

important as well (Knowlton K, Rotkin-Ellman M, King G, Margolis HG, Smith D, Solomon G, Trent R, English P. The 2006 California heat wave: impacts on hospitalizations and emergency department visits. Environ Health Perspect. 2009 Jan;117(1):61-7).

2) 1st paragraph, page 2. Suggested citation for the sentence starting with "Extreme weather events…": Drayna P, McLellan SL, Simpson P, Li SH, Gorelick MH. Association between rainfall and pediatric emergency department visits for acute gastrointestinal illness. Environ Health Perspect. 2010 Oct;118(10):1439-43.

3) 2nd paragraph, page 2. Lyme disease – as mentioned in the NRC document (ref #5) that is already cited – is another vector-borne disease that is climate sensitive and could be added to the sentence where West Nile and Dengue are mentioned.

4) 3rd paragraph, page 2. In addition to an earlier onset of the U.S. spring pollen season, recent evidence suggest a longer ragweed season in the Northern Midwest (Ziska L, Knowlton K, Rogers C, Dalan D, Tierney N, Elder MA, Filley W, Shropshire J, Ford LB, Hedberg C, Fleetwood P, Hovanky KT, Kavanaugh T, Fulford G, Vrtis RF, Patz JA, Portnoy J, Coates F, Bielory L, Frenz D. Recent warming by latitude associated with increased length of ragweed pollen season in central North America. Proc Natl Acad Sci USA. 2011 Mar 8;108(10):4248-51).

5) Last paragraph, page 3. The indicator is 3 or more days not one or more.

Question 2 – Indicator Text

Reviewer 1:

Yes- but are there references to support the methods? How was this measure compared to say one of the other combined measures chosen…what kind of group process went into the decision-making?

I am left with questions about the significance of some of the choices made for estimating the measure --- the reference time period is explained well. But why is 3 or more days per summer considered unusually high vs. 2 or 1 and can they be any 3 days? Wouldn't 3 consecutive days be more risky? Was there any consideration of a more conservative/less conservative cut-point?

I also understand the selection of the season as opposed to other times of the year but a little more justification for the number of days vs. hottest 1% or 5% would be helpful. Are any of the time series analyses focused specifically on kids or did they identify kids as particularly vulnerable? If so- this should be included as justification. A summary of available data should be included.

Why these data and not any modeled climate estimates used? A mention of these data and their limitations in utility for this report would be helpful.

Are there plans in subsequent reports to add additional climate measures?

Reviewer 2:

CL1 as defined in the document is a useless indicator of the heat exposure in children. First, it defines a baseline temperature for each county separately, as if children in each county may have a

different physiological response to heat. Thus averaging out the temperatures county by county is totally inappropriate, because the adverse effects of heat will depend on the temperature (and humidity), regardless what the past heat events are recorded in that particular county. In addition, the index as it is defined now, lumps together counties which may have only 3 high temperature events with those who may have 20 or more high temperature events in any one summer, and is therefore not really evaluating the number of children that may be exposed to high temperatures, which may be damaging to them and cause health effects.

More appropriate indicator would measure the number of the children in any given county, multiplied by a number of heat events in any given year and then divide it by the total number of children. The heat events should be defined based on average temperature at which there is an adverse effect of heat in children. This will probably depend on the age of children since younger children may be more sensitive to heat. This baseline temperature is the same since there is no reason to assume that the physiology of children changes between counties.

It is clear from the "result" of the rather convoluted calculation of CL1 that it is a meaningless indicator, since it varies all over the chart. One does not have to do any statistics to see that such a curve could not be averaged out, and particularly cannot show that there is a trend in increased proportion of children exposed to high temperature with possible adverse effects as a function of time.

Therefore, I strongly recommend to define a baseline temperature at which adverse effects in children may occur (based on known physiological and epidemiological studies in children), and then find a number of children in each county multiplied by a number of heat events (temperatures that are above the baseline temperature for adverse effects). The chances are that if the county has more or such heat events there would be more health problems associated with high temperatures than a county with fewer heat events. The increase of such elevated heat events in any given county and any given year will be a good indicator of the potential children health problems due to the global climate change.

Such a calculation will be a more meaningful estimate of the proportion of children in USA that are exposed to heat events in any given year. One can use the data that were used to calculate the ill-defined CL1 and simplify the calculation by taking the number of "heat" events in each county for each year, based on exceeding of a physiologically defined adverse effects temperature, which is the same in entire USA.

Reviewer 3:

Overall, the indicator description is concise and clear. Two suggestions: the choice of 3 non-consecutive days needs better justification and “heat event” needs a definition. Here’s the heat event definition from Ref #33 (EPA’s Excessive Heat Events Guidebook): “summertime weather that is substantially hotter and/or more humid than average for a location at that time of year. EHE conditions can increase the incidence of mortality and morbidity in affected populations.”

In addition, the citations supporting the idea of children’s vulnerability to heat events could be strengthened. First full paragraph on page 5, Ref # 33, cites the following in support of the statement that infants (under 1 year) are especially vulnerable:

American Medical Association Council on Scientific Affairs. 1997. Heat-Related Illness During Extreme Weather Emergencies. Report 10 of the Council on Scientific Affairs (A-97). Presented at

the 1997 AMA Annual Meeting. – **This document argues that infants are physiologically more at risk due to great surface area to mass ratio, dependency on adults, and inability to communicate discomfort from heat or thirst.**

NOAA. 1995. Natural Disaster Survey Report: July 1995 Heat Wave. National Oceanic and Atmospheric Administration, Silver Spring, MD. – **Very young included in heat risk advisory. No data or description given of increased health effects among children.**

Semenza, J.C., J.E. McCullough, W.D. Flanders, M.A. McGeehin, and J.R. Lumpkin. 1999. Excess hospital admissions during the July 1995 heat wave in Chicago. American Journal of Preventive Medicine 16(4):269-277. – **Did not specifically examine children as a sub-group.**

This reviewer agrees with the concept of underlying physiologic vulnerability in the very young. However, in reality children are often – though not always - protected from the effects of heat by their caregivers. An additional citation to support the idea that children experience heat event-associated effects is:

Knowlton K, Rotkin-Ellman M, King G, Margolis HG, Smith D, Solomon G, Trent R, English P. The 2006 California heat wave: impacts on hospitalizations and emergency department visits. Environ Health Perspect. 2009 Jan;117(1):61-7. – **Showed increased risk of ED visit for 0-4 year olds for heat-related illness and electrolyte imbalance during 2006 California heat wave.**

Question 3 – Indicator Presentation

Reviewer 1:

For bullet 1 lines 3-5 pg. 6 – translating this 4% increase into actual number of kids and using an analogy to describe the significance of this increase in total numbers would be helpful to better understand the total impact of these changes. 4 % every ten years doesn't sound too alarming but if you multiply this out by the total number of kids across the country you would get a much larger number

The graphical display is clear. An additional bullet describing the unusual peak in the late 80's (86-87) would be helpful – in addition a discussion of how representative the time period is would be helpful.

Why isn't there a map? – if this analysis was done for every county across the United States some geographic representation of estimates (real or smoothed) would be good.

What is the range of "unusually hot days" in the summer by year, over the whole time period, by county? --- e.g. do we see trends by region, by county in where the extremes are, or elevated numbers are? Where across the US do you see the most vulnerable populations?

Reviewer 2:

Indicator presentation is fine, but as long as the indicator is ill-defined it is meaningless. The form of the presentation could be the same but use a more appropriate definition of CL1.

Reviewer 3:

The graph and table are clear though somewhat redundant. Additional description of low- income or children 0-4 years of age – as those are both known risk factors for health effects during heat events – would strengthen this presentation – making it more useful to policymakers and public health officials - and seems that it would be possible from the metadata description.

Question 4 – Context and Utility

Reviewer 1:

I think the indicator selected for climate change is clear, concrete and quantifiable but additional indicator measures are needed to complete the picture – particularly one related to water that may suggest further investigation… or at least include a discussion of why these weren't included – also how does this topic relate to other topics in the report e.g. asthma/air quality etc.

Highlighting data gaps/limitations and spelling these out more in the topic area discussion would be helpful for policy audiences – if all of these factors are important for children's environmental health- why only 1 indicator measure?

This indicator does track well changes for policymakers and it is easily understood. I think it would have a greater impact if the actual number of children impacted and how many children this .04% annual increase really translates into would be helpful.

I think including some county level indices of social vulnerability and which counties will experience the highest number of days would add value and detail to the assessment that would add to the overall utility of the indicator for policy makers and their ability to make decisions regarding resource allocation, and implementation of more targeted adaptation strategies.

Reviewer 2:

Once a more appropriate indicator is defined which will take into account the heat events (based on exceeding the baseline temperature for adverse health effects) and the number of children potentially exposed to those heat events calculated, there may be a utility of such an indicator. I predict that such a calculation of the proportion of children exposed to heat events in any given county, averaged out for the entire USA, will give a rather smooth curve with an upward trend, similar to the average temperature given for the global climate changes. I would be very interested in seeing this CL1 redefined and recalculated as I had recommended above.

Also, I would like to see the heat exhaustion and heat stroke visits of children to emergency rooms and clinics, if those data are available.

Reviewer 3:

This reviewer finds that this indicator allows easy tracking of time trends and should be useful to policymakers – particularly in urban settings when debating urban heat island mitigation plans. The suggestions provided above for additional clarifications, justifications, and citations should help improve even more the utility and appropriateness in addressing the three principal objectives of the ACE.

Finally, this reviewer would suggest consideration of precipitation events – due to increasing evidence of association with diarrheal outbreaks even in the United States - as an additional indicator – if not in this edition then in future editions of ACE.

Question 5 – Documentation

Reviewer 1:

Yes- I think addition of a reference at the end of the sentence line 24 page 5 would improve the documentation for references.

In terms of understanding how the indicator was calculated the documentation looks good.

Reviewer 2:

[No comment was provided by the reviewer]

Reviewer 3:

Overall, the documentation is complete and transparent. However, a few clarifications and a possible correction would help. In the 1st full paragraph on page 15, the term 'bridged race' is not known to this reviewer and a brief description would be helpful.

On page 18, the number of counties (2,311) seems incorrect. Shouldn't it be 1,596 (as noted on the previous page) since those were the counties with three complete summer months of climate monitor data?

2.2 Contaminated Lands

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Deborah Bennett
- An Li
- Arnold Schecter

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

Page 1

Line 5 – 6: "Common categories of land contaminants …." – Change to "These contaminants commonly include …."

Lines 5 – 8: Consider adding a for example (e.g.,) after each contaminant with a list of one or two contaminants. This will help non-technical readers have a better understanding of these contaminants if they can link them to actual products (e.g, gasoline, oil) especially as it relates to naturally occurring substances. This is very vague.

Lines 14 – 15: Given that the document talks about wind carry dust later in the paragraph and that the indicators measure children within a given proximity to sites, I would add the phrase "or within proximity" after "residing on contaminated land".

Line 18: Remove the phrase "toxins, microbes, or other hazardous materials" and replace with contaminants. Keep the language clear and do not add confusion by suddenly introducing microbes. There is no mention of this anywhere else in the text.

Lines 21 – 23: The sentence regarding inhalation needs to be drastically changed. As it reads, is almost implies that large particles have no health effects and small particles "can be very damaging". More detail needs to be provided regarding this damage since they can not only have damage on the lungs, they can also enter the circulatory system. More common though are larger particles which can have just as serious health consequences including the exacerbation of existing health conditions (e.g., asthma).

Line 23: Replace "most crucial step" with "the optimal approach" to convey a technique rather than a series of steps within a single technique.

Line 27: Delete "potential"

Line 27 – 30: This sentence is too long and contains too much information and hypothetical situations. Consider breaking up into several sentences.

Lines 30 -32: Delete the last sentence. Not needed. Does not add to the paragraph and document.

Line 35 : Delete "company"

Line 37: Delete "or just under 1% of the entire US land mass". Interpreted as trivializing the amount of land. The statement regarding 22 million serves this point better.

Line 39: Delete "some of" – too tentative.

Line 43: With the sentence beginning "Other", insert the following phrase "The EPA is also responsible for …".

Page 2

Line 5: Delete "The focus" and replace with "The EPA's priority"

Line 9: A few more sentences are needed regarding PFP and what it means. This is needed for individuals not familiar with the EPA and its terminology.

Lines 11 – 12 : Delete the first sentences.

Lines 25 – 32 : This paragraph is very wordy. I'm not sure how to fix it.

Line 34: There is a lot of information missing in this paragraph regarding differential outcomes. Even two individuals are exposed to the same contaminant; factors including dose, length of exposure and pathway (e.g., lead exposure via ingestion versus inhalation) are far more likely explanations for an outcome. More discussion is needed regarding the more likely difference in outcomes.

Lines 37 – 38: Delete the sentence starting with "Some populations". It is redundant.

Lines 38 – 39: For the sentence starting with "Socio-cultural factors…", consider revising. The introduction is about health outcomes related to exposure to contaminated lands. All of a sudden, the reader is taken away from this focus and introduced to "physical and psychological health". There is no shortage of literature regarding the influence of socio-cultural factors on exposure. In fact, a good portion of the environmental social justice movement is based on these factors. The factors and outcomes in this paragraph should be very specific to contamination of land and exposure.

Line 42: Once again genetic factors are brought up, but unlike socio-cultural factors, no explanation is given regarding these factors. More information needs to be given if it is to be included in this paragraph. In fact, it should be removed or relegated to an "other" category along with the factors mentioned in my critique of line 34.

Reviewer 2:

The topic text appropriately describes the potential exposure pathways for children living near contaminated lands, and clearly defines the definition used in this document for contaminated lands, i.e. Superfund and RCRA Corrective Action program not designated PFP. While I agree that evidence documenting links between these contaminated lands and actual health outcomes is limited, there are some concrete examples and they could be cited (e.g. see reference (1) below. Another New Jersey example; the Dover Township childhood cancer cluster investigation literature, could be cited (2)). Where I believe this text needs strengthening is related to the last two paragraphs. It needs more depth of discussion about social disparities and environmental exposures. The indicators E9 and E10 are really about this issue – disparities and the environment, which is admittedly complex, and the text should not shy away from this. The article by Payne-Sturges and Gee (3) does an outstanding job of discussing the issue and I recommend applying more of concepts in that paper to this text, including the incorporation of the notions of cumulative risk, and that " inequities in illness and exposures …are at least partially mediated by factors association with the physical, social and build environments." I particularly like the representation of the issue in Figure 1 of that paper, but that may be beyond the scope of this text.

I believe the text should be understandable by people with varying levels of knowledge, but the addition of concrete examples (albeit rare) where contaminated lands have resulted in actual human health effects would be helpful, and expansion of the concepts of social disparities will add depth to the appreciation/understanding of the indicators as presented.

1. CDC. Mercury exposure among residents Of a Building Formerly Used for Industrial Purposes -- New Jersey, 1995. MMWR 1996 / 45(20);422-4. Available at www.cdc.gov/mmwr/preview/mmwrhtml/00041880.htm

2. New Jersey Dept. Health and Senior Services. Dover Township Childhood Cancer Investigation. Available at http://www.state.nj.us/health/eoh/hhazweb/dovertwp.shtml.

3. Payne-Sturges D, Gee G. National environmental health measures for minority and low-incomepopulations: Tracking social disparities in environmental health. Environmental Research 102 (2006) 154–171. Available at http://yosemite.epa.gov/ochp/ochpweb.nsf/content/Disparities2.htm/$file/Disparities2.pdf

Reviewer 3:

The authors were very clear and did a nice job providing a laypersons overview of the topic. I would prefer to see more peer-reviewed literature in the reference list. I do not think that a PBS special (ref #8) is an appropriate reference. A quick PubMed search revealed a lengthy list of possible articles that would be appropriate.

Question 2 – Indicator Text

Reviewer 1:

Page 4

Line 5: Consider using household income as an income measures. It is more robust and captures many more household types than family income. Further, there might be a racial/ethnic bias to using family income (i.e., more likely to capture the household arrangement of whites and not minorities).

Line 16: The use of site latitude and longitude is very controversial. Having done ground truthing (i.e., verification of EPA sites) of EPA sites, I find that the lat/long coordinates are not accurate especially is produced as a result of geocoding. Further, for large and irregular shaped sites, a single point measure is inadequate.

Page 5

Line 11: The 2005-2009 American Community Survey (ACS) file should be used. The 2000 data is already 11 years old. The most recent data should be used. All of the same measures used as indicators in this document are available down to the block group level.

Reviewer 2:

The overview should include the fact that the 2000 Census was used for these indicators. Somewhere there should be an explanation why the 2010 Census wasn't used, given that this project still is being completed in 2011. (The one small footnote about the differences between 2000 and 2010 census is probably not sufficient.)

Would it be possible to have a map of the sites enumerated in the section "corrective action and superfund sites"? Perhaps in an appendix? Or add the number of sites in each state to one or more of the tables in the Appendix. By making comparisons only to the entire US population oversimplifies the distribution of contaminated lands in the U.S.

Line 25 on page 5: add "national": "…indicators at the *national* and state level…

Starting on line 38 of page 5, this seems to be a discussion of the limitations of the data, or the limitations to interpreting the data. It does a good job of this, as far as it goes, but does not have any discussion of the interpretive issues around the social disparities aspect of the data. Can that be added? And give a header to this section?

Reviewer 3:

The authors did a nice job explaining how the site areas were estimated. I also appreciated the note explaining why 2009 census data were not used.

Page 5, lines 27-33: Is it possible to separate the Hispanics from the other groups? It may be more beneficial to include Hispanics, regardless of race, as one category and then the other categories are non-Hispanic whites, non-Hispanic blacks, Asians, and so on. Hispanics are different from other

populations in terms of pregnancy rate, pregnancy outcomes, poverty, and various health indicators, thus combining them is unlikely to be valid. For example, the epidemiologic paradox has been frequently published on and indicates that while many Hispanic populations are more similar to non-Hispanic blacks in terms of income and other SES indicators, they are more similar to non-Hispanic whites in terms of pregnancy outcomes and childhood health. Combining these groups may mask a possible reason for these discrepancies (different residential environments and associated exposures). In turn, this may impede identification of research questions that examine health disparities or identification of at risk populations.

Question 3 – Indicator Presentation

Reviewer 1:

Page 7

Line 6: More discussion needs to be provided regarding why racial/ethnic minorities are more exposed to contaminated land. Even for non-technical readers, a few sentences regarding the living conditions of African Americans in central cities and proximity to industrial land is sufficient. But for someone like myself who is familiar with these issues, the increased exposure for groups including Asians and NHOPI is perplexing given the later is a very small part of the US population.

Page 9

The figure is too busy and confusing. Please revise.

Reviewer 2:

For the sake of accuracy, table titles and text should be reworded regarding the year involved, because 2009 is the year for the site data, not the population data. Thus for example, the first bullet under indicator E9 could be reworded to say: "Approximately 6% of all children in the United States lived within one mile of sites designated in 2009 as Corrective Action or Superfund sites without a "Protective for People"(PFP) designation."

I would like to see the titles of both indicators to more accurately describe the content of the indicators. For E9, I would recommend: Percentage of children in the United States living within one mile of Superfund and Corrective Action sites that were not PFP in 2009, by race/ethnicity and income.

For E10: Distribution by age/ethnicity and family income of children living near selected contaminated lands in 2009, compared with the distribution by age/ethnicity and income of children in the general U.S. population. Accordingly, the titles to the data tables should changed.

The two figures and the data tables give the reference to EPA after "DATA" but should also include "2000 U.S. Census".

In indicator E10, a vertical dotted line between the race pie charts and the Hispanic ones might be helpful, because, when printed out in black and white it takes a few minutes to figure out what the pie charts are about that are on the right hand side.

"Eight percent" of children sound like "a lot" of children. This could be interpreted to mean that no matter where you live, 8% of children might be living near contaminated lands. I assume these sites are clustered in urban areas. This goes back to my point above about providing a map. There needs to be some kind of geographic context. Comparing the distribution of race/ethnicity/income around these sites to the entire U.S. is oversimplifying. Can you also add some comparisons in some major urban areas, to show, by example, how the comparison might differ when using a locally constructed comparison population? Or at least acknowledge this in the discussion.

The bullet points for both indicators are appropriate and clear as related to the displayed data.

Reviewer 3:

Indicator E9 was clear and informative. E10 was also informative, but I think that the main point, that there are racial/ethnic disparities in the proportion of children that reside near contaminated lands, could be depicted in a more straightforward way. Would it possible to incorporate a graph that displays the proportion of all black children that live near contaminated lands (# black children near contaminated lands / # black children in the US) and the proportion of white children that live near contaminated lands, and so on for each race-ethnicity?

Question 4 – Context and Utility

Reviewer 1:

Indicator - % of children 0-17 years living within one mile of Superfund or Corrective Action sites that were not PFP, 2009

This indicator provides a concrete and quantifiable indicator of the possible environment of children living near these types of contaminated lands. There might be an issue with trend analysis in the future if 2000 US Census data is used. Because of differences in the US Decennial Census and the new American Community Survey, certain indicators might not be comparable between the two data sets. It is better to build this indicator using ACS data in order to ensure trends analysis.

Unfortunately, the lack of geographic detail for this indicator will prevent many state and local policymakers and stakeholders from making meaningful policy decisions. While this indicator shows racial/ethnic differences in relation to contaminated lands and geographic differences between states, policy that is needed to address these problems require more detailed information (e.g., county level).

Again, in order to track and understand public health impacts of these sites, more detailed information is needed and it should rely on the use of the ACS.

Indicator - % of children living near selected contaminated lands by race, ethnicity and family income, compared with children's distribution in the general U.S. population, 2009

I find this indicator redundant and not needed. Much of the detail needed is provided by the first indicator.

Unfortunately, the lack of geographic detail for this indicator will prevent many state and local policymakers and stakeholders from making meaningful policy decisions. While this indicator

shows racial/ethnic differences in relation to contaminated lands and geographic differences between states, policy that is needed to address these problems require more detailed information (e.g., county level).

Again, in order to track and understand public health impacts of these sites, more detailed information is needed and it should rely on the use of the ACS.

Reviewer 2:

Many of my comments above have addressed these questions to some extent.

In addition, using 2000 Census data for this indicator, in the context of understanding "time trends", is of course quite problematic. Explicit commitment to updating the indicator when the full suite of 2010 Census data become available would be very helpful. Plus, the intercensal data from the American Community Survey may make some data calculations more timely than once every 10 years (although I'm no expert in this).

Another issue that isn't explicitly addressed in the narrative is – what would be a *measure* of success? Less PFP sites? The indicator data doesn't provide much data on the number, or for that matter, the types of sites or any characterization of types of potential exposures. Fewer potentially exposed children? What if the numbers of children went down because of changes in the locations of sites, rather than because there were fewer sites because of clean-up etc..? What if the numbers of children went down but the percent of the population didn't? What would be a measure of success specifically in relation to the disparities data? Would it be a measure of success if the proportional distribution by race/ethnicity/income around the sites was the same distribution as the entire US? The importance of the disparities data may be in directing priority investigations and follow-up, particularly the need to investigate at the local level, rather than a benchmark to measure success.

Reviewer 3:

As I mentioned above, I think the indicators would be of greater value if Hispanics, regardless of race were considered as separate group. I also think indicator E10 needs to be clarified. If this is done, I think it will be more informative for policy makers and the general public.

Question 5 – Documentation

Reviewer 1:

Page 22

For states without data, please provide a footnote indicating the reason for the missing data. The reader is left wondering if data is not available or no children live near contaminated sites. This comment pertains to Table A1 and the remaining tables.

Reviewer 2:

A metadata table for the Census data would be very helpful. Right now information about the Census data is in the narrative throughout the methods section. It would be much clearer if more of it were explained in the more transparent form of the metadata table.

The description of the methods used to generate the data seemed clear and detailed, although I did not attempt to recreate the data myself.

Reviewer 3:

It seems to be complete, but the headings for the tables in the appendix (pages 22-25) should be clarified. It is somewhat unclear how the "Total children's population" column differs from the "All children" column. A second header line indicting total population or population residing within one mile of selected contaminated lands would be helpful.

A similar strategy could be applied to Tables A2 and A3. I think the clarity of the tables would be enhanced if the text that reads "% below poverty in proximity who are" were removed from each column and replaced with a row across the applicable columns that states "% below poverty."

2.3 Criteria Air Pollutants

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Michelle Bell
- Catherine Karr
- Morton Lippmann

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

The text could note that smaller particles, which penetrate more deeply into the respiratory system, appear to be more harmful than larger particles, although strong scientific evidence exists for harmful human health effects from both sizes of particles.

Note that "ground-level ozone" is tropospheric ozone. Given the confusion between tropospheric and stratospheric ozone, it may be worthwhile mentioning that the ozone of interest here is the harmful ozone in the breathing zone, not the protective ozone in the ozone layer related to the "ozone hole" in the stratosphere.

Children are highlighted as a potentially sensitive subpopulation (page 1) but other subpopulations could be mentioned, such as the elderly and those from lower socio-economic groups.

Instead of "no assessment is made regarding the frequency with which the standards were exceeded for these children [living in counties without monitors]" consider alternate wording such as "no assessment can be made using monitoring data . . ." to avoid suggesting that such analysis was possible with this data set.

The issue of changing standards may be confusing to some readers, for example during the discussion of $PM_{2.5}$ for the AQI (page 12). In the introductory text, note that the EPA periodically

revises the standards based on current scientific evidence. This is implied (page 1), but not made perfectly clear.

Instead of "intensity of pollution" consider "degree of air pollution" or something related to "air quality". I'm concerned that readers may misinterpret "intensity."

The text noting that a single exceedance of the standard does not necessarily indicate that the county is in non-attainment (page 26) is helpful.

The section on particulate matter (page 2) does describe that particles are a complex mixture, but I don't think it really conveys the degree of heterogeneity of the particle mixture. More text to highlight this issue is warranted.

The general introductory text (pages 1-4) should note that some pollutants are directly emitted and others are formed through chemical and physical transformation in the atmosphere.

The phrasing "short-term standard" (indicator E2) could be misinterpreted to imply that the standards apply for a short time period. Consider alternate wording, such as "short-term exposure standard."

The introduction text focuses heavily on anthropogenic sources, which is appropriate; however, it neglects the contribution of natural sources. This is particularly striking for the discussion of ground-level ozone, for which biogenic sources are major contributors. Biogenic sources are mentioned in general terms in the description of particulate matter (page 2). The concept of natural air pollution may be counter-intuitive to some readers, so it would be helpful to provide a few specific examples.

The statement that "EPA distinguishes between two categories of particles based on differences in sources, properties, and atmospheric behavior" (page 2) is misleading. The distinction is purely size (PM_{10} versus $PM_{2.5}$), which has some overall, but not distinct, trends in sources, behavior, etc.

Explicitly note that $PM_{2.5}$ is a subset of PM_{10}.

The language "Since 1999, 1-5% of children have lived in counties that exceeded the current three-month standard for lead" is a bit misleading as it implies data on multiple residences of children over multiple years. Please fix with new wording of this type of text on page 9 (last 2 bullet points).

The limitations text on the AQI (E3) indicator (page 12) is helpful.

The text "This percentage includes days for which no AQI was reported in counties where the AQI is sometimes reported . . ." is unclear, so please revise (pages 14-15). In general, it is not clear how indicator E3 was calculated.

Reviewer 2:

Overall the section is clearly written brief summary of the criteria air pollutants and their health effects. Below are a few specific suggestions regarding evidence of the more recent chronic disease implications of criteria air pollutants as well as consideration of avoidance of jargon that may not be accessible to audiences with less technical background such as concerned parents.

Regarding language that may not be accessible to lay audiences. "Anthropogenic" line 24 page 2, consider change to manmade or human activity related. "Thoracic region" page 2, line 32 consider change to "into the lungs".

The emerging and important evidence base linking criteria air pollutant exposures, particularly those linked to traffic sources, to key chronic conditions in children – asthma and allergic rhinitis, is not represented. These links are mentioned in the ACE 3 respiratory disease chapter and should be consistent in related sections here.

Page 2, line 19. Please add something to reflect evidence regarding role of ozone in development of asthma, such as "There are also suggestive data linking chronic ozone exposure to development of asthma in children." (see ACE 3 respiratory disease chapter Ref 11. McConnell, R., K. Berhane, F. Gilliland, S.J. London, T. Islam, W.J. Gauderman, E. Avol, H.G. Margolis, and J.M. Peters. 2002. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 359 (9304):386-91)

Page 3, line 7-9 sentence regarding suggestive evidence, add "and development of asthma. "

Related references:
Ref 32 in ACE3-Respiratory Disease. Clark, N.A., P.A. Demers, C.J. Karr, M. Koehoorn, C. Lencar, L. Tamburic, and M. Brauer. 2010. Effect of early life exposure to air pollution on development of childhood asthma. Environmental Health Perspectives 118 (2):284-90.

Ref 20 in ACE3-Respiratory Disease. Gehring, U., A.H. Wijga, M. Brauer, P. Fischer, J.C. de Jongste, M. Kerkhof, M. Oldenwening, H.A. Smit, and B. Brunekreef. 2010. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *American Journal of Respiratory and Critical Care Medicine* 181 (6):596-603.

Ref 13 in ACE2-Respiratory Disease. Kajekar, R. 2007. Environmental factors and developmental outcomes in the lung. *Pharmacology & Therapeutics* 114 (2):129-45.

Page 3, line 37 consider adding something such as, "There is some suggestive evidence for associations between prenatal exposure to carbon monoxide and risk of birth defects, specifically certain cardiac defects."

Beate Ritz, Fei Yu, Scott Fruin, Guadalupe Chapa, Gary M. Shaw, and John A. Harris Ambient Air Pollution and Risk of Birth Defects in Southern California. Am. J. Epidemiol. (2002) 155(1): 17-25.

Gilboa SM, Mendola P, Olshan AF, Langlois PH, Savitz DA, Loomis D, Herring AH, Fixler DE Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000.Am J Epidemiol. 2005 Aug 1;162(3):238-52. Epub 2005 Jun 29.

Reviewer 3:

Does the topic text appropriately and clearly describe the topic and its importance for children's environmental health?

In general, the topic text does appropriately and clearly describe the topic and its importance for children's environmental health. However, there are a surprising number of factual misstatements that should be corrected and/or clarifications that should be made. These are:

Page 2, line 19: insert "daily" before "mortality".

Page 2, line 31: insert "into" after "penetrate".

Page 2, line 33: insert "maximum" before "diameter".

Page 2, line 34: change "produced" to "formed".

Page 2, line 35: change " chiefly by combustion processes (including" to "chiefly of combustion products from".

Page 2, line 37: change "PM_{10}" to "Thoracic coarse particles". (Note: PM_{10} includes both coarse and fine particles)

Page 2, line 40: insert "excess" before "mortality".

Page 3, line 13: change the 2nd "in" to "by".

Page 3, line 27: change "sulfur dioxide" to "sulfate particles".

Page 3, line 39: change "Nitrogen dioxide" to "Nitric oxide (NO) and nitrogen dioxide (NO_2) are".

Page 3, line 40: after "equipment" insert ", and NO is oxidized to NO_2 in the atmosphere".

Are there additional aspects of the topic's importance for children's environmental health that should be included?

Yes. The text does not clearly differentiate the health effects of criteria pollutants on children from those that primarily are associated with those occurring in adults. For example, the NAAQS for CO was most strongly influenced by the onset of angina in elderly cardiac patients, while the NAAQS for Pb was most strongly influenced by the neurobehavioral effects in children. The NAAQS for SO_2, NO_2, O_3, and PM were all influenced by concerns about pulmonary function effects, and especially among asthmatic children. There should be a discussion of which health effects that are associated with criteria pollutants are of most concern for children when each pollutant's concentration approaches or exceeds its NAAQS.

Is the relevant literature appropriately summarized? Are there other important references that should be added?

No. While the draft did provide a list of the references cited, it only cited a limited number of the references that should have been cited.

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Yes. In addition to providing a more complete listing of the literature supporting the statements being made, a bibliography should be provided to EPA and other documents that provide further background and support for the brief descriptions in the Overview statements.

Question 2 – Indicator Text

Reviewer 1:

The text on statistical testing (page 7, page 12) is vague. Change over time of what? Of the percentage of children in areas not meeting the NAAQS? Of the air pollutant levels themselves? This section mentions annual values, which are not previously discussed. In general, this section is poorly written and should be revisited. Similar issues arise when the text states "the decline [in the percentage of children living in counties exceeding any standard?] over the years 1999-2009 was statistically significant." (page 8). Do not use language such as "the trends for sulfur dioxide and nitrogen dioxide" (page 9), but rather specify what trends. Given the nature of this document and the intended audience, I don't find the results for statistical significance to be particularly helpful. I would cut this text entirely. To the general public it may be intimidating and confusing, but to a biostatistician it is not very sophisticated. I think reporting the general trends (e.g., decreased over time) is sufficient.

The calculation of indicators E1 and E2 is unclear. Is this the denominator (total number of children) those in the entire United States or those in counties with air quality monitors. As written, it appears as if the total U.S. was used, which assumes that 100% of counties without monitors have exposure levels below the NAAQS (e.g., see top of page 7, page 30), which is a very problematic assumption and will generate an underestimated estimate of the number of children at risk.

It's not clear why ozone and $PM_{2.5}$ have special indicators for "short-term" air quality standards for 2009 and the other pollutants do not, or why only the year 2009 is used for this indicator (E2). E1 contains both long-term and short-term exposure standards (see $PM_{2.5}$ on Figure page 8). However, other pollutants also have both short-term and long-term exposure standards (e.g., NO2, SO2). What is the standard used in indicator E1? The figure on page 8 has two standards for $PM_{2.5}$ but is missing multiple standards for other pollutants. I'm not sure what is going on here. Please revisit this indicator and the explanation.

Reviewer 2:

The indicator text is very well written and clearly understandable for broad audiences.

Reviewer 3:

Do the indicator texts provide sufficient information about the data set and the indicator calculation to enable an understanding of the indicators?

For reasons that are not explicitly described, the presentation is divided into three specific indicators, i.e.:

E1 - % of children ages 0 to 17 years living in counties in which NAAQS were exceeded, 1999-2009;

E2 - % of children ages 0 to 17 years living in counties with exceedances of short-term NAAQS for O_3 or $PM_{2.5}$, 2009;

E3 - % of days with good, moderate, or unhealthy air quality for children ages 0 to 17 years, 1999-2009.

The three specific indicators that were chosen for data tabulation and selected illustration within the indicator texts are, at best, marginally useful for guidance to parents and public health professionals on precautions that can be taken to avoid harmful exposures of children to ambient air pollutants of outdoor origin. First and foremost, the indicators are not uniformly useful for understanding the health risks of such pollutants to children because:

the NAAQS are only partially relevant to children's' risks, with some driven more by risks to adults;

the stringency of the NAAQS varies greatly from pollutant-to-pollutant for historical reasons, and for the great variation in the size and quality available data on exposure and exposure-response relationships;

the concentration limits have changed over time as NAAQS revisions have been promulgated;

they do not reflect risk factors other than central monitoring site concentrations that will affect a child's exposure, such as:

Age;

Pre-existing disease, such as asthma;

Extent of physical activity, which affects breathing rates and volumes;

Proximity to local pollution sources, such as traffic and other combustion sources.

The text does not adequately explain why E2 is limited to O_3 and $PM_{2.5}$, while E1 and E3 are reflective of all six criteria pollutants. It could, and should, explain that O_3 and $PM_{2.5}$ have; 1) much more robust literature bases than the other criteria pollutants; 2) NAAQS that have little, if any margin of safety, compared to the NAAQS of the other four; and 3) that, as shown in the Figure on page 8, O_3 and $PM_{2.5}$ have far more exceedances than the other four.

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Yes. Provide text guidance for the known effects of each criteria pollutant on children, and how they can be protected against excessive exposure on days when a specific pollutant approaches or exceeds its NAAQS. For example, for O_3, keep children indoors, or restrict their outdoor activities to the morning hours before the concentration rises toward peak levels.

Question 3 – Indicator Presentation

Reviewer 1:

The figure on page 10 is going to be difficult to interpret for a non-scientific audience. A better option might be a single bar going from 0 to 100%, with different sections color-coded to reflect the categories (no monitoring data, no exceedances, etc.).

I think the use of showing exceedances of each individual pollutant's standard, as well as exceedances of any pollutant's standards (e.g., Table E1) is very useful.

Table E1a needs more description. For example, are 40.9% of White non-Hispanic children living in areas exceeding the 8-hour ozone standard? Why is this table just for 2009, especially as the note for this table refers to "all years shown"? The same applies to later tables (E1b).

Why does Table E2 group years 1999-2005, and then 2006-2009?

The issue of counties missing monitors is very important. Although mentioned (pages 6-7), the text should demonstrate this in some way, such as a map of counties with and without monitors, or some other mechanisms.

As indicator E3 is based on the percentage of days with various air pollutant levels, it does not relate directly to children as opposed to the general population, or to a particular age group. The labeling of these results with "children ages 0 to 17) is confusing (see figure on page 14, title text on page 11). How are these "children's days" (page 14)?

Reviewer 2:

Graphics and points made are appropriate, clear and understandable. A few minor suggestions:

For table E1b and E3b add a definition to clearly explain what is meant by < Poverty Level and ≥ Poverty Level in the comments provided under the table since these will be unfamiliar demographic variables to non technical audiences.

In the final draft avoid page breaks in the middle of tables such as for table E2 in this draft version. Such breaks make reading/interpreting the data in the tables awkward.

Reviewer 3:

Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data?

Yes.

Are there ways in which the presentation and description of the indicator values could be improved?

No.

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Yes. Provide more background on: 1) why compliance for short-term limits is judged on limiting the number of days that the numerical concentration limit is exceeded, rather than by a single exceedance; 2) that fact that compliance with a NAAQS is intended to provide protection for sensitive subgroups (such as asthmatic children) and is therefore conservative for others; and 3)

while restricting childrens' outdoor activities can reduce the effects of pollution, it can also limit the health benefits of such activities.

Please comment on the appropriateness of the comparisons made in the indicator(s) and whether other comparison populations and/or benchmarks may be informative to the public.

Provide a cautionary note that the comparisons are based on the inappropriate assumptions that: 1) each NAAQS exceedance has adverse effects on children; and 2) that any cumulative effects are based on the number or frequency of exceedances. In that respect, it should be noted that in terms of chronic health effects, such as reduced lung growth during childhood is much more closely related to annual average $PM_{2.5}$ concentration than with the number of short-term (daily) exceedances of the $PM_{2.5}$ or O_3 NAAQS.

Question 4 – Context and Utility

Reviewer 1:

This indicator relies on threshold values (other than the AQI results), which is appropriate, but the text should highlight this limitation as the approach implies the same level of adverse health outcomes for any level above the threshold. Another limitation is that health effects have been observed for very low levels of criteria pollutants, and no "safe" level has been identified. This has been demonstrated for ozone and particulate matter in studies that estimate the exposure-response curve. This could be noted and referenced.

The current state of the science limits our ability to understand how the complex air pollution mixture affects human health and instead relies on single-pollutant science. The use of the single-pollutant science in this indicator approach is appropriate, but this limitation could be noted, along with text to highlight that this is a limitation of the current state of the science, not a choice by the authors.

For indicators dealing with the number of days on which a threshold was exceeded (figure on page 10, Table E2), what is the meaning of the number of exceedances. IS this per year (in 2009 as in the figure on page 10, over 1999-2009 as noted in Table E2)? If so, this is not appropriate as the number of days with measurements will vary widely by monitor and county. For example, an ozone monitor exceeding the standard 10 times in a year is not a meaningful number unless we know how many times the monitor measured throughout the year (10 vs. 300)? Similarly, the freque3ncy of measurement for ozone (typically daily for the warm season) differs dramatically from that of $PM_{2.5}$ (typically yearly but every 3 or 6 days), although the figure invites comparisons between the two pollutants. This entire indicator needs to be reconsidered.

Reviewer 2:

These indicators are concrete, quantifiable and relevant and context provided is appropriate. Limitations are described appropriately, particularly the issue with a large proportion of children living in counties with no data.

Reviewer 3:

For E1, the data summary presentation in the Figure on page 8 is informative, showing that: 1) decreasing percentages (over time) of children living in counties with NAAQS exceedanaces other than for lead (which, for today's children, have been and remain very low); 2) with the exceptions of O_3 and $PM_{2.5}$ (24- hr), the percentages in recent years have reached very low levels.

For E2, the data summary presentation in the Figure on page 10 is informative, showing that: 1) the short-term NAQQS for O_3 and $PM_{2.5}$ are exceeded many times each year in many US communities. This demonstrates that meeting the NAAQS for these two criteria pollutants will be unlikely in the near future even if the NAAQS are unchanged. (Note that reductions for both of these NAAQS are currently under consideration, but that even the lower levels being considered will not prevent future NAAQS exceedances in some parts of the U.S.).

For E3, the combination index of all six criteria pollutants is inherently meaningless insofar as it equates the likelihood of meaningful effects of an exceedance of the NAAQS for O_3 and $PM_{2.5}$ with those that have been associated with an exceedance of the NAAQS for those of CO, SO_2, NO_2, and Pb. On the other hand, the actual numbers of days with exceedances is, in fact, driven by the numbers of days with exceedances of the O_3 and $PM_{2.5}$ NAAQS. Thus, the Figure on page 14 ends up being another "feel-good" plot. However, it would be best to simply drop the E3 index and the associated text and plot.

Question 5 – Documentation

Reviewer 1:

Note that the number of monitors varies by time period, or otherwise indicate that not each county and year will have the same number of monitors or frequency of measurement. This could be mentioned in the introductory text and also the metadata table (page 22). The meta-data table should note that not all data are available for all years, not "1980-present." (page 23).

All of the indicators that are not based on the whole U.S. need to state the number of counties included.

The sentence "Because not all counties have air quality monitoring stations, children living in counties with no monitoring data are also tracked in Indicator E3" is confusing. Is this a typo? The exposure of children in counties without monitors cannot be assessed, so they cannot be tracked in this AQI-related indicator.

How was poor data quality addressed for the air pollutant measurements (e.g., measurement flagged with lab issues by EPA, etc.)?

Reviewer 2:

The documentation is complete and transparent. See small comment under 3 above.

Reviewer 3:

Yes.

2.4 Drinking Water Contaminants

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Susan Jobling
- Kathleen McCarty
- Kellogg Schwab

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

The text clearly describes the topic and its importance for childhood health. The introduction gives an overview of the types of drinking water contaminants that are of concern for children's health and the sorts of health problems that have been linked to these types of contaminants.

A selection of appropriate references are present (it would be impossible to include all).

Additional aspects: Arsenic should be included and so should mercury. Growing evidence suggests that excess manganese (Mn) in children is associated with neuro-behavioral impairments. Exposure to these elements in groundwater is commonplace yet, little research has examined the impact of many commonly occurring environmental exposures on mental abilities either during the aging process or during early neurodevelopment in children. Inorganic arsenic is a known neurotoxin that has both neurodevelopmental and neurocognitive consequences. Long-term low-level exposure to arsenic is significantly correlated to poorer scores in global cognition, processing speed and immediate memory. Additional work is warranted given the population health implications associated with long-term low-level arsenic exposure.

Recent studies have examined the associations between perfluorooctanoic acid (PFOA) levels in cord blood and maternal plasma with lowered birth weight and gestational age in humans. These are not mentioned.

The sampling method used to measure lead for example may vary and that variation will affect the concentration measured and whether or not it reflects that at the consumers' taps. In consequence, non-compliance with standards can be under- or over-estimated. These issues are relevant to the implementation of any policy on Water and Health and to drinking water safety planning and should be discussed

Reviewer 2:

General Response to Questions:
The review covered the appropriate range of contaminants (microorganisms, inorganic chemicals, organic chemicals and disinfection byproducts). However, as written the report may mislead health professionals, government officials and concerned parents and educators. Consistently throughout the document there are no exposure levels (ranges of exposure) provided for any of the studies. Many of the studies are from very high exposures (for example the inorganic arsenic studies) and there is no mention at all of the exposure context for the health outcomes that are observed and how this compares to observed levels in the United States from public drinking water systems, or private wells. For lead the issue of nutritional status of the child should be discussed (lead exposure is a great concern for children who are deficient in calcium and iron- again defining what is meant by deficient). These children are extremely susceptible to lead exposure and often this is tied to SES issues. It is crucial to give the lay reader an exposure context to compare the results of the studies. If I read this report without being familiar with some of these studies, or access to full text articles in pub med and an understanding of environmental health I would think that tap water was dangerous. There are contaminants that need better regulation, or are in the process of improved regulation and this is important, but keeping the other exposures in context actually highlight the need to reduce exposures where actually necessary.

Additionally the document cites animal studies, but provides no discussion about the assumptions, limitations and difficulties in trying to extrapolate animal data to humans. If this document is meant for government officials, medical doctors and nurses and concerned parents and educators this is extremely important to make this difference clear so that results can be understood for their importance but interpreted cautiously.

The report does a good job of covering all of the exposures, however it needs to be improved by including data on exposure levels and putting some of those health findings in meaningful context compared with the MCLs and if possible with a range of the actual exposure levels observed in the violations (if that data is available).

Page by page suggestions:

Page 1 line one “drinking water sources may contain a variety of contamination that **at elevated levels** are associated with….” The biggest issue here is that exposure and dose is not even covered- it is not any exposure that results in these health outcomes but exposures at a certain level, for a certain duration of time, given individual susceptibility factors.

Page 1, line six : should say “dose” rather than “exposure”

Page 1 line 24, Include a statement that drinking water municipalities are supposed to reduce lead exposure in drinking water taking into account the probability of lead in pipes and lead solder. It is their responsibility to regulate water quality out of the tap- not out of the water treatment plant. This needs to be clarified so that individuals aren’t now worried about their town pipes (which is

fine if they have violations but all communities are not equally impacted and this needs to be clear). Most municipalities are meeting EPA standards and when they are not it is important for communities to know this.

Page 1, line 28-30 Please provide the exposure levels and duration(if given in the papers) for the observed health effects. It is true there are associations, but please make it clear at what dose these are observed. Also how these levels differ from the MCL or violation data (mean and SD?)

Page 1, line 38 Please provide the exposure levels and duration(if given in the papers) for the observed health effects. It is true there are associations, but please make it clear at what dose these are observed. Personally I have done research in Bangladesh and the levels are up to 120-150 times the current standard for arsenic in the US, and Bangladeshis drink on average from 6-8L of water per day- as opposed to the assumed 2L a day for a standard US male of "average weight".

Page 2, line 78- it is mentioned that most of this inorganic arsenic exposure is "generally higher than in the US" and while it is true that there are low exposure regions/wells with less than 10 ug/l of inorganic arsenic these aren't the individuals with those health effects. I will include a paper suggestion for reduced immune function from a doctoral students work on mice and inorganic arsenic exposure at low levels- this should be included in this paragraph- however with a statement about the difficulties of going from animal to human studies. Also please provide the current standard for the US so the reader can put the exposure levels in context.
Suggested paper:
Kozul CD, Ely KH, Enelow RI, Hamilton JW. Low-dose arsenic compromises the immune response to influenza A infection in vivo. Environ Health Perspect. 2009 Sep;117(9):1441-7. Epub 2009 May 20.

Page 2, line 19-25, please provide the exposure levels of disinfection byproducts associated with bladder cancer, reproductive effects, birth defects, neural tube defects, and oral clefts. If necessary make a table.

Page 3 line 11-60 please give levels of exposure associated with the health outcomes, also for the studies with no association. Again a table may make it easier for the reader.

Page 3, line 33 please give levels of exposure associated with the health outcomes, also for the studies with no association. Again a table may make it easier for the reader

Page 5 OVERVIEW paragraph- how often are the data compiled?

Page 6, line 43, 62% of health based violations were reported…is there any data on why the other violations were not reported? What is being done to improve reporting? How do we know 38% were not reported?

Page 7, line 5-6 – what does the indicator tell us if it doesn't take into account what percentage above the standard the violation was and how long it occurred? So the same weight is given to a violation 1ug/l above the standard as 200 ug/l above the standard? Is it possible to also create an indicator that takes into account these differences? Right now it looks like a violation equals any other violation.

Page 7, line33 It would be worth mentioning that FDA regulates bottled water so that the reader knows that bottled water is regulated as well.

The tables and figures on pages 9-12 are well done.

Additional references

Reviewer 3:

This section of ACE focused on drinking water contaminants and the effect of contaminants on children's health. Two indicators were proposed: Indicator E6: Percentage of children ages 0 to 17 years served by community water systems that did not meet all applicable health based drinking water standards, 1993–2009 and Indicator E7: Percentage of children ages 0 to 17 years served by community water systems with violations of drinking water monitoring and reporting requirements, 1993–2009. The topic text provided a general overview of water contaminants. There were a few missing contaminants and in general may of the references were older and from reports, not peer-reviewed literature. Additionally many of the references were from international data sets (refs 23 and 26 for example) and perhaps it would be good to use U.S. data where possible. Specific comments focusing on these issues are provided below.

Page (P) 1, line (l) 4 add "endocrine disruption" to developmental effects in addition to learning disorders. Pharmaceuticals and personal care products are of concern regarding endocrine disruption during childhood development

P1, l 11 what about both microbial and chemical emerging contaminants? These should be listed in the "Several types of drinking water contaminant examples."

P1, l 12 I would add a microorganisms from each class of microorganisms (e.g. bacteria, viruses and protozoa) thus the sentence would read "….include microorganisms (e.g., E. coli, norovirus and Giardia)"

P 1, l 18-21 The order of these two sentences should be switched

P1, l 22-24 This short introduction on lead should be expanded especially since the Washington DC lead issue received so much attention

P1, l 28 How is the disinfectant by products reference (#30) connected to nitrates?

P1, l 28-30 Thyroid hormone levels are affected by many substances not just nitrates. I would separate this section from a specific compound

P1, l 32 "Arsenic, which is odorless and tasteless"… many compounds are odorless and tasteless, it would be good to be consistent when describing the compounds

P1, l 35 With respect to referencing this and other sentences (e.g. ref 32 in this case) why not cite peer-reviewed literature?

P 2 l 5-8 So what does this mean for U.S. health? This should be explained

P2 l 9-25 This section on disinfection of drinking water needs to be reviewed by an EPA water treatment specialist such as Nick Ashbolt or Al Dufour. There are many data gaps and inconsistencies in this paragraph, a few of which are listed below

P2 l 11 replace "deactivated" with "inactivated"

P2 l 11 add "the volume of water to be treated" at the end of the sentence

P2 l 13-15 this sentence is inaccurate (filtration does not remove dissolved particles!); a rewording could be "Surface and groundwater systems use various treatment methods including coagulation, flocculation, sedimentation and filtration to physically remove particles (e.g. turbidity). Turbid and clear water con contain microorganism including parasites, viruses, and bacteria.

P2, l 15 add ozone and ultraviolet radiation to the list of disinfectants

P2 l 16 the statement "an unavoidable consequence" is not true. Much work has been done to reduce disinfectant by product precursors (e.g. using enhanced coagulation, alternative disinfectants besides chlorine etc).

P2 l 27-28 add " and enter groundwater through abandoned wells on farms." to the end of the sentence.

P3 l 17-25 This section on personal care products should be expanded

P3 l 18 add "and triclosan and triclocarban" after veterinary medications

P4 l 3 It might be good to add a paragraph on defining the indicators and how they are used for ACE. Currently the paragraph starts "The two indicators…" which is not informative

P4 l 6-12 This paragraph needs additional development

P4 l 10-12 The last sentence needs expanding. What are the percentages referring to?

Question 2 – Indicator Text

Reviewer 1:

The indicator text provides sufficient information about the data set to enable an understanding. This reader finds it difficult to put the data into context, however. Will this be done? So for example, if only 62% of violations of health based standards are reported, how can any parallels be drawn between epidemiological data in children and these violations. Do any trends in children's health trends (for example neural tube defects) follow the time trends in percentage of children served with water with violations of drinking water monitoring and reporting? Will this context be given for politicians and public?

The significance of the time related increase in violations for nitrate/nitrite, disinfectants, chemicals and radionuclides should be discussed.

Reviewer 2:

Response to Questions: I think the descriptions of the indicators are very clear. I wouldn't suggest any changes to those. The only minor change I would suggest is that the violation indicator doesn't take into account the % of the exposure level above the standard (the text indicates that duration is not taken into account). I would suggest another indicator that takes into account the amount that the violation exceeds the standard and the length of time it has occurred to truly have a better idea

of children's risk of exposure to these contaminants and whether appropriate actions should be taken.

Reviewer 3:

The E6 and E7 Indicator text was problematic. The Overview paragraph would benefit from a few sentences on why the change in the estimated percentage of children served under each indicator is important. It would be helpful to state what the take home messages regarding the strength and validity of using these two indicators are and why this is important.

Additional justification is needed to support using the two developed indicators if as quoted on page 7 "Indicators E6 and E7 are not intended as indicators of children's exposure to drinking water contaminants or of risk to children. Indicator E6 does not take into account the duration of a violation. A large water system with a single violation of short duration during the year may significantly affect the indicator value. Nor does the indicator reflect the extent to which a water system's distribution system may not have been affected by a violation." What is the value of generalized data if no actual contaminant levels are reported (as quoted on page 7 "The ability to examine children's potential exposure to contaminated drinking water is limited by the type of information collected and stored in the SDWIS/FED database? Public water systems are not required to report the actual contaminant levels measured to SDWIS/FED; instead, they report when standards are not met. As a result, SDWIS/FED data cannot be used to analyze national or local trends in contaminant concentrations.")?

Additionally why use these indicators at all if changes over time cannot be assessed (as quoted on page 7 "An analysis of the statistical significance of changes over time in indicators E6 and E7 has not been conducted because of these changes in regulatory standards between 1993 and 2009.")? The three quoted sections listed above need to be supported in the document by providing a justification for using indicators that are not specific or applicable to multiple regions.

Specific comments are:
P5 l 7 The Overview paragraph would benefit from a few sentences on why the change in the estimated percentage of children served under each indicator is important. It would be helpful to state what the take home messages regarding the strength and validity of using these two indicators are and why this is important.

P5 l 11 "These indicators.." this needs to be more specific. Define which indicators

P5 l 24-26 The complete definition for community water systems should be included

P6 l 29-35 How are these data temporally justified to predict children's health risks?

P 7 l 4-8 If the statements in this paragraph are correct, why use this indicator system at all?

P 7 l 10-16 What is the value of generalized data if the actual levels of contaminants are not reported? How will this correlate to children's health?

P7 l 24-26 Why use the indicators at all if changes over time cannot be assessed?

Question 3 – Indicator Presentation

Reviewer 1:

By enlarge, the graphs data tables and bullets provide an appropriate summary of the underlying data. Does the total percentage violation adequately describe the individual listed violations or are there other significant unmentioned violations. This should be adequately discussed and made clear for politicians.

Reviewer 2:

One way that could make these exposure levels more understandable to the general public is to make a chart comparing these exposures to risks that people understand (a cigarette smoke exposure, or something that they can relate to). An example of an older paper where this is done is: McCarty K, Swallow J, Vanderslice R, Combs WS Jr. Water systems to report drinking water quality to all customers: how can health professionals prepare for the questions that these reports will generate? Med Health R I. 2000 May;83(5):140-3.

Reviewer 3:

The Indicator presentation was also problematic. What is the relevance of providing percentages of children served by community water systems that did not meet all applicable health-based drinking water standards (E6) or with violations of drinking water monitoring and reporting requirements (E7) if these figures do not reflect actual data with respect to magnitude of contaminant exposure, length of time of exposure, or true percentages of children exposed, all of which was outlined in the supporting text?

Question 4 – Context and Utility

Reviewer 1:

Indicators E6 and E7 clearly present quantifiable indicators of key factors relevant to the environment and children in the USA concerning drinking water. As a basis for understanding time trends in children's health, however, they are of limited value unless the children's health trends are presented alongside these contaminant related trends.

Indicators E6 and E7 will be useful in informing discussions among policymakers and the public on how to improve federal data on children and the environment if combined with health trend data

E6 and E7 should be good indicators that could be used to track and understand the potential impacts of contaminants on children's health, however more detail is perhaps required in order for it to be useful from an epidemiological perspective. For example, separate chlorine, chloramines, chlorite , bromates etc.

The chemical and radionuclide category is far too broad and needs separating. Radionuclides must be presented separate from the chemicals and each type of chemical from each other type. The biological effects of different types of chemicals are usually very different and so for the data

collected to be useful, chemicals must be presented individually as well as collectively .

Reviewer 2:

Indicator E6

A) Indicator 6 provides the percentage of children ages 0-17 yrs served by community water systems that did not meet all applicable health-based drinking water standards, 1993-2009. It does provide a concrete indicator of key factors that provide some understanding of time trends in violations in classes of exposures over the 16-year period. The indicator does not give any information on the severity of violations (no information on exposure violation levels compared to standards, nor duration of violations in that time period). So the indicator tells us the number of violations in those years but doesn't really provide information as to extent of the violations. For example are these violation barely over the standards and does that matter to human health in terms of risk assessment? Or are these violations severely over the standards and do they repeat over time?

B) As they are the indicators give policymakers information on compliance in communities and how the trend varies over time, but there is no real concrete exposure data that gives policy makers the information they may need to perform calculations to protect vulnerable subpopulations.

C) This indicator cannot really be used to track impact on children's health because there is no quantitative data. You need exposure levels, dose and time of exposure to study impacts on children's health with any degree of certainty- otherwise you are just correlating incidence of health outcome with number of violations of a certain exposure-, which doesn't prove causation. If we are certain the standard protects children's health for a certain exposure the indicator is adequate- the problem is we often discover new health outcomes associated with exposure (often at a lower level) and we cannot use this indicator to assess new health outcomes (for example arsenic being associated with cognitive developmental changes in children in Bangladesh, or current research looking at hypertension and low level exposure in Romania (not published). Without quantitative data, these indicators cannot be used in the future as optimally as they could be if quantitative data was used.

Indicator E7

A) Indicator E7 provides the percentage of children ages 0-17 years served by community water systems with violations of drinking water monitoring and reporting requirements 1993-2009. This indicator does provide some information in terms of time trends in violations.

B) As they are the indicators give policymakers information on compliance in communities and how the trend varies over time, but there is no real concrete exposure data that gives policy makers the information they may need to perform calculations to protect vulnerable subpopulations

C) This indicator cannot really be used to track impact on children's health because there is no quantitative data. You need exposure levels, dose and time of exposure to study impacts on children's health with any degree of certainty- otherwise you are just correlating incidence of health outcome with number of violations of a certain exposure-, which doesn't prove causation. If we are certain the standard protects children's health for a certain exposure the indicator is adequate- the problem is we often discover new health outcomes associated with exposure (often at a lower level) and we cannot use this indicator to assess new health outcomes (for example

arsenic being associated with cognitive developmental changes in children in Bangladesh, or current research looking at hypertension and low level exposure in Romania (not published). Without quantitative data, these indicators cannot be used in the future as optimally as they could be if quantitative data was used.

Reviewer 3:

With respect to context and utility it is unclear how Indicator E6 and Indicator E7 present concrete, quantifiable indicators of key factors relevant to the environment and children in the United States for the reasons outlined above.

Question 5 – Documentation

Reviewer 1:

As indicated above, the documentation is incomplete without separation of different environmental contaminants for use in risk assessment

Reviewer 2:

He document is transparent in that it is well referenced and balanced. It does need to put some exposure context around the statements so that this can be interpreted and used by non-environmental health professionals. I can suggest additional papers to help support the statements.

Some additional papers:

Luben TJ, Olshan AF, Herring AH, Jeffay S, Strader L, Buus RM, Chan RL, Savitz DA, Singer PC, Weinberg HS, Perreault SD. The healthy men study: an evaluation of exposure to disinfection by-products in tap water and sperm quality. Environ Health Perspect. 2007 Aug;115(8):1169-76.

Luben TJ, Nuckols JR, Mosley BS, Hobbs C, Reif JS. Maternal exposure to water disinfection by-products during gestation and risk of hypospadias. Occup Environ Med. 2008 Jun;65(6):420-9. Epub 2007 Nov 21.

Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, Kline J, van Geen A, Slavkovich V, Loiacono NJ, Levy D, Cheng Z, Graziano JH. Water arsenic exposure and intellectual function in 6-year-old children in Araihazar, Bangladesh. Environ Health Perspect. 2007 Feb;115(2):285-9. Epub 2006 Oct 18.

Reviewer 3:

The Metadata also is challenging to asses due to limitations in the data set. For example: -Metadata for- “Are raw data (individual measurements or survey responses) available?” the SDWIS/FED response states “Separate reports for each violation of drinking water standards or monitoring and reporting requirements for individual public water systems are available; measured contaminant

levels are not available in SDWIS/FED." How can these raw data then be used if measured contaminant levels are not available?

Additionally, the -Metadata for- "Are the data comparable across time and space?" the SDWIS/FED response is "Violations across time are often not comparable because of changes in regulations and changes in drinking water standards (maximum contaminant levels), and variability over time in monitoring and reporting violations. Data may not be geographically comparable due to variations in state enforcement and database quality." These types of statements in the Metadata table suggest that results in the Figures would be challenging to extrapolate for determining children's environmental health.

2.5 Food Contaminants

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Lucio Costa
- Alex Lu
- John Meeker

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

This section presents a brief overview of a number of food contaminants. Those chosen are no doubt relevant, as they include methylmercury, PCBs, PBDEs, bisphenol A, phtalates, PCFs, perchlorate, and organophosphates. However, it should be explained why many other food contaminants are not discussed or mentioned. For example, there is little emphasis on other halogenated compounds (e.g. dioxins or older orgnaochlorine insecticides, or other brominated compounds) that are often found as contaminants.

There is no mention of compounds such as acrylamide or furans, which, though not contaminants, as they are formed from endogenous substrates in certain foods upon cooking, are present in foods, particularly in some eaten by children.

Additional details on the specific foods containing the contaminants would be useful. For the polybrominated diphenyl ethers, there is no mention of breast milk which is a major route of exposure for infants. The fact that PBDEs may also be endocrine disruptors, by interfering with thyroid functions, may be mentioned (a general reference for the last two issues could be the review by Costa LG, Giordano G. Developmental neurotoxicity of polybrominated diphenyl ethers. Neurotoxicology 28: 1047-1067, 2007, or specific references therein).

Organophosphates may be better indicated as insecticides rather than pesticides. It is unclear why only organophosphates are mentioned, and not several other important classes of pesticides (e.g. fungicides, present as residues in strawberries).

Reviewer 2:

The topic text for food contaminants describes the topic and its importance to children's health clearly and appropriately. The literature included in this document is very thorough and reflects the current publications for each individual contaminant. However, the list of food contaminants should also include pesticides, such as pyrethroids, neonicotinoids, and common herbicides.

Reviewer 3:

Overall the topic text seems appropriate and clear for its intended use. The text gives a nice overview of a number of environmental chemicals found in food, though indicator data was only presented for organophosphate pesticides. The relevant literature was summarized in a manner that seemed thorough yet concise.

Were any other chemicals considered for inclusion in the topic text, or was it simply limited to the chemicals included as biomarker indicators?

Also, wondering if it would be of interest to discern between organophosphate "pesticides" or "insecticides"?

Question 2 – Indicator Text

Reviewer 1:

This section should better justify the choice of these four food items. Are really carrots and tomatoes main staples of a child's diet? Some comments on the results should be added (e.g. there appears to be a decrease from the late 1990s). As data are not complete (several years are missing) even for these four food items, it would be interesting to add information on other fruits and/or vegetables, if available.

Reviewer 2:

The choosing of the 4 most common consumed food items needs to be further explained. It seems to the reviewer that peach/nectarine should be more frequently consumed than grapes. Regardless, the source of "frequent components of children's diets" needs to be cited, since the frequency of consumption is an important criterion, much more important than the frequency of OP residue detection.

Also, the justification of selecting two fruits and two vegetables should be explained and justification. What if the consumption of and the OP residues in carrots are less than the 3rd fruit item on the list? For the risk perspective, such reporting does not address the issue.

Reviewer 3:

Indicator text was clearly written. I thought perhaps the list of the 46 OP pesticides included should have been placed in a more prominent position, but perhaps that's not important for most of the target audiences. Some place in the indicator text it may be important to note that, even though the detection rates for OP pesticides in these foods may appear to be going down (which makes sense since several of them have been restricted from certain uses such as these), the 46 OP pesticides included here may be getting replaced by other types of OP pesticides not on the list of 46, or by other classes of pesticides such as carbamates and pyrethroids. Basically want to avoid the potential for a false sense of security that residue detection rates are going down when this only represents a fraction of what may be in these foods.

I am also curious if the authors considered also using other pesticide databases, such as the FDA Pesticide Program Residue Monitoring Reports, or the FDA Total Diet Study?

Question 3 – Indicator Presentation

Reviewer 1:

The presentation of the indicator, as a graph and a Table, is satisfactory. The bullet-points summarize the main information of each graph. As said earlier, additional comments would be useful.

Reviewer 2:

It should be noted the reasons of missing data in various years for those food items. Readers could easily think those "missing" data are non-detectable, or 0% detection, which is not true.

Reviewer 3:

I think the graph, bullet points, and data tables were well-organized, and no statistical comparisons were made. Was the inclusion of sample size for each produce item in each year in the main figures considered?

Also, in the text it states that the gaps in the figure represent years where it was not measured, not 100% non-detect; I think this fact needs to appear somewhere on the figure or in a footnote.

Question 4 – Context and Utility

Reviewer 1:

One may argue that the selection of organophosphate insecticide residues in four food items may not be the best indicator of potential problems arising from food contaminants. The data shown are % of foods with "detectable levels" of organophopshates. As tolerances are set by the EPA, the presence of residues in food items does not represent per se an alarm. Would it have been better to indicate the % of food items that exceeded the tolerance levels?

Also, other food contaminants may have been reported with perhaps more relevance to potential adverse health effects in children.

Reviewer 2:

The reviewer believes that the indicator text and the presentation would mislead the policymakers and the publics on the aspect of pesticide residues in foods. According to the graphs presented, it is intuitive for the publics and the policymakers to come to the conclusion that OP residues in foods are decreasing over years. Whether or not this is true, the indicator text should EMPHASIZE that EPA only look at OP, NOT THE OVERALL PESTICIDE RESIDUES IN FOODS, in this indicator document/text/presentation, and maybe should explain, or at least attempt to explain the decreasing trend of detection of OPs in those 4 food commodities.

Reviewer 3:

The text appropriately and objectively reflects the strengths and limitations in our current knowledge of this indicator. I think this report represents a very important consolidation of national data for a wide range of audiences. These indicators should be highly referenced by researchers and policymakers alike, and should serve as a useful resource for medical professionals, other various groups, and citizens. It may also lead to additional food monitoring programs to enhance the data.

Question 5 – Documentation

Reviewer 1:

This appears to be adequate and is presented transparently.

Reviewer 2:

Except for the comments made for Question 4, this document is complete and transparent.

Reviewer 3:

The one point of confusion I had was whether all 4 of the foods were tested for all 43 of the pesticides at each time point. At one point in the document it seems to indicate that they may have attempted to measure a much smaller subset of the 43 pesticides on any given food/year combination for those with data presented. I think this needs to be made more clear, since if, for example, grapes in a certain year were only analyzed for a list of 5 of the 43 OP pesticides, and those 5 also happen to less commonly used or more rarely detected on this or other types of foods, the percentage may seem lower than it may have actually been had they attempted to measure all 43 of the pesticides. I'm not sure the best way to convey this, but seems like it may be an important point.

2.6 Hazardous Air Pollutants

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Michelle Bell
- Timothy Church
- Gregory Pratt

General Comments (If Any)

Reviewer 1:

General comment: The reviewer questions seem to be asking more for feedback on how well the document describes the indicator rather than about the appropriateness of the indicator itself or how that indicator might be improved. I have taken the liberty of addressing these latter questions in some of my responses. In general from my perspective the text is quite readable and the technical level is appropriate for the intended audiences. However, there are some gaps in the description, some concepts that are omitted, and some ways in which the indicator itself could be improved. The description of this indicator is a mere few pages in length. It might need to be longer to give due diligence to some of the issues that arise from trying to develop an indicator of potential effects on children's health due to exposure to hazardous air pollutants.

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

Overall, the text clearly describes the topic and its importance for children's environmental health. In general, I think the description of the HAPS indicator strikes a good balance between being understandable to a general audience, but including enough detail for expert readers to understand the methods. Below are some specific suggestions to improve communication of the methods and results. The most difficult part of this indicator to interpret is the non-cancer effects as this could range from a mild health response to a non-cancer related mortality.

Reviewer 2:

The topic text is well written and instructive.

The text does not adequately discuss indoor air vs. outdoor air or address domestic use of toxics and the uncertainties surrounding children's exposures via this source. The rationale for separating out indoor air quality in a separate section is not adequately described. A sentence or two about these issues might remedy this.

Byun, H., et al., Socioeconomic and personal behavioral factors affecting children's exposure to VOCs in urban areas in Korea. Journal of Environmental Monitoring, 2010. 12(2): p. 524-35.

Johnson, L., et al., Low-cost interventions improve indoor air quality and children's health. Allergy & Asthma Proceedings, 2009. 30(4): p. 377-85.

Reviewer 3:

The text provides only a rudimentary justification for using the percentage of children living in counties with estimated HAPs concentrations above benchmarks as an indicator of children's health. I think the description of the indicator could be more complete and could provide a better justification for why this indicator is appropriate.

Many of the citations are to studies of adult and worker exposures and impacts. Some of these studies are important and have been used to establish toxicity benchmark values, but they do not specifically address children's exposures and potential health impacts. There is a growing body of published research about children's HAP exposure in homes and schools. In addition there are several studies showing associations between HAP exposures (often related to proximity to traffic) and several adverse health outcomes in children. This body of work has not been mentioned in the text or cited and it should be.

In general the level of technical detail seems fine to me. Many of the relevant caveats are mentioned (inadequacy of monitoring data, limitations of modeling, difficulties in comparisons over time, the fact that exposure is not equal to ambient concentration, etc.). A few important caveats are not mentioned, however. First, there is a range of health effects that can be caused by HAPs ranging from irritation to life threatening outcomes to cancers to adverse effects on development. This range of outcomes is lumped into three metrics. It would be good to try to convey some of the nuance regarding the health effects of HAPs, though I know this is difficult.

Secondly, the NATA modeling results do not capture the spatial complexity and heterogeneity in HAP concentrations. For example, we expect high concentrations of many HAPs near busy roadways, but the 2002 NATA air dispersion modeling produces only a single concentration for a census tract. Many published studies show that there are significant changes in air concentrations within a few hundred meters downwind of high traffic corridors, and thus concentrations may be quite different within a given tract. This is a limitation in using the NATA data and introduces uncertainty in the use of the indicator. This uncertainty should be recognized, and to the extent possible, quantified in the description of the indicator.

Thirdly, the toxicity benchmarks used in this indicator are appropriate for adults, but they do not reflect the higher respiratory rates among children, and the increased sensitivity of developing children. This fact is mentioned, but is not flushed out, nor is there any indication given about the magnitudes of the errors that might be introduced by this limitation.

The prioritization of the heath benchmarks used for this indicator should be explicitly stated (p. 2, lines 26-28). In addition, the question of how changes in benchmarks will be updated should be addressed.

Question 2 – Indicator Text

Reviewer 1:

The methods are a bit unclear in places. In some cases, the approach used is well described but the rationale for that approach is not. See specific comments below.

Page 14: ACCESS files with ASPEN estimated concentrations were obtained for 175 HAPS, not the full 183?

Page 2: Note the total number of official HAPS, which are more than the 183 used in this analysis. If possible, note why the remaining 6 were not included.

Page 3: The "adverse health effects other than cancer, such as respiratory or neurological effects" and "other health effects" is too vague to be meaningful. Does this include non-cancer mortality, or just morbidity? Please provide some additional examples and give indication of the severity of symptoms. Currently this benchmark is difficult to interpret as it could mean anything from coughing to death.

Currently HAPS that are known carcinogens and suspected carcinogens are grouped. This is alluded to on page 5, but should be mentioned in the earlier text. It would be useful to include all the potential levels ("known human carcinogens", "probably human carcinogens", etc.) and to note which levels of HAPS were included in the cancer benchmarks. How does this relate to the language such as "each carcinogenic HAP" (page 15)?

The two cancer benchmarks are based on different levels of risk. Another option is to use different levels of certainty on whether the HAP is a causal agent of cancer (see note above).

The use of counties for the main analysis, but census tracts for the schools is very confusing. If exposure data are available at the census tract level, why use county levels? The earlier text implies that the modeled exposure estimates are at the county level, but the metadata table notes that both county and census tract exposures are available. Is the issue that EPA calculated health risks at the county level but not the census tract level? If that is the case, and county-level estimates are appropriate, using the county for school locations would avoid this confusion.

Chromium's valence states affect its toxicity, so the combination of all chromium compounds to Chromium VI compounds (page 14) is an odd choice.

Does the Private University School Survey contain information for all private schools in the U.S.?

For the analysis based on schools, specify the denominator used (total population) as this should be the total for school children, not children including those who are home schooled.

Page 14: The sentence " . . . we used the file directly supplied by EPA OAQPS instead of the file on the website" is confusing and calls into question the quality of EPA's data. Is it possible to give more detail and to note which group with OAQPS? Can EPA provide a reason as to why these files are

slightly different? I recommend re-doing the analysis using the website's file and seeing whether this alters the results. If not, then the document could note that other versions of this file gave identical (or similar) results for the indicator.

Reviewer 2:

Generally the text is clear and sufficient. A few specific issues are given below.

(Line 5, page 2) The heading (and all other text) denotes Indicator E4, while the blockquote denotes E5. I assume the blockquote is from a previous version, but this is not immediately obvious to the reader.

(Lines 19-22, page 2) Are any modeled values statistically significantly lower than measured values?

(Lines 4-7, page 3) This sentence is confusing. Is the third benchmark for minimal risk or for risk for other health effects?

(Lines 13-14, page 3) As I read the previous sentences, only 50 had both cancer and non-cancer risks estimated. Perhaps line 13 should read "…cancer **or** non-cancer risks…"

Text is understandable to an educated person.

Might consider some additional explanation of why adult benchmarks are used (e.g., because childhood benchmarks are not available?) in lines 15-19 on page 3.

Reviewer 3:

The technical level of the text seems appropriate to me. The information is good as far as it goes, but there are some areas where the description could be improved with additional information. See responses to #3, and #4 for more details on the enhancements that could be added.

Question 3 – Indicator Presentation

Reviewer 1:

The organization of the text is a bit confusing as it seems to bounce from methods to results. Consider re-organizing the bullet points (pages 5-6) as the first three are about the central analysis, then a point about a separate analysis (diesel), then two more points about a separate analysis of children's schools in census tracts. Perhaps subheadings would help divide the analysis.

The metadata question about "spatial representation" provides the study area (e.g., national), but may be misinterpreted to mean the spatial resolution (e.g., nationwide estimates). I suggest adding the spatial resolution information to this row.

The metadata seems to describe the data that are available, not the data that was used. This needs to be clarified within the table, such as noting that 2002 data were used, and 1996 and 1999 data are also available.

Page 3: The language "The three benchmarks generally reflect health risks to adults" is a bit vague. Does this mean that the benchmarks are based on studies of adults?

The text in the metadata table noting that "Data may not be comparable over space" brings the entire indicator into question. Please add some text (to the main text, not the table) on what this means for the indicator approach.

Reviewer 2:

Graph, bullet points and data tables are all simple and easy to grasp. They generally summarize the data well.

Although they would be long, tables giving the indicators for each HAP might be a helpful adjunct, as an appendix, perhaps.

Straightforward presentation makes this information very accessible to the educated audience. The general public may not be as ready to comprehend the meaning of the indicators, but it's not clear how this could be remedied without extensive background information that ultimately would be unlikely to be read by concerned parents with low educational levels.

Comparing the benchmarks to measured/modeled HAP levels by county seems to be a reasonable compromise between specificity and actually available data. The URE seem to come from a 2005 document, which presumably has not been updated since then. A more recent version could be used when it becomes available.

Reviewer 3:

Only one graph is presented for this indicator. It is a fine graph, but it would be of great interest to policy makers to break this information down into some relevant subcategories. In particular it would be useful to see the percentages of children living in areas above benchmarks broken down by race and socio-economic status. That breakdown would be facilitated if the census tract level data were used (see response #1). On page 11, the metadata table poses the question, "Can the data be stratified by race/ethnicity, income, and location?" In fact the data can be stratified in those ways, but the table does not directly answer the question.

I also think it would useful to present a graph or table showing the results if diesel particles were included in the analysis.

The risk driver chemicals are stated in the text, but it would be useful to have more quantitative information. Policy makers will want to know which pollutants from which sources are contributing to this indicator. Appropriate actions (targeted at the right pollutants and sources) can only be undertaken with information about which pollutants and sources might be problematic. One additional graph or table could show the number of HAPs above benchmarks in each census tract. Information could be given in some format naming the pollutants and listing the sources contributing to the risk driver HAPs.

Question 4 – Context and Utility

Reviewer 1:

Overall, I think the indicators are useful, with the caveats of the limitations described above, especially regarding the usefulness of the non-cancer indicator.

This text does not adequately describe the strengths and limitations of the indicator approach. As many limitations may be common across multiple topics, the document may include a summary of limitations elsewhere, and not in each individual chapter. Specifically, limitations that should be addressed are the reliance of the indicator method on the underlying science. The true health effects of an individual HAP may not be fully known. Further, the threshold approach implies the same level of adverse health outcomes for any level above the threshold, whether it be 1 or 50 $\mu g/m^3$. While the indicator's application of thresholds is useful, this step function for health impacts is unrealistic for real-world conditions, and this limitation should be discussed.

Although limitations are described, it may be useful to also note whether a particular limitation is likely to make the indicator approach an under- or over-estimate. For example, consideration of inhalation as a route of exposure, but not dietary exposures, may lead to an under-estimate. Currently limitations are spread throughout the document. Consider having a section devoted to limitations instead, which could be grouped on whether they lead to under- or over-estimates, or whether the direction is unknown. This could be framed as limitations and/or areas of future research and data needs. An additional limitation is the varying sensitivity of different individuals. The document should note that while the indicator approach estimates the number of people exposed to a certain level, there will be some variation in how those individuals response with respect to health outcomes.

Reviewer 2:

As mentioned above, little text is devoted to assessing the strength of knowledge regarding the URE for each HAP, which figures largely into the indicators. It is not clear how this could be done in a brief and concise manner, since according to the source document there is a great deal of heterogeneity in how UREs and calculated and the depth of data available to inform them. This applies to both E4 and E4a.

E4 and E4a are both somewhat bare-bones indicators for the health impact on children of HAP in the ambient environment. More specific information regarding individual HAP could augment this, but the contribution of the home environment would still be missing. Some integration of the home and ambient air quality impact might remedy this.

The indicators certainly are valuable augmentations to discussions on policy regarding the impact of the environment, not just on children but on the population as a whole.

See b). In addition, tracking the values of E4 and E4a over time but updating the exposure as well as the risk data would increase the utility of these indicators for assessing the impact of policy changes.

Reviewer 3:

The 2005 NATA is now available and is substantially improved over the 2002 version. I would strongly suggest that the indicator be updated to use the 2005 NATA data. The emissions used in

NATA 2002 are no longer current. Many sources have changed in significant ways since then. Policy makers want the latest available information upon which to base their decisions. Using the old 2002 information may lead to conclusions and point in directions that are no longer warranted.

In addition, the data are available at the census tract level. There can be very wide variability in air concentrations across a county, and the use of county-level data will result in considerable mischaracterization of the exposures occurring in the county. Using tract level data would reduce this source of error. I would strongly suggest that census tract level NATA data be used.

Diesel particles are not included because EPA has not settled on a toxicity value, though it is widely accepted that diesel particles are important carcinogens. This omission is a big problem. In many locations diesel particles constitute the greatest inhalation risk to children (and adults), using any of the range of possible toxicity benchmarks. Omitting this pollutant introduces a very large error into the results. The document describes this issue and gives an idea of the magnitude (p.6 lines 3-9). I think this bullet should be more prominently highlighted.

This indicator addresses only chronic and cancer toxicity endpoints. However, acute exposures can be very important. Asthma attacks and other significant health events may be triggered by short-term, acute air pollution episodes. This is another gap in the indicator that should be flushed out in the description.

Trends in this indicator will be of use to policy makers. The ACE program staff should be thinking about how to show trends. NATA methods changed from 1999 to 2002 to 2005, and they will likely change again in future versions of NATA. If results cannot be made comparable over time, then the utility of this indicator is decreased. For that reason, it would be useful to try to make comparisons among the different years of NATA data. Are there particular risk driver HAPs for which changes can be identified or quantified, e.g., have toxicity or emissions data changed? Are there risk driver HAPs for which things have not changed, and for which the results are truly comparable? I believe more attention should be devoted to the issue of determining trends as the program goes forward.

Question 5 – Documentation

Reviewer 1:

The documentation is appropriate overall. Some suggestions on the presentation of methods are given above. Below are some additional suggestions.

Page 1, end of first paragraph: The sentence “The “criteria” air pollutants such as ozone and particulate matter are excluded from the HAPs list” might also mention that these pollutants are addressed in a separate chapter, so the reader does not think they are excluded entirely.

Page 1: The sentence “EPA and state monitoring programs currently do not adequately cover all the places where people live in the United States” is true, but may leave readers from the general public wondering why not. Can this be rephrased to seem less of a criticism of EPA?

Page 3: The paragraph that begins “Actual exposures may differ from ambient concentrations.” is a concept that could be expanded, as many readers may not be familiar with this issue. The paragraph mentions indoor levels with some examples, but it would be helpful to explicitly note that exposures will differ across children, with some having higher exposures and some lower.

Page 13: The sentence "From discussions with EPA OAQPS staff, we discovered ..." needs a reference. This could be a personal communication that notes the EPA staff.

Reviewer 2:

The write up is generally very clear and concise. The mathematics are simply and straightforwardly described and easy to follow.

(Lines 16-18m page 12) "The lifetime cancer risks posed by HAPs in each county were calculated by multiplying the ambient concentration of each HAP by the inhalation unit risk estimate (URE) of that HAP." How is the URE determined? A brief description, coupled with a link to the website would help the reader here.

Reviewer 3:

The citations in the document are good, but should be supplemented as indicated in response #1.

2.7 Indoor Environments

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Paloma Beamer
- Michelle Bell
- Bruce Lanphear

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

The topic text appropriately and clearly describes the topic and its importance for children's environmental health.

There are a few additional aspects of the topic that would be appropriate to include for this audience.

There has been increasing evidence of the importance of children's third hand exposures to ETS. Children who live in homes where the parents do not smoke around the child, or have quit but the house still remains contaminated with ETS residues on surfaces also have elevated cotinine levels from exposure to ETS through dermal and incidental ingestion exposure. Although this is still a topic that is relatively new, it would be important to introduce it to this audience. Adding some information about this topic. Here are an example of a few articles on this topic (need some references): [No references provided by the reviewer]

In addition to comparing blood lead levels for children across race/ethnicity and SES, it would also be important to consider urban versus rural children. As one of the primary sources of lead in house dust is from contaminated soil, and soil is impart contaminated from historical airborne emissions from leaded gasoline use, it would be important to see if children in urban areas with high historical traffic have higher levels of blood lead. Consider the following references (find some additional references):

Consider the following edits as ways to make the text more readable to a variety of audiences.

page 1, line 7 add toys as an example of consumer goods

page 1, line 20 remove "such as PFOS and PFOA". There are no specific examples of chemical given for the other classes, and providing the specific chemicals PFOS and PFOA, is not going to make the class of perfluroinated chemicals more understandable to your audience. You may want to consider, adding common descriptions of the uses of these chemicals.

page 1, line 39-40, please rewrite as "higher nicotine concentrations in air"

page 2, line 13, please rewrite as "based on national survey data of homes"

page 2, line 29, "wheezing" illnesses would be clearer

page 2, line 30, are you sure ETS is a known "cause" or just a known "risk factor" of SIDS

page 2, line 34-35, please rewrite so that you say either reduction in birth weight or "risk of low birth weight" but not both

page 2, line 38, please add "in children" after asthma

page 3, line 39-41, seems like there should be a citation for this statement

Reviewer 2:

The introductory material does a good job of briefly explaining the wide variety of environmental exposures to children in indoor environments (page 1). I thought this section achieved a good balance of being readable and understandable to a general audience, but also providing specifics.

The text could mention that unlike many of the environmental exposures in this report, indoor environments are not regulated. For example, federal regulations exist for many outdoor air pollutants, but not indoor pollutants outside of occupational settings. This may help illuminate the challenges of developing indicators for this topic.

Given that the dataset used to evaluate interior lead exposure also measured arsenic, pesticides, and mold, was there a reason these other interior health hazards were not considered for an indicator? Please provide this rationale.

Reviewer 3:

Somewhat, but this section needs to be rewritten and extensively edited. The text initially reads like a laundry list and then abruptly shifts to focus on only two exposures because there is, presumably insufficient data for all of the other hazards. But there are some national measures or estimates for several other indoor exposures, including indoor allergens. It would also be preferable to think about how to organize the laundry list so that it doesn't read like one.

The relevant literature is included, but it is not always adequately cited in the text. For example, Gergen, et al. should be specifically cited to show that children younger than 3 years appear to be more susceptible to ETS. There should also be more consideration of using serum cotinine instead of parent reported SHS exposure. I don't think readers would have a problem accepting serum cotinine instead of parent reported exposure. Indeed, you will dramatically underestimate exposure if you rely on parent-report (see Braun, et al, and Kalkbrenner, et al). For example, Braun et al, found that 74% of children who did not report a smoker in the household had detectable cotinine levels (Braun J, et al. EHP 2008).

Question 2 – Indicator Text

Reviewer 1:

Indicator E5
The indicator text does provide quite a bit of information regarding the data set and the indicator calculation. There are, however, a few areas that could be made more clear. For example, on page 5, line 17, it says that relevant follow up questions were then asked according to the response but does not provide what those questions were. If these questions were relevant, then they should be provided. For example it is not clear to me at what point smoking on a regular basis was defined as four days or more per week. Was that a question from the NHIS, or was that calculated using data from those "other relevant questions."

The text for this indicator is not as clearly written as for others and should be closely edited. Consider the following edits.

page 5, line 12 should be "children age 0 to 6 years"

page 5, line 18, should be "NHIS only in"

page 5 , line 26-27, should be "researchers have used these data to associate ETS exposure with adverse effects on childhood lung function and other health outcomes.

Page 6, line 1, should be "Children age 6 years"

Indicators Dust1
The indicator text does provide quite a bit of information regarding the data set and the indicator calculation. However there is one thing that is not clear. On page 9, line 7, it states that the HUD surveys are nationally representative. However on lines 18-19 it states that the survey used federal guidelines to "identify" homes with lead contaminated dust. Where homes identified with lead contaminated dust, and then sampled? That would bias the results. Or is it meant that the federal guidelines were used to classify children in homes with interior lead hazards based upon the data collected from the surveys? I believe the latter occurred, but it is not clear from the text as it is written.

Through the discussion of this indicator, including in the title, the term children ages 0 to5 years is used. This is confusing consider replacing with children age 0 to 5 years or children 0 to 5 years of age.

Otherwise the text should be understandable to various audiences.

Reviewer 2:

The indicators are based on two potential sources of exposures in indoor environments: environmental tobacco smoke and lead in homes. Many other exposures exist, which is noted clearly in the text. The explanation for why these two exposures receive attention and others are not addressed is provided largely through a single sentence "Other indoor environmental hazards in children's homes generally lack nationally representative data necessary for development of indicators" (page 2). This needs to be expanded so the reader understands why these two indicators were selected and why others were omitted. There could be a paragraph, or even small section, on the challenges. These include lack of data, high variability across households and other indoor environments, lack of clear information linking the exposure to children's health endpoints even if suggestive evidence exists, etc.

There needs to be some indication on whether the two indoor environmental exposures (smoking, lead dust) are the most important to children's health in comparison to exposures that are not used in the indicators, or acknowledgement that this information is unknown.

The wording on page 5 implies that the children themselves were surveyed, but the survey was for adults in the homes where children ages 0-6 years live. This is mentioned in the metadata section (page 20), and can be fixed with wording changes in the earlier text on page 5.

It would be helpful to have some justification for the time period (1994 to 2005) and ages (0 to 6 years) for the indicator to the degree possible, briefly mentioning the data availability. This could be provided in each chapter, or could be elsewhere in the document. This is particularly important as the ages used for each indicator differ (e.g., 0-6 years for smoking exposure versus 0 to 5 years for lead exposure). For example, are ages 0-6 selected because they have been identified are more susceptible specifically, as implied, or also because data is available for those ages (page 5)?

The discussion of lead should further emphasize that the measure is exposure in homes not measures of lead in children, although biomarkers do exist.

Because the smoking information is based on self-reporting rather than a biological measure and because the exposure can be considered socially undesirably, reporting bias is very likely. This needs to be mentioned in the report. There are studies on this topic, which could be referenced. A key limitation in the exposure information is that the presence of smoking is estimated but not the degree of smoking. The report needs to discuss this issue given the strong exposure response relationship for smoking exposure. Similarly the lead exposure indicator is based on a threshold (e.g., 40 mg/ft2 or more for a floor wipe sample) although children in the "unexposed" category could have some lead exposure and not all children in the "exposed" category are exposed equally. The language explaining how the smoking indicator was constructed is a bit unclear (page 26). There do not appear to be problems in the construction of the indicator, but the explanation could be made clearer.

Please clarify how observations for persons of multiple races were processed in calculation of the indicators by racial group.

An additional assumption that needs to be discussed in explaining the indicator is that all different types of smoking were considered equal (i.e., cigarettes, cigars).

The discussions of difference by race or income need to discuss how these variables are related to each other. Statements about statistically significant differences should be clear regarding whether differences are adjusted or unadjusted (as details given on page 34).

Define primary sampling unit, or use alternate phrasing (page 22).

It's unclear what is meant by "supplementary files" on page 25.

The last sentence of the second paragraph of page 34 should read "could be significant but the adjusted difference (taking into account income) may not be significant" rather than "would be significant but the adjusted difference (taking into account income) would not be significant".

Reviewer 3:

Similar to the lead epidemiology section and the neurodevelopment section, there is actually TOO MUCH information about methodology and how the data were analyzed. The vast majority of people will be discouraged from reading the report because there is too much attention to the methodology.

You could use serum cotinine or both serum cotinine and parent report of a child living in a household with a smoker. Relying only on parent report will lead to a large underestimate of children's SHS exposure. It also results in several empty cells in Table E5a.

Question 3 – Indicator Presentation

Reviewer 1:

Indicator E5
Yes the indicator graph does provide a nice understanding of the underlying data. However the graph is hard to read in black and white, and it is not apparent if there are supposed to be gridlines. The text should be understandable to a wide variety of audiences. Please consider changing "below poverty" to "below poverty level" throughout. Consider changing the text of the statistical note, to first state that for children below the poverty level, several differences were observed between race and ethnic groups, and the just describe those differences.

Were there statistical differences by race/ethnicity for the other income groups? If not it would still be important to report that there are not differences.

Although the overall rates of ETS exposure were extremely low among Hispanic children as a whole, the rates between Mexican American and Puerto Rican children were very different. Were these differences significant? Considering how high the rates were for low-income Puerto Rican children, it would be important to discuss that in the indicator text.

Indicator Dust1
As for indicator E5, the graph does provide a nice understanding of the underlying data. But the color and gridlines are hard to read.

The text should be understandable to a wide variety of audiences.

Reviewer 2:

The information on differences in the indicator by race would work well in a figure. This could be similar to the figure on page 7 for income. Information by race and income could also be presented graphically (e.g., trends in indicator by income within a given race).

The low number of observations for the data forming the basis of the lead exposure indicator is disconcerting, especially when considering subgroups. The document does note that the samples were intended to be representative, but further information on this point would be helpful (e.g., some examples or descriptions of the way in which the originally sampling methodology was designed to be representative).

Because there are many health risks from other exposures outside of these indicators, consider a table that presents examples of other exposures along with health responses and, to the degree possible, a measure of how certain the association is (suggestive evidence to strong scientific evidence). This will help deliver the message that the document presents indicators, not summaries of children's health in relation to indoor exposures.

Reviewer 3:

No, table E5 loses important data because it is restricted to parent reported SHS exposure. Although using serum cotinine is a biomarker and there is a separate section on biomarkers, I think it makes more sense to rely on biomarkers to estimate exposure rather than using parent reported SHS exposure. If you relied on serum cotinine, you could show the trends more clearly because there is more ongoing data available from NHANES.

I would also use figures similar to those used by Robert Jones, et al. for showing differences in the distribution of blood lead levels for various groups and by age. This would illustrate that younger children and African American children have higher serum cotinine levels in a way that is more visual.

You might also consider showing differences in serum cotinine by multiunit dwellings (see Wilson K, et al. PEDIATRICS Vol. 127 No. 1 January 2011, pp. 85-92 (doi:10.1542/peds.2010-2046) from NHANES.

One option is to incorporate the section on indoor environments into the section on biomarkers. As written, the only thing lost from this section is the laundry list of other exposures. If you incorporate other exposures – such as fungi or cockroach allergen, then it would make more sense to retain this section.

Question 4 – Context and Utility

Reviewer 1:

Indicator E5
This indicator is very useful and appropriate for the addressing the three principal objectives of ACE. It is also an exceptional example of where substantial improvement has been made for protecting children from environmental hazards like ETS. However examining the data tables (E5 and E5a) it may be appropriate to enhance the indicator text so that it would be more readily apparent to

policymakers and the public what areas still need improvement. For example, were there statistical differences by race/ethnicity for the other income groups? If not it would still be important to report that there are not differences, for policymakers and public health professionals to determine how to best target their messages about "smoking bans". I think the indicator also needs to make the rates among Puerto Rican children more apparent, as they will be a key group for policymakers and health professionals to target in the future.

Indicator Dust1
This indicator is very useful and appropriate for addressing the three principal objectives of ACE. It is clear that much work is still to be done on reducing lead-based paint. It is also interesting to see that lead dust has decreased more substantially than deteriorated lead-based paint indicating that perhaps other sources are more important for decreased lead dust in children's homes and should be targeted by policymakers. If at all possible it would be useful to examine this data by urban versus rural environments, and geographic region to determine if there would be additional informative information for policymakers and public health professionals.

Reviewer 2:

Generating indicators that fully represent children's health responses to exposures from indoor environment is not feasible, so this project appropriately selects some representative examples. A key concern for this document is that the reader fully understands that these are examples, both in topic and in form of the indicator. This concept could receive more attention throughout the chapter to help all readers understand this point. As an example, the document needs to be careful to not give the impression that children of ages outside those used in the indicator are not susceptible to adverse health responses from these exposures. As another example, the indicator is based on children who are "regularly exposed" defined as smoking in the home four or more days a week. This is mentioned a few times in the document, but is not highlighted. In this sense the indicator is an underestimate of the overall smoking risk to children as there are children exposed to smoking that are in the "unexposed" category. This document needs to be carefully worded to not give the impression that exposure to levels of smoking averaging less than 4 days a week is in any way safe for children's health.(In addition to explicitly stating this, the document could add sensitivity analysis with an indicator based on a different number of days smoked/week.). I think that in this chapter, text explaining the limitations, purpose, and interpretation of the indicators needs to be greatly expanded so that the indicators are not misinterpreted. Some of the key issues that need to be made for this particular chapter are:

There are many other indoor environmental exposures. The introduction section does a nice job of explaining these, but it's not clear how the two selected exposures compare to the overall risk. Are they the largest risks or just the ones we can measure for an indicator?

The ages used are for the purposes of the indicator and to some extent based on data availability. Children of older ages can also be at risk.

These indicators do not group children into "safe" and "unsafe" levels of exposure, as some children in the "unexposed" category may also suffer health responses, and the children in the "exposed" category represent a range of exposures. The degree of exposure is associated with the severity of the health response.

Reviewer 3:

As noted above, the section on parent reported SHS exposure is inadequate because it relies on parent report. It could replace this or augment it with serum cotinine.

For each indicator, please comment its utility and appropriateness addressing the three principal objectives of ACE:

a) to presents concrete, quantifiable indicators of key factors relevant to the environment and children in the United States. These indicators are designed to offer a basis for understanding time trends for some factors and for further investigation of others.

I indicated in my other comments on lead and neurobehavioral effects that the focus of the EPA Report should ultimately be on the exposures and regulations related to those exposures. This section addresses some of those concerns, but it might be worthwhile to incorporate them into one section of reference them in the other sections.

b) to inform discussions among policymakers and the public about how to improve federal data on children and the environment.

This document should emphasize the reasons for the decline in SHS exposure, including bans on public smoking.

c) to provide indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children.

The document should expand on the other regulatory efforts that have been instituted to reduce exposures to SHS. Although the report describes smoking bans in housing, it misses the opportunity to describe smoking bans in public places. It would also be worthwhile to cite the two studies showing decreases in asthma visits following smoking bans in Kentucky and Scotland (see cites immediately below).

1. Daniel Mackay and others, "Smoke-free Legislation and Hospitalizations for Childhood Asthma," New England Journal of Medicine 363 (2010): 1139-45.
2. Mary Kay Rayvens and others, "Reduction in Asthma-Related Emergency Department Visits after Implementation of a Smoke-Free Law," Journal of Allergy and Clinical Immunology 122 (2008): 537-41.

Question 5 – Documentation

Reviewer 1:

The documentation is very thorough and transparent. It would be possible for someone to replicate all calculations.

Reviewer 2:

The language on statistical significance is useful, but will apply to multiple chapters and indicators (page 6). I have reviewed only a subset of the overall document, but it may be more useful to have this type of information in a separate section rather than repeated throughout the document. There could still be brief mention of this issue in the chapter, and perhaps reference to the section with more information.

Reviewer 3:

Yes, with exceptions noted above.

3.0 HEALTH

3.1 Adverse Birth Outcomes

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Jennifer Adibi
- Cynthia Bearer
- Dawn Misra

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

The topic does an excellent job of describing these indicators, their relevance to children's health and the various demographic and environmental factors that might explain some of the temporal trends and differences among subsets of the population. The authors might want to add that, conversely, post-term birth (delivery after 40 weeks) is also associated with increased risk of maternal and infant mortality and morbidity (Olesen. Am J Obstet Gynecol. 2003; Hilder Br J Obstet Gynaecol. 1998). There have been some reports of environmental factors, including DEHP exposure, related to post-term delivery (Adibi et al. AJE. 2009; Shea Epidemiology. 1998). Post-term delivery is also associated with increased risk of delivery by C-section. Authors could state that the rate of preterm birth is approximately double the rate of post-term birth, which is why this document will focus its discussion on preterm birth.

In terms of the biology, we do not fully understand the mechanisms of parturition and labor which is why we cannot fully understand how specific environmental or other factors are capable of disrupting the process. However, we do know that it is the result of complex cascade of signals between the fetus, the mother and the placenta. Exposures or factors that cause defects in any or all of these compartments can contribute to changes in the timing of parturition and labor, and or in fetal well-being which can precipitate early delivery.

Authors might want to mention the theory of fetal origins of adult disease which is another reason why we care about length of gestation and birth size. The theory or Barker hypothesis postulates that certain types of chemical, nutritional or stress-related exposures in utero can alter the programming of fetal cells in ways that are not apparent at birth, but are highly predictive of disease risk later in life, i.e. cardiovascular disease, obesity, metabolic disorders, cancer. Preterm delivery and birthweight are used at the population level as proxies for these types of changes and have been shown in some populations to be correlated with diseases in adulthood. It seems in the Birth2 indicator, by limiting to LBW among term births, that the authors are specifically studying growth restriction which is one of the pathways through which fetal programming of adult disease is believed to occur.

Page 2, line 16: Authors might want to mention in this section that exposures in the first trimester when the placental-fetal unit is developing are believed to be the most harmful and possibly the most correlated with adverse outcomes at delivery. Therefore both research and prevention strategies should perhaps over emphasize pre-conception and the first 3 months of pregnancy as critical periods for minimizing exposures.

It is important to state in this section that the potential causes of these adverse birth outcomes in humans are taken from observational studies where we can only measure correlations. We cannot measure cause and effect, nor can we remove all of the sources of bias. Human studies are very important and can reveal relationships that may have a true biologic basis, but findings must be confirmed in multiple populations and/or in an experimental system before we can conclude that there is a causal relationship.

Be careful not to mix up the terms prevalence and rate. It seems in this study, the authors are reporting prevalences and comparing them over time.

Reviewer 2:

I thought that the introductory paragraph was confusing. I have rewritten it below:

Gestation is a period of time that is a crucial in the development of an infant's health and survival for years to come. Two measures that may be used to understand the quality of an infant's gestation are 1) the length of his/her gestation (length of the pregnancy) and 2) his/her birthweight. Normal term pregnancies continue for 37 to 41 weeks of gestation, allowing for more complete development of an infant's organs and systems.[1] An infant is considered preterm (or premature) if he/she is born between **22 (is this right?)** and 37 completed weeks of gestation. The second indicator, birth weight, is determined by two factors: the length of gestation and fetal growth. A baby may be born with low birthweight because the baby is premature or the baby is undergrown or both. Low Birth Weight babies (LBWs) are defined as weighing less than 2500g (5 pounds, 8 ounces). To try to distinguish whether an LBW infant is premature or undergrown, other measurements are used, such as birth length, head circumference, and abdominal circumference.

Other adverse birth outcomes that are not discussed here include birth weight greater than expected (large for gestional age, LGA), neonatal mortality, and birth defects, a specific group of adverse birth outcomes that include structural and functional abnormalities.

Other edits:

The introduction uses low birthweight as any baby born less than 2500g, but the indicator is for term babies less than 2500 g. The introduction should make this clear (I tried to in my rewrite of the first paragraph.

Since preterm infants are a subset of LBWs, I tried to use this way of thinking about it in the subsequent paragraphs.

Page 1, Line 20: "Preterm and low birth weight infants" should be changed to "LBWs including preterm infants.."

I'm assuming that when the term "low birthweight infants" is used throughout this paragraph, it means "low birthweight infants including preterm infants" and should be changed to this phrase to make it clearer.

Would it be useful to add a line or two about the complications of term low birthweight infants since that is the indicator that is being used.

Page 1, line 33. The word "health" should be deleted.

Page 1, line 34. I would change, "a child's life" to "the infant's life through adulthood." This emphasizes that these effects also affect adults.

Page 1, line 40. I would change "increases" to "previous increasing preterm birth".

Not defined is the lower gestational boundary of preterm birth. At some point, births are considered miscarriages or abortions. Is this lower limit defined?? Has this definition changed as we've become more successful at saving smaller and more immature infants? I think a discussion on this point should be include. How preterm infants are defined (22 – 37 weeks gestation?) or how they are not defined at the lower limit.

Page 2.line 2. Change "preterm birth and low birthweight" to "preterm birth and growth restriction"

Page 2 line 2. Delete the word "fetal"

Page 2, line 24. Change "that concluded" to "concluded that"

Page 3, line 5. Define PFOS and PFOA

I think there are also some recent articles on chlorpyrifos and growth restriction, and exposure to urban traffic pollution (benzene, toluene and ethanol) and growth restriction.

Page 4, line 24. Preterm births needs to be either better defined or explained for the lower limit.

How do hospitals decide on what is a preterm birth and what is a miscarriage/stillbirth/spontaneous (or therapeutic) abortion?

Could a change in the definition, or the fact that babies at lower gestational ages are being resuscitated or are being attempted to be resuscitated, change the way a birth certificate will be filled out? This definition is not clear on Page 24 line 15 in the Methods section.

Reviewer 3:

An excellent overview of low birth weight, fetal growth, and preterm birth is provided. This is a frequent area of confusion, even within the scientific literature, and the overview here is very good at explaining the overlap as well as differences. The description of the epidemiology of preterm birth is very well written and covers the key issues. The description of racial differences in birth outcomes, and how these might relate to environmental toxicants is quite well written and the key issues are highlighted. Finally, all of the sections in the topic text are up to date with current scientific research in this area.

While the issues are complex, the presentation of the topic seems understandable for a wide range of audiences. The synthesis of past work on this topic is particularly well written with regard to the issue of understandability.

Question 2 – Indicator Text

Reviewer 1:

The indicator text is clearly written. I notice that the author is careful to use prevalence and not rates in the Statistical Testing section. This should be consistent throughout.

Reviewer 2:

Be clearer in Introductory paragraphs that very low birthweight as discussed there includes preterm infants, as opposed to the indicator where only term low birthweight infants are used. This is nicely discussed in the Indicator section.

Preterm birth needs a better definition as it doesn't include spontaneous abortions and miscarriages. Is there a clear definition of the lower limit of gestational age? Or is it how the hospitals choose to fill out the birth certificate?

Reviewer 3:

The first indicator, percent of preterm births, is an important and easy to comprehend indicators. The second indicator, percent of LBW in term births, is also a good choice as a proxy for fetal growth restriction. While a measure of growth restriction would be ideal in an etiologic study of fetal grow, it is not a feasible measure to use as an indicator for surveillance as it is more complex and the quality of data required to have a refined valid measure is difficult. Therefore, the indicator of percent LBW among term births is a good choice of an indicator.

Each indicator will be presented for each of five race/ethnicity groups which is important to do, given the considerable disparities in both outcomes and exposures. The indicators will also be done separately by singleton/multiple status in supplemental tables; again, this is important because of baseline differences in risk for these two groups.

The rationale for applying statistical testing to determine significance of longitudinal changes is not convincing. In the U.S., data collected in vital statistics is not necessarily treated as a sample.

Presumably, the entire population of births is included in vital statistics. The comment made regarding the fact that small differences would be statistically significant in a "sample" of 4 million can still be an issue if statistical tests are not applied. But regardless, small differences in vital statistics data are indeed real differences. So any interpretation of the results should take this into account.

Question 3 – Indicator Presentation

Reviewer 1:

The indicator presentation is effective as it simultaneously shows the time trends and the differences by racial/ethnic groups in the two outcomes. In the Indicator Birth 1 Figure, you could restrict the y axis to 6-20% which would allow a higher resolution look at the lines squeezed between 8 and 14%. Similarly, in the Indicator Birth 2 Figure, the y axis could be restricted to 1-5%. The text and descriptions are very clear and understandable to a broad audience.

However, given that the purpose of this document is to make connections between these trends and environmental factors, and NHANES has extensive data on environmental exposures at the population level, would it be possible to do a separate figure somehow relating the two? Or similarly, looking at a trend in these two indicators in relation to a trend in a health disorder in children possibly related to fetal programming?

Could the data tables include a p-value or indicator of trends that were significant over time?

Reviewer 2:

Aside from my edits suggested above, I think it was nicely written and quite clear. Define preterm birth!

Reviewer 3:

The "statistical" notes should be removed, per the comment in #2 regarding statistical significance.

The text states that the rate of LBW stayed the same between 1993 and 2007 for all race/ethnicity groups but that does not seem to the case for Black births. It seemed to drop to almost 4% in 2001 and had risen to ~4.5% at the end of the period.

Question 4 – Context and Utility

Reviewer 1:

a) Birth1. Yes, this section presents an overview of why gestational age might be an important indicator of in utero events related to environmental exposures, and also related to postnatal health. The time trends and differences between racial/ethnic groups are moderately interesting; however pretty well known and I am not sure how the authors are trying to make the connections between the two: environmental causes and the actual trends. Do we conclude that the indicators

are not changing dramatically and therefore the effects of the environment on these indicators have stabilized? Is there an "ideal prevalence" that we think would be an indication that our reproductive health is not at stake or a threshold that if we cross, we have entered in a critical danger zone? It might help make the connections if authors can state why it is important to monitor these trends at the population level and what they might tell us. It might be interesting as well for the authors to state the prevalence of both indicators in 1968 when the NVSS data was first collected. Are we doing better or worse with the advent of the green movement and environmental regulations?

Birth2. Birth weight is a multi-factorial outcome and is very difficult to study. In this case, the authors have controlled for gestational age by restricting to term births in their estimates of low birth weight prevalence over time and demographic groups. There are a series of papers in the literature (instigated by reproductive epidemiologist Alan Wilcox) that argue that we should not control for gestational age when studying birth weight. It could be working as an intermediary variable and it could be introducing bias in our estimates.

b)Birth1-Birth2. There is enough detail on the database to inform a discussion on the strengths and limitations on the data. It would be helpful if the authors or statisticians who analyzed the data provided specific suggestions on how these data could be improved, or made more amenable to these types of exploratory analyses.

c) Birth1-Birth2. These data can and should be used to monitor for adverse trends, clusters where there might be a disproportionate burden of a particular hazard, and/or improvements in the reproductive health of our population. However, it seems that we would need more sophisticated statistical techniques to look at correlations of exposures and endpoints over time and within specific subpopulations and within specific geographic regions.

Reviewer 2:

I think that preterm birth needs a better definition for the lower limit as I've mentioned before. I think the use of term low birth weight is very useful and concrete. Perhaps more emphasis should be placed on the fact that term baby is determined by the mother's LMP, and therefore some babies considered term may not be, and be weight appropriate for their gestational age. Has there been a systematic change in the way that gestational age is determined? Sometimes obs will use an early ultrasound rather than LMP to determine gestational age.

Reviewer 3:

Both of the indicators of adverse birth outcomes meet the objectives as described above.

Question 5 – Documentation

Reviewer 1:

The tables are helpful and humbling in terms of a giving an idea of sample size. Could the authors put in parentheses the percentage missing of the total birth certificates, for the 2 categories? It would be easier to assess than looking at the actual numbers.

Page 29, line 4-6: It is not clear how the number of births in the denominator was restricted by gestation length? Should it be out of all live births?

Page 29, line 11-13: Similarly, how was the birth weight restricted for this analysis?

Tables 1-3. It would be helpful if the tables could include a column to indicate the direction and/or magnitude of the difference between the two groups. If there is not a good statistic, even an arrow up or down would be more informative.

Reviewer 2:

Yes, except it doesn't describe how a birth is considered preterm or a miscarriage/spontaneous abortion. What is the lower limit or how is this decided?

Reviewer 3:

Yes.

3.2 Childhood Cancer

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Gang Chen
- Susan Jobling
- Kirsten Malecki

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

Does the topic text appropriately and clearly describe the topic and its importance for children's environmental health?
--- The childhood cancer incidence, as well as mortality in the US, is clearly described in the topic text. In addition, important environmental factors that have been linked with childhood cancer risk are discussed briefly. Based on available knowledge, the importance of children's environmental health as it relate to childhood cancer is described. This discussion is appropriate and clear for the topic.

Are there additional aspects of the topic's importance for children's environmental health that should be included?
--A brief description of the association between radon exposure and risk of leukemia should be included. In addition, for the benefit of policy makers and the public, important negative findings may also be included in the text. For example, cell phone usage and living near power lines, respectively, have long been speculated for causing brain tumor and leukemia; therefore, study results that address these concerns should be summarized briefly.

Is the relevant literature appropriately summarized?
-- Yes.

Are there other important references that should be added?

--- Radon exposure is an important source of environmental radiation, and it may be associated with an increased risk of cancer in children. Papers that study the relationship between radon exposure and cancer risk should be included.

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?
---In general the text is understandable for readers with a diverse background of knowledge. However, the description of carcinogens from page2, line 38 through page 3, line 4 seems to deviate away from the focus of the topic and may be removed.

Reviewer 2:

Answers: The introductory text describes the general topic and its importance for children's environmental health very clearly. It is a shame, however, that this is not then continued throughout the document delving into this topic in a bit more detail. Most of the document appears to concentrate on time trends, but not much on their relationship with environmental factors. There are 19,218 hits on the ISI web of knowledge using the keywords childhood AND cancer. Of course not all of these are to do with environment and cancer but it is still a large subject area and although difficult to cover in a relatively short document, more could be done. The document succeeds in capturing most of the issues in outline, but is this enough for the policy maker?

There are a couple of things of current importance that I would emphasize/add. The first is the fetal origin of many childhood diseases. This is really an emerging area. So on line 31, I would add, "and an increasing number of studies indicate that many cancers may have an origin in the womb". MATERNAL exposure to pesticide during and after pregnancy has been positively associated with childhood leukemia, with the strongest risk for exposure during pregnancy. Outdoor exposure and exposure of children (after pregnancy) were not significantly associated with childhood leukemia, for example.

There could then be a paragraph on what this means. It is not necessarily an easy concept to grasp. This would be prelude to the next paragraph that mentions maternal occupational pesticide exposure in connection with leukemia. From twin studies and the use of neonatal blood spots, for example, it has been possible to back track the first initiating genetic events within critical haemopoietic cells to foetal development in utero for most. For some leukemias, the first event appears adequate to create a malignant clone but for the majority, further 'genetic' changes are required, probably postnatal. It appears increasingly likely that delayed, dysregulated, responses to 'common' infectious agents play a major part. A list of environmental risk factors identified should be included in the document.

Epigenetic mechanisms mediate genomic adaption to the environment and epigenetic alterations can contribute to the development of disease phenotypes, as can genetic variants. Give an introduction to epigenetics, and hypothesis on feasible approaches for the study of epigenetics in childhood cancer. Many environmental risk factors for common, complex human diseases have been revealed by epidemiologic studies.

Heritable mutations may result in a wide variety of detrimental outcomes, from embryonic lethality to genetic disease in the offspring. Despite this, today's commonly used test batteries do not include assays for germ cell mutation. Current challenges include a lack of practical assays and concrete evidence for human germ-line mutagens, and large data gaps that often impede risk assessment.

Moreover, most regulatory assessments are based on the assumption that somatic cell mutation assays also protect the germ-line by default, which has not been adequately confirmed. In light of these challenges, an urgent need exists to develop new approaches to evaluate the potential of toxicants to cause germ-line mutation. The application of new technologies will greatly enhance our understanding of mutation in humans exposed to environmental mutagens.

Page 2 first paragraph: Be careful not to fall into the trap of "evidence inconclusive=no evidence" We live in a complex world where multi-causality is common. A paragraph should be included to explain this to the politician. My view is in fact that we would not expect to find associations between for example proxy measures for vehicle exhaust emissions and leukemia. It is highly unlikely that this is the only factor involved and the effects of other factors may "dilute" measurement of association with any one factor. There is no single cause for childhood leukemia and for most individuals a combination of factors appears to be necessary; all involving gene-environment interactions. Exposure in childhood to organophosphorus and perhaps to carbamate insecticides in combination with a reduced ability to detoxify them may be associated with some cancers for example. This is not clearly explained or reviewed

Action points for policy makers etc are missing:

What about tobacco? Is banning smoking in public places helpful? Has it been? Is there any evidence

There is not much in this document for the policy maker or the public. The Precautionary Principle should be mentioned. This is an increasingly influential aspect of modern policy making, challenging regulators to take steps to protect against potential harms, even if causal chains are uncertain. There has been much discussion of the principle in abstract and general terms, but its meaning and role in the practical management of minor and uncertain risks is ambiguous and controversial. The European Commission (EC) has taken a leading role in fostering discussion on the application of the Precautionary Principle, mainly through a communication which establishes guidelines for applying it. This should perhaps be discussed. For example, for childhood leukemia and for example, power frequency magnetic fields, the main evidence for a risk is an epidemiological association observed in several studies and meta-analyses; however, the number of highly exposed children is likely small and the association could be due to a combination of selection bias, confounding and chance. Corroborating experimental evidence is limited insofar as there is no clear indication of harm at the field levels implicated; however, the etiology of childhood leukemia is poorly understood.

Page 28, " a p value below 0.05 implies the difference is statistically significant". What about 0.06? What do we say? There is a tendency to interpret this as no relationship or association when in fact all we mean is that we can say that there is an association with 94% confidence but not with 95%.

Similarly in the sections where each indicator is described, some attempt should be made to explain to the politician why for example there are sex differences in the incidence of cancers and why the rate declines between ages 5-9 and 10-14. Page 10: same question. The reader wants to know why we think this ?

Reviewer 3:

While all of the key elements of the text are here, I feel the text is lacking in 1) helping the reader to understand what childhood cancer is, and 2) why it is an important environmental health issue –

e.g. why is this important enough for inclusion a national EPA report. With regards to #1 – the first sentence is not helpful to any lay audience in describing childhood cancers, this sentence should bring the reader into the topic – e.g. " Childhood cancers refer to a cluster of diseases, some related and others not that have varying degrees of relationship to environmental exposures." Childhood cancers with the strongest evidence are …. Those with suggestive evidence are …. Etc.

To be added - in addition to describing the potential contaminants—what are the pathways of exposure that make children most vulnerable to childhood cancer, and what is known about different windows of vulnerability and subsequent cancers as well as latency between exposures and cancer. There is a lot of discussion about prenatal exposures but what does this mean for intervention and prevention? How does childhood mobility impact exposure assessment, why is it hard to make a conclusive association?[7] Also- there is one line about combination of genetic predisposition and environmental exposures but I think this warrants additional discussion/emphasis.[8]

Furthermore- skin cancer is not discussed but it is a growing cancer in young adults and exposure in childhood is very important to prevent in children, some mention of this is important

References: - an updated lit search should be done. There are at least two new reviews in the literature for pesticide exposure and childhood leukemia. Also, the last sentence for paragraphs 4, 5 and 6 on page 2 – end with the same reference – the Surgeon General's report. I would imagine there are specific references in this report that would give this assessment more credibility and these should be cited. I would also consider reworking this, it appears to be a cut and paste but it starts to look redundant.

References to Consider:[9] [10]
Paragraph 7- pg 2 – the first and last sentences are inconsistent – is there or is there no evidence that Wilm's Tumors and Ewing Sarcoma's are environmental – e.g. there is limited evidence to suggest that both ionizing radiation and pesticides may contribute to the incidence of Wilm's and Ewing Sarcoma but the only known causes are birth defects and genetic conditions.

I think it would help to move paragraph 8 up in the text, maybe even as the first paragraph.

Reference #3 – is almost a decade old and seems inappropriate for the sentence – why is the SEER Registry report the only reference on trends in cancer incidence? --- the newer references cited in lines 30-31 seem more appropriate.

Pg. 1 lines 15 and 16 – should state the changes are too rapid to be caused by by genetics "alone" there may be a gene-environment interaction that increases susceptibility to changing environmental exposures that may cause a rapid rise. ----

Pg. 2 lines 35-37 are not consistent with the rest of the paragraph –

[7] Smith, M.T. Advances in understanding benzene health effects and susceptibility. *Annu Rev Public Health* **31**, 133-148 132 p following 148 (2010).
[8] Holland, N., Fucic, A., Merlo, D.F., Sram, R. & Kirsch-Volders, M. Micronuclei in neonates and children: effects of environmental, genetic, demographic and disease variables. *Mutagenesis* **26**, 51-56 (2011).
[9] Van Maele-Fabry, G., Lantin, A.C., Hoet, P. & Lison, D. Residential exposure to pesticides and childhood leukaemia: a systematic review and meta-analysis. *Environ Int* **37**, 280-291 (2011).
[10] Turner, M.C., Wigle, D.T. & Krewski, D. Residential pesticides and childhood leukemia: a systematic review and meta-analysis. *Environ Health Perspect* **118**, 33-41 (2010).

Pg. 2 – paragraph starting at line 38 – this paragraph has a lot of good information that coule be moved up to frame the issue prior to going into each separate cancer.

Pg. 3 – line 11 and 12 severity should really read magnitude – the death and survival really measure the severity.

Question 2 – Indicator Text

Reviewer 1:

Does the indicator text provide sufficient information about the data set and the indicator calculation to enable an understanding of the indicator?
--Yes.

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?
--While overall this text will be understandable for audiences with different background knowledge, the sentence on page 4, line 12 to 14 can be improved. In this sentence, the differences between SEER population and U.S. general population are point out, however, how these differences may impact the indicators D5 and D6 are not discussed. This statement may cause confusion among the readers. It is suggested to either delete this sentence or add a discussion on how much impact these differences may affect the usefulness of the SEER data set.

Reviewer 2:

The information presented is very clear. Shortcomings are already presented.

Reviewer 3:

This is a bit confusing and seems a bit out of place, I think a sentence or two comparing the SEER registry with state based registries and why SEER – because of its high quality and consistent national data is a better choice than state based cancer registries. Much of this discussion of SEER I think detracts from the indicators themselves and could be contained in an appendix/methods section. It would be helpful to know the geography of the SEER sites.

Information from the metadata re: spatial representation of the database would be helpful to include in the descriptive text for the indicators.

Pg. 5 lines 8-16 contain important messages/main message of this section but are buried in the methods, I would suggest moving this text up to improve “the story” and how it is told.

Pg. 6 – this concept of statistical significance and stability would be much easier to understand by a government of lay audience if you included an illustrative example.

Question 3 – Indicator Presentation

Reviewer 1:

Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data?
--Overall the indicator graphs provide an understandable summary of the SEER data.

Are there ways in which the presentation and description of the indicator values could be improved?
--Even through age-adjustment is clearly stated in the text for the indicator, the graphs and tables need be labeled clearly. The incidence and mortality should be clearly stated as age-adjusted to the 2000 US Std Population. Same criticisms for the tables- they should be clearly labeled.
--The term, "a statistically significant increase", in the first sentence on page 7, line 3, should be "a statistically significant trend of increase"

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?
-- The first sentence on page 7, line 8 sounds a little bit technical. It may be simply stated that cancer incidence and mortality rates are higher in boys than that in girls.
-- The paragraph on page 7,line 13 to page 8, line 3 seems to just repeating the numbers in Table D5b, and therefore should be deleted. The statistical note on page 8, line 40 to line 9 seems appropriate for this bullet point.

Please comment on the appropriateness of the comparisons made in the indicator(s) and whether other comparison populations and/or benchmarks may be informative to the public.
--The comparisons made in the indicators D5 and D6 are appropriate. There is a trend of increase in childhood cancer incidence in the US from 1992 to 2007. In addition, the comparisons made in the tables D5a through D5c clearly demonstrate that cancer incidence is associated with race, gender, and age. Indicator D6 illustrates cancer incidence for each of the 15 most common types of childhood cancer.

Reviewer 2:

The indicator graphs and data tables are an appropriate and understandable summary of the data. It is disappointing that the causation of childhood cancer is not tackled in more detail. Beyond saying the evidence is inconclusive and weak , we should perhaps offer suggestions to policy makers/public to help in interpretation of results…..

For example:

Point out advantages of using the results from pooled analyses for risk assessment; i.e. their larger numbers and the harmonisation of the statistical approach to analyse the data. Looking at individual studies is of little use to evaluate consistency, because individual studies have only few, if any, subjects in the exposure categories that demonstrated an association in the pooled analyses.

Point out that no clear explanation for an observed association between a risk factor and the prevalence of a cancer does not matter; it could arise if the risk factor has a causal role in the development of the disease or, alternatively, it could arise as a result of a statistical artefact

reflecting selection bias, confounding or chance. The probability is often that selection bias alone is not sufficient to explain the entire association, although it is likely to have led to an over-estimation of the observed association.

Point out that lack of effect seen overall in the experimental laboratory studies could in part be due to lack of appropriate models for the complex processes that lead to the development of childhood cancer, for example. This needs to be considered in the context of how little is known about the development of the disease.

Reviewer 3:

Indicator D5 – 1) suggest adding a footnote about the spatial representation of these data – e.g. a subset of US population sample.

Pg. 7 – line 8-11 bullet 2 – the issue of gender differences is seen overall, but when you look at gender differences by race/ethnicity for Black – there is no gender difference, for American Indians the gender difference are not seen. I think it is worth noting that gender differences are not consistent between racial groups particularly since the next bullet describes these.

Pg. 8 – how "representative" are the racial and ethnic minority groups of the nation as a whole in the SEER population?

Pg. 8- age is important – there are differences in the types of cancer by age which has a significant relationship to different childhood cancer etiologies and windows of vulnerability from exposure – perhaps something to be included in the discussion as well.

Indicator D6 – the final bullet on page 10, line 13 – this seems out of place here and could be important contextual information to include in the indicator "topic" discussion.

Question 4 – Context and Utility

Reviewer 1:

For each indicator, please comment on whether the text appropriately and objectively reflects the strengths and limitations of existing knowledge regarding relationships between environmental conditions and children's health that are relevant to the topic.

--The text for indicators D5 and D6 clearly and objectively reflect the knowledge regarding childhood cancer incidence and mortality in the US. Important environmental conditions that are associated with the childhood cancer risk are described objectively in the text.

For each indicator, please comment its utility and appropriateness addressing the three principal objectives of ACE:

to presents concrete, quantifiable indicators of key factors relevant to the environment and children in the United States. These indicators are designed to offer a basis for understanding time trends for some factors and for further investigation of others.

-- Childhood cancer is one of the major causes of death in children. Indicator D5 presents the incidence and mortality of cancer for children age 0-19 from 1992 to 2007. Indicator D5 offers a clear base for understanding time trends of incidence and mortality for childhood cancer. As indicated in the text, there is a significant increasing trend in the incidence of childhood cancer in the US from 1992 to 2007. However, it is not clear if any environmental factors were responsible for this increase. The incidences of each type of cancer are clearly summarized in indicator D6, which offers an objective base for understanding the time trend for each type of childhood cancer incidence from 1992 to 2007.

to inform discussions among policymakers and the public about how to improve federal data on children and the environment.

--Childhood cancer is one of the major causes for death in children in the US. Indicators D5 and D6 clearly demonstrate the scale and increasing severity of childhood cancer. These indicators inform policymakers and the public the impact of childhood cancer on children's health in the US.

to provide indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children.

-- Indicator D5 and D6 can be used conveniently by policymakers and the public to track childhood cancer and provide an objective base for evaluating the potential impacts of environmental factors on childhood cancer risk.

Reviewer 2:

This is really the crux of the whole document: Does it offer a basis for understanding the time trends? Not really, no.

Does it inform discussions among policy makers and the public? Not enough.

Does it provide indicators that can be used by policymakers and public to understand potential impacts of environmental contaminants on children's health and to identify ways to minimize this? No

As mentioned previously, there is no single cause for childhood leukemia and for most individuals a combination of factors appears to be necessary; all involving gene-environment interactions. If a study may have missed a true effect, the reader needs to understand why this may be.

For example, Topical issues are things like mobile phones and cancer in children. A single linked case-control study by Elliott and colleagues, assessed whether proximity to masts during pregnancy raises the risk of children developing leukemia or a tumour in the brain or central nervous system. The study identified 1397 British children registered with leukemia or a tumour in the brain or central nervous system between 1999 and 2001, and it compared each of these children with four controls sampled from the national birth registers who were matched for sex and date of birth. The study found no association between the risk of cancer in early childhood and exposure to a mobile phone base station during pregnancy.

What are the limitations of this study? The first, and probably the most important, is the size of the study. Elliott and colleagues' study is the first to look at phone masts in Britain as a whole and is the

largest of its kind. The study would have had a greater than 90% probability of detecting a doubled risk of brain cancer between the 85th and 15th percentiles of modeled power density; for childhood leukemia (which has a higher incidence) the figure is over 99%.

Secondly, the exposure variables considered may be inadequate surrogates for the true exposure we would ideally measure. Any methodology that permits the measurement of individual exposures would be scientifically valuable.

The third possible reason is case-control bias, but the use of register data largely eliminates this. Lastly, we have the universal epidemiological problem of confounding. The authors adjusted for certain demographic variables, specifically socioeconomic status and population mixing, both of which have been associated with childhood leukemia.

To date few clear preventative measures have emerged, except the complete avoidance of first trimester X-rays in pregnancy; a healthy diet with adequate oral folic acid intake both preconception and early in pregnancy; and the early exposure of children to other children outside the home to facilitate stimulation and maturation of the natural immune system. None of this is mentioned more than in passing in the report.

There are 14 Centers for Children's Environmental Health and Disease Prevention Research supported by the US National Institutes of Health and the US Environmental Protection Agency; a global network of Pediatric Environmental Health Specialty Units supported by the US Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry; new postdoctoral training programs in pediatric environmental medicine; and the National Children's Study, the largest prospective epidemiological study of children's health ever undertaken in the United States, which launched in 2009 and will follow 100,000 children from conception to age 21 to assess environmental influences on health and development. These research initiatives have delineated the exquisite vulnerability of fetuses, infants, and children to toxic hazards in the environment. They have led to discovery of new environmental causes of disease and disability in children. Surely this review should be able to say more about this to the lay public and to the policy makers.

Reviewer 3:

these indicators show important temporal trends in childhood cancers over time

if these are the only reliable childhood cancer data a section on limitations of data availability for studying chidhood cancer nationally is needed.

More emphasis on what is unknown about childhood cancer and what these patterns of uncertainty mean and/or what can't be said is needed to provide policy makers with the evidence they need to increase support of environmental contributions to childhood cancer. Policy makers also need to be aware of the challenges faced by environmental epidemiologists in conducting these epidemiologic investigations. Also needed is better risk assessment data to support a list of carcinogens that impact young children….none of this is included in the indicator discussion or background…. How will this be included if at all?

I think having a discussion on regional variations in cancer incidence would be useful, having only temporal trends by gender, age, race/ethinicity limits the utility of these indicators. Understanding that nationally, state cancer registries are variable in their quality, I think it would still be useful to

see if any type of state/regional analyses could be provided or if not a discussion of why only SEER and not something else would add to this.

Question 5 – Documentation

Reviewer 1:

Is the documentation complete and transparent?
--Yes.

Reviewer 2:

The document is transparent but as already outlined above, it feels a little incomplete to me.

Reviewer 3:

Yes- with the exception of the race/ethnicity data---data on race/ethnicity are presented and yet the metadata states "Cancer mortality data has significant percentages of persons with unknown ethnicity in a few states"….how is this accounted for in the analyses?

Pg 23 – the example column (6) – the text explains this but it is not clear from the table at the outset how this "proportion" is calculated, it is once you read the text but may want to add a footnote.

REFERENCES:
Smith, M.T. Advances in understanding benzene health effects and susceptibility. *Annu Rev Public Health* **31**, 133-148 132 p following 148 (2010).

Holland, N., Fucic, A., Merlo, D.F., Sram, R. & Kirsch-Volders, M. Micronuclei in neonates and children: effects of environmental, genetic, demographic and disease variables. *Mutagenesis* **26**, 51-56 (2011).

Van Maele-Fabry, G., Lantin, A.C., Hoet, P. & Lison, D. Residential exposure to pesticides and childhood leukaemia: a systematic review and meta-analysis. *Environ Int* **37**, 280-291 (2011).

Turner, M.C., Wigle, D.T. & Krewski, D. Residential pesticides and childhood leukemia: a systematic review and meta-analysis. *Environ Health Perspect* **118**, 33-41 (2010).

3.3 Neurodevelopmental Effects

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Lucio Costa
- Bruce Lanphear
- Leslie Rubin

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

The introductory section summarizes the most relevant information on four major neurodevelopmental disorders, namely attention/deficit hyperactivity disorder (ADHD), learning disability, autism spectrum disorders, and mental retardation. While most, if not all, emphasis is on environmental pollutants, it should be emphasized that a causal link between exposure and neurodevelopmental disorder has been established to a satisfactory degree of certainty only in case of ethanol and perhaps some drugs. For most other chemicals, only suggestive, though important, associations have been reported. For ADHD, there is also a body of literature on food colors/additives that may be mentioned as it permeates the literature, even with a critical comment. For autism and thymerosal, it may be mentioned that the major, original study linking vaccination to this disorder, has been recently retracted. This section is well documented, and provides a large number of pertinent references.

Reviewer 2:

No, the text was very poorly written and does adequately describe neurobehavioral conditions. It needs to be rewritten and extensively edited. The text often reads like a laundry list and doesn't adequately describe the toxicants that have been examined to a much greater extent than other chemicals or suspected toxicants.

On the other hand, the relevant literature is adequately cited. One additional behavioral problem associated with childhood lead exposure and prenatal tobacco exposure that deserves to be described is antisocial behaviors. This was done reasonably well in the document on lead, but it is relevant to at least describe it here and cite the lead section.

There are a few paragraphs that need to be re-organized (see attached pdf with comments). For example, I would describe the prevalence of the various neurobehavioral conditions after the initial definitions and then describe the environmental toxicants that are associated with them.

Ideally, and most relevant to the US EPA, the document should describe what regulatory efforts have been instituted to reduce exposures to environmental toxicants associated with neurodevelopmental disabilities. The report could either show the decline in blood lead levels and active smoking in women or refer to other relevant sections of the report.

Reviewer 3:

There are 2 areas in the domain of neurodevelopmental disabilities that are not adequately covered: sensory impairments, especially vision and hearing, as well as mention of sensory integration disorder, and the motor disorders characterized by cerebral palsy. It may be conjectured that cerebral palsy represents a more discreet and situational condition caused by birth asphyxia or birth trauma but today many children with cerebral palsy are born prematurely or of low birth weight. Furthermore, there is no much discussion on prematurity which is a significant birth outcome or adverse factors operating during pregnancy and not only are the adverse environmental factors causing the prematurity but the prematurity renders the infant vulnerable to other adverse environmental factors that might not have as significant a consequence if the infant is born at term and resilient.

Another important area that is not sufficiently addressed is the area of social and economic factors that operate at all levels and at all times directly and at times indirectly. The data glaringly show that there is an economic (se poverty) and social (see racial disparities) determinant to outcomes. Although there is mention, it is not confronted directly. The direct factors that operate e.g. with lead reflect that poorer people tend to live in houses that are more likely to be old and have lead contamination, but they do not point out to a sufficient degree that there are other indirect factors in the neighborhoods that adversely affect children's health, e.g. proximity to superfund sites and indirectly the violence and absence of green space. Although this is not directly related to environmental causes of neurodevelopmental conditions in children, the quality of schools plays a significant part in the identification and remediation of learning and other disabilities in children. Poorer children go to schools that are less likely to identify and remediate the children and therefore the children are more likely to fail, to drop out, fill the ranks of the unemployed and perpetuate the cycle of environmental health disparities and disadvantage and disability.

If indeed we are talking about the environment and neurodevelopmental disabilities we need to recognize that not only are neurodevelopmental disabilities caused by environmental factors but the environment can also play a part in early identification and remediation through appropriate screening and early detection with early intervention and education. The CDC has identified this as a priority in the case of Autism where there is a major national campaign called "Learn the Signs – Act Early". So, if the CDC has identified this as a public health priority it deserves mention in a forward thinking document such as the ACE 3rd Edition. I would want the ACE to take the data of the past and demonstrate what action there needs to be taken to assure healthier environments for children, not only in the present, but more so in the future.

Although this may not be in the radar of environmental factors, television watching, fast foods and violent videogames are serious environmental factors that affect the learning, behavior and socialization of children today especially ADHD.

I would also like to suggest that there be a stronger statement about epigenetic principles and patterns because although it is easy to draw a straight line in cause and effect between the presence of lead and neurodevelopmental outcomes, it may be less difficult to make cases for man of the other factors that are mentioned and discussed in the text. The field of epigenetics is still in its infancy but consideration should be given to a better description and discussion as an important operating principle, the relevance of which that will become reveled in the future. Here again is the opportunity for the section and the ACE 3rd edition in general to not only stat what we know now, but look at the important avant guarde areas that will become sections in the ACE 4th edition.

After all, the brain of a fetus and infant is most vulnerable to environmental factors be they chemical, physical psychological or social and the environmental factors can not only cause damage resulting in disorders, but can also provide healing and nourishment and nurturing to reverse damage and to promote optimal function and realization of full functioning potential.

While the data represent what we have learned and what we know, this introductory section should challenge us to take what we have learned and what we know to apply our knowledge to develop new knowledge and new strategies to understand the impact t of the environment of the growth health and well-being of children.

Question 2 – Indicator Text

Reviewer 1:

The introduction to this section is straightforward. It is stated that NHIS data may "underestimate" the prevalence of neurodevelopmental disorders. This would need to be better substantiated, since the numbers presented are already high. It should also be indicated whether the same child may have more than one diagnosis. Otherwise, a superficial look at the data would lead to the conclusion that about 25% (1 out of 4) of American children have some kind of neurodevelopmental disorder, a frightening perspective for the future of this country.

Reviewer 2:

Similar to the lead epidemiology section, there is actually TOO MUCH information about NHIS methodology and how the data were analyzed. The vast majority of people – I would reckon 99.9% of readers – will actually be discouraged from reading the report because there is too much attention to the methodology.

The text to describe the data set and the indicator should be no longer than one page.

Reviewer 3:

The indicator text is good.

Question 3 – Indicator Presentation

Reviewer 1:

Four indicators are presented corresponding to the four neurodevelopmental disorders indicated above. Data are shown as graphs and Tables. Data for each gender for the period 1997-2008 are presented. Additional Tables present data for the period 2005-2008 by children's age, and data by race/ethnicity.

Data of ADHD for boys (Fig ND1 and Table ND1) are somewhat strange, as they appear to suspiciously "zig-zag" year after year. The bullet-points under the graphs summarize the main findings. Why are data for boys and girls not indicated in graph ND4?

Reviewer 2:

No, the tables showing trends in ADHD and other neurodevelopmental disabilities should be shifted to graphics to more visually show the trends. The tables are clumsy, at best. The tables in which most of the cells are insufficient should simply be deleted. The description of the various neurobehavioral outcomes needs to be revised, especially ASD (see attached comments).

Reviewer 3:

The presentations are good and quite straight forward and easy to follow and think about.

Question 4 – Context and Utility

Reviewer 1:

Some interpretation/comment on the indicators would be useful. For example, the higher incidence of learning disabilities among American Indians may be due to alcohol consumption (Table ND2b). In this respect it is unfortunate that data on mental retardation are not reported for this group (Table ND4b).

Reviewer 2:

I would recommend that you dedicate at least one paragraph to lead and another to prenatal tobacco exposure to review the literature on their association with ADHD. Both have been extensively studied and deserve additional mention than the laundry listing for other toxicants with one or two studies. I would also provide estimates for the population attributable risk for lead, tobacco or either lead or tobacco. (It is >30%, which is considerable). Some may argue that this doesn't account for genetic risk factors, but that is a bit silly because if you remove the environmental "causes" then "genetic susceptibility ceases to matter", right? (This is based on Geoffrey Rose's book, A Strategy for Prevention.

There should also be a discussion about the limitations of the research linking environmental toxicants with ADHD. In addition to the usual suspects (e.g., unmeasured confounders), there

should be specific mention that most – but not all – studies failed to adjust for parental psychopathology.

For each indicator, please comment its utility and appropriateness addressing the three principal objectives of ACE:

a) to presents concrete, quantifiable indicators of key factors relevant to the environment and children in the United States. These indicators are designed to offer a basis for understanding time trends for some factors and for further investigation of others.

The key factors have not been adequately described. The focus is primarily on neurodevelopmental problems, but the focus should ultimately be on the exposures and regulations related to those exposures in an US EPA report.

b) to inform discussions among policymakers and the public about how to improve federal data on children and the environment.

In addition to describing the neurobehavioral endpoints, this document should also describe the status of exposure and regulations for the putative risk factors.

c) to provide indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children.

See comment above. Ultimately, US EPA should emphasize the major sources of exposures in addition to neurodevelopment endpoints because policymakers must rely on exposure measurements to continue to reduce children's blood lead levels.

Reviewer 3:

They definitely present the rends

They do indeed inform discussions

They are significant enough to use for policy planning

Question 5 – Documentation

Reviewer 1:

The methodology is exhaustively presented, and would be useful to the specialist, less to the generic reader.

Reviewer 2:

See comments above and attached pdf.

Reviewer 3:

The documentation is good. A little heavy in parts and lighter in other parts but easy to identify in relation to the text.

3.4 Obesity

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- John Meeker
- John Roberts
- Catherine Yeckel

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

Overall Impressions: Health/Childhood Obesity
It is wonderful that childhood obesity is being presented in this edition of ACE. It is the perfect opportunity to introduce this topic to the EPA community.

Suggest EPA consider childhood obesity by Rural versus Urban status under this topic.
I was surprised by the choice of poverty level. Poverty is of course important, but I would argue that the rural vs. urban is more relevant for EPA based on primary readership, which is coming from an exposure perspective. It also follows more closely, and logically to the topic text. Note: I do not mean provide the geographical summary that the CDC has used for many years to showcase the growing prevalence of obesity.

Work published for at least 10 years indicate a higher prevalence of obesity in children living in rural versus urban environments. Some recent reports use the NHANES data, e.g., These data use USDA based urban influence codes (UCI) to assign residences status for analysis. This topic is beginning to get a lot of traction around the world. Besides the potential for environment based on diet and physical activity, etc., unexplained differences leave open the question of potential environmental exposure. The topic of exposures such as chemicals etc. is brought up briefly in this draft introduction on obesity, as is the topic of the "built environment," but these factors don't lead into what has been chosen for the current indicators. I believe the EPA has an important role to play in evaluating and monitoring environmental factors that may contribute to childhood obesity. At this nascent level, both rural and urban living may hold distinct risk factors that require environmental action to protect children. However, we are far from understanding these factors. Bringing in rural and urban differences, and esp. trend data could stimulate hypotheses from EPA's large exposure-based audience.

Question 1 – Topic Text

Reviewer 1:

Overall the topic text seems appropriate and clear for its intended use. A nice discussion of why obesity is an important public health issue, how obesity is defined (and inherent limitations in that definition), known risk factors for obesity such as diet and exercise, and the growing hypothesis surrounding "obsesogens" are included. In addition, mention of the built environment is included which is highly relevant to the overall report on children and the environment and likely a risk factor for obesity as well.

Reviewer 2:

(Please note that throughout, I have grouped the 3 questions above in bold together in my responses, as I think it is hard not to describe an additional topic without immediately commenting on the references you included and suggesting other references)

Appropriately and clearly describe topic: Overall I think this entire document and the topic text in particular is well written and clear. It appropriately cites the CDC growth charts, and also comments on the difficulty with BMI as a measure in terms of muscle mass. While acknowledging the limitation, you also make the point that BMI is probably the best we have.
Additional aspects of topic's importance for children's environmental health/ relevant literature summarized:

Page 1, line 9-10—this is fairly controversial, and at least one study by the same group of authors as reference 24 found early breast development and no relation to obesity. (in their analysis, BMI did not affect the age at onset of pubertal development (in this case breast development). Interestingly, the does make the point that other environmental chemicals may play a role in pubertal development. I realize this is about obesity and not pubertal development, I think in general I would probably revise lines 9-10 into perhaps 2 sentences, more clearly acknowledging the weakness of the literature or even controversy in the literature about this, as otherwise as stated, the reader may think the line between onset of puberty and obesity is better defined than it is. (**Aksglaede A 2009; this is a different article by the same author you have cited**).

Also in lines 9-10—this would be an appropriate place to discuss the importance of assessing pubertal development through palpation, not observation. (**Herman-Giddens et al 1997**)

Page 1, Lines 36-38—I think this sentence is a bit of a stretch. Not sure I have any better reference—but I think I am more uncomfortable with the fact that throughout this document you routinely include 2-3 references per fact, this only has one reference.

Page 2, Lines 40-46—The AAP has a policy statement on the built environment that should probably briefly summarized here. (reference at the end of this review)

Page 3, lines 1-11, It would probably fit well in this section to discuss some of the papers that describe a "green environment" with general child well-being and greater activity. You kind of describe a little of this with lines 8,9; but I think it can be expanded upon. Authors from the National Environmental Education Foundation summarized the evidence on outdoor play and natural environments may have a positive impact on health and well-being, obesity included.

(**Winterbottom K, 2010 listed at the end of this review**—and/or this reference may supply you with some primary references.)

Lacking items:
The AAP has a policy statement (Section on Sports Medicine) that discusses the importance of physical activity.

Also, there is a lacking of a discussion of screen time and hand held video games.

Unfortunately there is a lack of evidence that attempting to reduce screen time in children has so far been unsuccessful.

Ways to make text more understandable: As mentioned, I believe it is already concise and well written. Perhaps revising some of the items suggested above will help with the understandability as well.

Reviewer 3:

Obesity introduction:
1st paragraph is a bit awkward because it is merging the definition of obesity with health-risk. I would recommend splitting the topic by subheadings (see below). I think this would help the EPA audience to understand (right from the outset) that determining obesity in children is not simply calculating BMI. It also makes it clear that the initial paragraphs are simply setting the definition. The second, public health section provides substantial NHNANES and large population-based information regarding childhood obesity. The third, environmental section is the area that is still lacking in research so should be enticing to the EPA audience and provide a stimulus for innovative research, but it should also make clear the rationale for the choice of EPA indicators, which presently is lacking in this draft.

Suggested revision (something like) —Please note I have cut-n-pasted from the document to allow easier re-organization, review, and revisions

Definition of Childhood Obesity
Obesity is the term used to indicate the high degree of body weight for a given height of an individual. Definitions of overweight and obesity for adults are based on set cutoff points directly related to an individual's body mass index. Body mass index (BMI) is calculated as the body weight in kilograms divided by height in meters squared. Essential to this definition is that a high degree of body weight be associated with a large amount of body fat. In children and adolescents, BMI varies with age and sex more than it does in adults. Thus the designation of a child or adolescent (ages 2 to 19 years) as either overweight or obese is based on comparing his or her BMI to a sex- and age-specific reference population (the CDC growth charts). Children and adolescents between the 85th and 94th percentiles of BMI-for-age are considered overweight; those greater than or equal to the 95th percentile are considered obese. The percentiles used to identify children as overweight or obese are fixed, and based on data collected from 1963–1980 (or, for children ages 2 to 6 years, data from 1963–1994).[1,40,]

The prevalence of excessive body weight in the United States population has been increasing for several decades, though it has stabilized over the last several years.[36-39] BMI is the most common

screening measure used to determine whether an individual may be overweight or obese. However, BMI does not measure body fat directly, but is used as a surrogate measure since it correlates with direct measures of body fat, especially at high BMI levels, and is inexpensive and easy to obtain in a clinical setting. The significance of a child being overweight is complicated by the BMI's inability to distinguish between differences in mass due to muscle or due to the unhealthy accumulation of fatty tissue. A recent study found that less than half of "overweight" children had excess body fat, and that there are differences among race/ethnicity groups in the amount of body fat for a given BMI in children.[42] Among children with an elevated BMI, some may have excess body fat, and others may be incorrectly identified as overweight because they have a higher amount of mass attributed to nonfatty tissue. Despite the limitations imposed by measuring the BMI, a rise in the prevalence of overweight children is cause for public health concern.

— grouping these sections under an obesity definition subheading will allow a smoother transition into the health concerns of obesity.

Public Health Concerns over Childhood Obesity
(see some suggested rewording and additional references from lines 3-10 on pg 1)
Obesity has rapidly become a serious public health concern in the United States. It is associated with adverse health effects in childhood, including psychological stress, insulin resistance [2], hypertension, dyslipidemia, asthma, pre-diabetes [3], and type 2 diabetes. Obesity has also been implicated in the timing of the onset of puberty and early menarche in girls, though the extent to which the obesity epidemic contributes to early puberty is unclear. Obesity in childhood increases the risk of obesity in adulthood [4]. The cumulative exposure of excess weight over the lifetime [5] will likely increase the public health burden associated with type 2 diabetes [6], cardiovascular disease[7], and cancer.

Metabolic syndrome has been identified in obese children and adolescents, and studies suggest a developmental origin of the condition.[30-32] Metabolic syndrome is a cluster of adverse health effects (obesity, hypertension, dyslipidemia, and other metabolic abnormalities) that may have a common biological mechanism. While the clinical utility of a diagnosis of metabolic syndrome is debated in the medical literature,[27-29] prospective data demonstrate the relevance to health-risk of metabolic syndrome in obese children for both type 2 diabetes [6], cardiovascular disease[7]
Moreover, the consideration of obesity and metabolic effects as a group is supported by findings of an environmental exposure nature. Given these relationships, obesity and other health conditions related to metabolism are discussed below.

line 13 replace "insulin resistance" with dyslipidemia
— insulin resistance is thought to underlie the pathophysiology of metabolic syndrome, but it is not part of the clinical parameters measured.

—Note, the current use of "elevated lipids" is incorrect. HDL cholesterol goes the opposite direction from total Cholesterol, LDL, and triglycerides. Suggest term like, "dyslipidemia"
—Note, there is nothing raised about the race/ethnic disparity in the health concerns of obesity.

Emerging Environmental Exposure Perspective for Obesity
Obesity is primarily due to an imbalance between caloric intake and activity. Increased caloric intake and reduced physical activity are likely the major drivers of obesity in children, but there is increasing recognition of the possible roles of certain environmental chemical exposures. These chemicals, which are referred to as obesogens, are thought to be capable of disrupting the human body's regulation of metabolism and the accumulation of fatty tissue.[45] Some chemicals have also

been associated with obesity and diabetes. Early-life exposure to certain organophosphate pesticides in laboratory animals was shown to disrupt adult lipid metabolism, induce weight gain, and cause other metabolic responses that mimic those seen in obesity and type 2 diabetes.[33-35] Type 2 diabetes results from the inability of the hormone insulin to regulate blood sugar levels in response to dietary intake. Excess body weight is a risk factor for Type 2 diabetes. Type 2 diabetes is positively associated with the increasing rates of obesity in the U.S. population.[46] In the past, Type 2 diabetes has been diagnosed almost exclusively in adult populations, but it is now being diagnosed in youth—although with low prevalence (0.25%).[46-49] The clinical state of prediabetes, however, is prevalent in obese youth[3]

While the relative contribution of chemical exposures to obesity is not clear, a growing number of animal and cellular studies provide evidence that environmental chemical exposures may be contributing to the increase in obesity, as well as rates of diabetes. Data supporting associations between chemical exposures and obesity in children are still limited. A recent study identified an association between prenatal hexachlorobenzene exposure and increased BMI and weight in children at 6.5 years.[50] Another recent study identified an association between prenatal exposure to polychlorinated biphenyls (PCBs) and DDE (the primary metabolite of the pesticide DDT) with increased BMI during early childhood.[51] In adults, PCBs and dioxins have both been associated with the occurrence of diabetes.[52,53] Organochlorine and organophosphate pesticides have also been associated with an increased risk of diabetes in adults.[54] Several animal and cellular studies suggest that endocrine-disrupting chemicals (including bisphenol A, diethylstilbestrol, and tributyltin) may contribute to increased weight and diabetes.[55-59]

Air pollution has also been associated with obesity and diabetes. In one recent study, adult mice fed a high-fat diet and exposed to particulate air pollution ($PM_{2.5}$) experienced an increase in blood glucose levels and insulin resistance, which are precursors of diabetes.[60] Other studies in animals and children demonstrate that obesity may result in greater susceptibility to the adverse effects of airborne pollutants such as $PM_{2.5}$ and ozone, including airway inflammation, cardiovascular effects, and increased deposition of particles in the lungs.[18,61,62] Air pollution may increase the prevalence of childhood obesity by limiting the number of days when air quality is appropriate for outdoor recreational activity, particularly in children with pre-existing respiratory conditions such as wheeze and asthma.[63]

Other environmental factors are thought to contribute to the increasing rates of overweight and obesity seen in the U.S. population. The term "built environment" is used to describe the physical elements of the environment for a population.[64,65] Several properties of the built environment have relationships with overweight and obesity and/or levels of physical activity in children, including the level of urbanization, the level of safety in the neighborhood, the extent of urban sprawl, the density of housing in an environment, the distance to fast food restaurants, and the distance to playgrounds and/or green space.[64-69] The relationship between characteristics of the built environment and obesity is likely more significant in children than adults, because children are less able to leave their local environment without the help of an adult.[70,71] Built environments that promote exercise through the inclusion of nearby recreational areas and walkable communities, and those that provide healthy eating options through reducing the number of fast food restaurants while providing access to fresh produce, are thought to reduce the frequency of obesity in

children.[64,65] Factors contributing to the prevalence of obesity may differ among environments. Socioeconomically disadvantaged populations are more likely to be located in built environments with characteristics that promote lifestyles that increase rates of obesity in children.[72-74] However, a child living in a suburban community with a higher socioeconomic status may spend greater amounts of time commuting in a car rather than walking, which may also contribute to a sedentary lifestyle that promotes obesity.[75,76]

The following indicators present data for obesity rates in the U.S. child population. The first indicator shows the prevalence of obesity among children ages 2 to 17 years from 1976–2008. The second indicator presents the prevalence of obesity by race/ethnicity and family income in 2005–2008.

Note, if the Rural vs. Urban is taken under consideration… it fits in very nicely into this discussion. Obviously, there are strong differences in air pollution and chemical exposures between urban and rural settings. The "built environment" topic also has distinct challenges based on urban vs. rural, which is touched upon in the introduction.
Only at the end, is the topic of socioeconomic status raised, but it seems one step removed in the logic that is created in the other parts of the Introduction. Likewise, Race/ethnicity is not really mentioned, except in the context of potential methodological issues. There factors make up OBS2 so they really require a rationale.
Therefore, if rural versus urban status were added the whole Topic Intro would flow better. Poverty level could be presented last:
Trend over time
Trend by race/ethnicity
Trend (or current status) by rural and urban… but trend would be very interesting
Trend (or current status) by poverty level

—Framing the document in this manner would provide a very unique twist to the EPA presentation that is distinct from the CDC. It would also provide an excellent foundation for tracking and monitoring environmental exposure concerns for childhood obesity related to potential changes in, e.g, air pollution standards, pesticide application, or factory emission laws. In addition to changes in policy related to built environments and to diet and exercise interventions.

Suggested additional referenes (blue high-lighted in text)

Davis AM, Bennett KJ, Befort C, Nollen N. Obesity and Related Health Behaviors Among Urban and Rural Children in the United States: Data from the National Health and Nutrition Examination Survey 2003-2004 and 2005-2006. Journal of pediatric psychology 2011.

Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. Diabetes Care 2006;29(11):2427-32.

Li C, Ford ES, Zhao G, Mokdad AH. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among U.S. adolescents: National Health and Nutrition Examination Survey 2005-2006. Diabetes Care 2009;32(2):342-7.

The NS, Suchindran C, North KE, Popkin BM, Gordon-Larsen P. Association of adolescent obesity with risk of severe obesity in adulthood. Jama 2010;304(18):2042-7.

Lee JM, Pilli S, Gebremariam A, Keirns CC, Davis MM, Vijan S, Freed GL, Herman WH, Gurney JG. Getting heavier, younger: trajectories of obesity over the life course. Int J Obes (Lond) 2010;34(4):614-23.

Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic Syndrome in Childhood Predicts Adult Metabolic Syndrome and Type 2 Diabetes Mellitus 25 to 30 Years Later. J Pediatr 2008;152(2):201-

Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. Pediatrics 2007;120(2):340-5.

Stewart ST, Cutler DM, Rosen AB. Forecasting the effects of obesity and smoking on U.S. life expectancy. N Engl J Med 2009;361(23):2252-60.

Question 2 – Indicator Text

Reviewer 1:

The indicator text overall provides sufficient information. One point of uncertainty though is whether the 2000 CDC growth charts were derived from populations with similar distributions for race/ethnicity and income as the NHANES populations. If these populations did not have similar distributions for these variables it seems as though this could be problematic. Thus, I think it may be appropriate to include a more indepth description of the 2000 CDC growth charts.

Reviewer 2:

Response to Questions:
Does the indicator text provide sufficient information about the data set, etc:
Three things I found unclear—
When I read the Indicator in bold and even the paragraph in the overview, I was immediately looking for the percentage. I realize you are presenting the actual prevalence in the next section—" indicator presentation". However, I think it would be a little more clear if you said: " Indicator OBS1 shows the trend in obesity prevalence from 1976-2008, changing from x% to y%. Indicator OBS2 presents comparisons of ……. changing from x % to y%. Complete data on these indicators to follow." This is just my opinion, but as I mentioned, in response to your question, I was really looking for the result right up front. Perhaps that is the researcher in me.

The other thing I found unclear is that I don't understand by Indicator OBS2 was only looked at from 2005-2008. It is a data issue? An arbitrary decision? I think you could be clearer as to the reasoning for the choice of years for this indicator.

On the slide Indicator OBS2—by "all incomes" do you really mean "all children?" would that be a better way of saying it than all incomes, since children don't really have incomes, it is their family?

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge?

The two graphs are fairly clear. I would suggest putting the small title (Indicator OBS1) in larger font and centered. (It took me a few seconds f flipping back and forth that the graph was your indicator—not a really long time, but I think the title position/size would help a little).

I would suggest putting the last of the 4 sentences in the solid bullet into its own bullet. (i.e. "However, between 1999-2000….. was observed" as its own solid bullet. It really says something different than the rest).

Consider including p values in the text here. While I understand you are trying to get it down to a lay audience, since it is really for all audiences, I think it would be ok to include the p values here so the other part of your stated audience (researchers, government officials, medical doctors and nurses) can quickly find what they are looking for without needing to scroll through the complicated methods section you have online. They can always go to that for more info if they need to.

Third text bullet on Indicator OBS2, I would suggest using the word "controlling" rather than "accounting"—"When controlling for differences by…" It is the proper statistical term, and that should still be clear enough for the lay audience

Reviewer 3:

The text is generally clear and straightforward.

Suggested revisions:
Line 8. Replace "These indicators" at the beginning of the sentence with OBS1 and OBS2 indicators use….."

Line 15. Determination of obesity in children, like adults, is based on the calculation of body mass index (BMI), which is correlated with body fat. In children, however, it is also necessary for BMI estimates to take into account age and sex. First, the BMI is calculated by….. Second, for children….

Question 3 – Indicator Presentation

Reviewer 1:

I think the graph, bullet points, and data tables were well-organized, and the comparisons that were made statistically seem appropriate. Was the inclusion of sample size in the main figures considered? Other than that, the figures and bullet points seem simple and relatively straight-forward. They are presented in a manner that should be interpretable by multiple audiences.

Reviewer 2:

Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data? Overall, I really like the tables, and I could see how I would use them.

Are there ways in which the presentation and description of the indicator values could be improved? Yes, again consider the use of p values in the table. I know that you have the information in the methods section, which would be available on line. However, the parts in the methods section are very complex too.

Where I am specifically referring to is the % listed for All races/ethnicities and White non-Hispanic, under the columns 1999-2000 and 2007-2008. Simply eyeballing the numbers, the difference between 13.8% and 16.9% looks significant, as does the difference between 10.5% and 15.4% for Whites. Yet, when I went to the larger tables, it looks like the p values were 0.078 and 0.084. So close, but not quite significant, at least by the .05 standard. All the others were nowhere close. If possible, it might be worth including at least the comparison p values from 1999-2000 to 2007-08. The point here is that in some ways, it almost seems that in the effort to simplify for the lay audience, you took away almost too much level of detail. (the methods are great, but they are very complex, and it seems there should be some intermediate level of detail to please the physicians/nurses without confusing the lay audience.

An alternative to the above suggestion about the p values could be the use of asterisks. One for $p < .05$, another for p values $< .1$, and then others.

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)? See above, I think my responses speaks as much to this question as to the above question.

Please comment on the appropriateness of the comparisons made in the indicator(s) and whether other comparison populations and/or benchmarks may be informative to the public.
I think these are very appropriate comparisons. The only question as to before is to be more clear on why the dates for OBS2 were only from 2005-2008.

Reviewer 3:

General Organization.
Data should be presented in a consistent order. Figure 1 shows the primary trend over time. Therefore, the first table should be this primary trend by age (currently presented as Table OBS1a, second in the order of tables). Figure 2 brings in the race/ethnicity and poverty data. Therefore the second table should be OBS1 (currently 1st), and the last table remains OBS2
In addition, because the tables providing the race/ethnic data have an ALL category, the table OBS1a should also have an ALL ages (2-17 yrs) category placed at the top of the table.

Tables and figures need a consistent format, e.g. if ALL race/ethnic group is presented at the top of the tables, it makes sense to have it at the top of the figure as well.

Figure 1 is clear and attractive.
Re: Bullet points. ***Suggest revising*** the bullet points to separate out significant overall trend.

Between 1976 and 2008, the percentage of children identified as obese has increased. In 1976-1980, 5.4% of children ages 2 to 17 years were obese. This percentage reached a high of 17% in 2007-2008.

Statistical Note: From 1976-2008, the increasing trend in prevalence of obese children was statistically significant for children overall, as well as for children of each age group (Table OBS1a) and race/ethnicity (OBS1).

Between 1999-2000 and 2007-2008, no significant increase in prevalence of childhood obesity was observed.

I have inserted the "age group" as well. These data are featured in a table. However, based on the statistical analysis the table should be revised to reflect the age group 11-17 that was tested. At least my impression from the statistical table is that only categories 2-5yr, 6-10 yrs and 11-17yrs were analyzed.

Figure 2 is clear and attractive. (see note above: ALL category should be at the top of figure)
This figure should be able to stand alone….therefore, I suggest a foot note for what race/ethnic groups comprise "other" , esp. given the strong influence this category has on the poverty results.

First footnote. Text is clear and appropriate

Second footnote. Text is clear and appropriate. Except sentence should read…. "…more likely to be obese than children of the White non-Hispanic, or the "Other" race/ethnic groups."

—"other" in the current sentence is confusing, because "other" is also a category. White is a primary category so should be listed. (White is a different race than Black).

Third footnote.
First sentence is clear and accurate, but a bit misleading.
How much of the population is represented by "other"? —It cannot be very large.
Therefore the conclusion put forth is being based on a minor group.
Suggest revising text.
Among children overall, the prevalence of obesity is greater with family incomes below poverty level than in those above poverty level.
However, the major racial/ethnic groups comprising the US population did not show a significant effect of low family income on childhood obesity. Instead, only the "Other" category of race/ethnicity showed a statistically significant effect, after controlling for race/ethnicity and poverty status.

—The table in the Methods section only has the sample size by year, not any race/ethnic sample sizes. I think these data should be added to the table, or as an additional table. I can see not having the data with this figure to keep presentation simplified, but I think any conclusion for EPA presentation that is based on "other" is worrisome. What is surprising is that poverty status is clearly not a large factor for childhood obesity within the largest racial ethnic groups that comprise our US population.

Question 4 – Context and Utility

Reviewer 1:

The text appropriately and objectively reflects the strengths and limitations in our current knowledge of this indicator. I think this report represents a very important consolidation of national data for a wide range of audiences. These indicators should be highly referenced by researchers and policymakers alike, and should serve as a useful resource for medical

professionals, other various groups, and citizens. While BMI is not a perfect marker for obesity, it does have utility as a population-based indicator of trend as it is used here.

Reviewer 2:

Response to Questions:
a) to present concrete, quantifiable indicators of key factors relevant to the environment and children in the United States. These indicators are designed to offer a basis for understanding time trends for some factors and for further investigation of others.

In the text, you do a nice job of summarizing the various, possible environmental contributors. However, I don't think the data in the indicators themselves are compelling enough to compare to environmental factors. The data and indicators you prsenet are obesity trends, but there is no comparable environmental data. For example, you discuss the potential of early puberty and potential environmental factors. But to discuss this interaction, I think you would really need to present early breast development and how that may or may not be related to obesity trends. The puberty data are not here. Likewise, to compare obesity and other environmental causes, I'd like to see a comparison to measures of inactivity—screen time, lack of exercise, time spent in "green spaces", etc.

(To clarify, I'm not sure if it really needs to be presented, but I am just trying to respond to the question of "key factors relevant to the environment and children"—there are too many other factors related to the environment that aren't presented here. In the context of the entire report, my comment here may be irrelevant).

b) to inform discussions among policymakers and the public about how to improve federal data on children and the environment. I would hope that policy makers would review these data and conclude that we have a serious problem in the US. If there were some places that at least the measures of inactivity or even evidence of endocrine disrupting chemicals were included, it may have an even larger impact. However, I do like the data that you have presented.

c) to provide indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children. Again, I agree that you have provided some great indicators. My above suggestion is still relevant for this question as well.

Reviewer 3:

OBS1 is the most basic indicator. It is very appropriate to present here with respect to all of the goals outlined for ACE.

OBS2 in terms of race/ethnicity is also a basic indicator, and is very appropriate.
However, there is very little in the intro that establishes race/ethnicity as an important indicator.

OBS2 in terms of poverty level— poverty level very important, but in my opinion it is out-of-logical sequence for this presentation by EPA.
My recommendation is for rural vs. urban sub-analysis (discussed above)

Introduction brings in of some of the potential chemical exposures that may impact obesity, including air pollution.
—These topics are largely untouched by research, but they are appropriate here to open dialog and stimulate thinking.

An interesting (framing) topic that is not raised is the issue about obesity negating the heath benefits related to smoking cessation. One EPA issue tackled, only to be replaced with another, potentially more potent one.

Introduction brings in a discussion of diet and physical activity. These of course are gaining the most attention. However, these issues do not link to the indicators being discussed. Yet, these are the areas that have the most traction for policy change. They are being examined based on rural/urban comparisons, so again rural vs urban would be a worthy subindicator.

The topic of childhood obesity under the EPA is at its infancy —which means it is at the opening dialog, stimulating thinking and research stage. A better presentation as to why the specific indicators (OBS1 and 2) were chosen would be helpful. Simply acknowledging that these indicators are intended to establish a firm foundation regarding the basic trends in childhood obesity would help the audience.

Question 5 – Documentation

Reviewer 1:

Yes, the documentation appears to be complete and transparent.

Reviewer 2:

Overall I think it is very complete. A few comments:
P. 15-- The 5th question in the metadata table. I know the laboratory measurements are available, and perhaps for some sections of this overall ACE report are relevant, but no where in the obesity indicators do you use the laboratory measurements or attempt to make any correlations with these levels and child weight. For this particular indicator I don't know that this is so relevant.

The 7th question—I am surprised the individual answers are available to the public. If you are going to include this, I'd suggest adding a link to instructions on how to get it.

P.16—5gth question—data comparable across time and space—this is a supplement to my comments on #1 above, but since you don't have any correlation with the contaminants in NHANES and the obesity indicators, I don't think this row is relevant. I think **what is actually more relevant to this indicator would be the question: Are the methods used to measure weight and height consistent throughout the lifespan of NHANES?**

In the Methods section, starting with page 17, I think it is quite complete. However, there are a few items in here that should probably appear in the published report as well, not just the methods section in the on-line supplemental material. Then you can put the words: "see methods for further info", and put in the link.

P. 20, sentence beginning last part of line 5 and continuing through line 8. This is a great sentence, and while a little complicated it provides a little more information for the researcher and clinician in the published report. Put that in there, and then still keep it in this methods section.

P. 20, two sentences—lines 34-36—should also be in the published report along with the methods. (or consider even lines 34 through 42 (the 5 bullets). But at minimum, the two sentences of lines 34-36.

P. 25—lines 3-16. This section is very complicated, and the info in the published report about statistical comparisons is too simplified. I think at the very least, you should put that "logistic regression was used to test for significance" in your published, summary text.

P 25—line 16, it is not clear to me why you didn't adjust for multiple comparisons. I thought that in some cases, with multiple comparisons some statisticians use a p value of .01 instead of .05? at least explain here why that was not necessary. (if it wasn't).

Other references for your consideration

American Academy of Pediatrics, Committee on Environmental Health. The built environment: Designing communities to promote physical activity in children. Pediatrics 2009;123:1591-8.

Winterbottom K, McCurdy LE, Mehta S, Roberts JR. Using Nature and Outdoor Activity to Improve Children's Health. Current Problems in Pediatric and Adolescent Medicine. 2010;5:102-117.

American Academy of Pediatrics Committee on Sports Medicine and Fitness and Committee on School Health Physical Fitness and Activity in Schools. Pediatrics 2000;105(5)1156-7.

Herman-Giddens et al. Pediatrics 1997;99:505-12 Secondary sexual characteristics and menses in young girls seen in office practice

Aksglaede A, Sorenson K, Petersen JH, Shakkebaek NE and Juul A. 2009. Recent decline in age at breast development: The Copenhagen Puberty Study. Pediatrics 123: e932-9.

American Academy of Pediatrics Committee on Public Education Children, Adolescents, and Television Pediatrics 2001;107(2):423-6. (this one and the other AAP policy statement were re-affirmed).

Roberts JR, Kennedy SA, Basco WT, Darden PM. Prevalence of Obesity in Children: Comparing Children from the South Carolina Pediatric Practice Research Network to a National Sample. Clinical Pediatrics 2010;49:750-5. (measured weights/ heights better than self reported weight/height).

Cook S, et al. Growth Curves for Cardio-Metabolic Risk Factors in Children and Adolescents. J Pediatrics 2009;155:S6.e15-26. (Interesting article that creates a growth curve for risk factors such as LDL cholesterol levels, waist circumference, etc).

Elobeid MA, and Allison DB. Putative environmental-endocrine disruptors and obesity: a review. Current Opinion in Endocrinology, Diabetes & Obesity 2008, 15:403–408
(This is a good review article, although I do see that you already have some of the good primary references such as the Hugo 2008 article on bisphenol A, and Newbold 2007.)

Might consider the Stahlhut article below—I realize it is about adult males, but you are specifically looking at environmental chemicals, so it might be worth consideration, (what starts out in kids often may continue into adult hood, for good or bad):

Stahlhut RW, van Wijngaarden E, Dye TD, et al. Concentrations of Urinary Phthalate Metabolites Are Associated with Increased Waist Circumference and Insulin Resistance in Adult U.S. Males Environ Health Perspect 115:876–882 (2007).

Nicklas TA et al. Association between 100% juice consumption and nutrient intake and weight of children aged 2-11 years. Arch Pediatric Adol Med 2008;162:557-64.

O'Connor TM, et al. Beverage intake among preschool children and its effect on weight status. Pediatrics 2006;118:e1010-18.

Reviewer 3:

See topic text section for additional suggested references.

Appendix materials
The documentation is well done and appropriate for the audience, esp. given that it will be in an appendix format.

Methods Section: Data Summary Table page 17
Sample numbers like those appearing in this table of the methods section, should also be presented for each category of race/ethnicity group (additional table, or expanded existing table).
—This revision is important due to the poverty results. Also as indicated on pg. 20 Blacks and Mexican-Americans were intentionally oversampled making the "Other" category a bit worrisome.

Calculations of Indicator
Page 23
Given the topic of discussion obesity and body weight etc. The example here talks about survey weight, which I automatically thought was the body weight for that time point. This is obviously not the case… but it made it confusing, nonetheless. The example is very good, and helpful, but adding in an extra sentence, or using a different term to denote survey weight would be very useful here. *In general, I thought the level of explanation and the examples were very well done.*

Line 27 Has "Yes" responses to the third child where as in the previous paragraph the example has this third child as a "No" response.

Statistical analysis (tables)
I found these tables very interesting.
Note: As with the primary text/figures/tables, the tables here are not in a consistent order with the other material.

3.5 Respiratory Disease

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Paloma Beamer
- Catherine Karr
- Morton Lippmann

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

Yes, the topic text clearly describes the topic and its importance for children's environmental health.

In addition, to the nicely laid out review of criteria air pollutants and respiratory disease in children, it would also be nice to have a review of hazardous air pollutants and respiratory disease in children. If not much information is available regarding children's respiratory disease and EPA's hazardous air pollutants, then it would be important to highlight that.

It would also be important to discuss asthma and respiratory disease prevalence in the context of living in urban versus rural environments. Some researchers have demonstrated that the racial and ethnic disparities in asthma morbidity and mortality rates may be explained by the greater proportion of minorities residing in urban environments where asthma rates are higher regardless of race and ethnicity. Consider the following two additional references.

Aligne, A.C., P. Auinger, R.S. Byrd & M. Weitzman 2000. Risk Factors for Pediatric Asthma Contributions of Poverty, Race, and Urban Residence. Am J Respir Crit Care Med , 162, 873-877.
Litonjua, A.A., V.J. Carey, S.T. Weiss & D.R. Gold 1999. Race, Socioeconomic Factors, and Area of Residence are Associated with Asthma Prevalence. Pediatr. Pulmonol., 28, 394-401.

I think to make the text more understandable for audiences with varying levels of existing knowledge it may be important to differentiate criteria air pollutants from hazardous air pollutants more explicitly in a brief sentence. The term "ambient" may also not be intuitive to all audiences.

Consider the following detailed edits.

On page 1, line 17, consider using the term "criteria" over "common."

On page 4, line 13, consider using "respiratory disease" for "respiratory effects."

On page 4, lines 32-33, consider deleting "with asthma" after children since it is already implied and this would improve readability.

Reviewer 2:

Overall the section is clearly written brief summary of the importance of children's respiratory health and environmental factors. Two aspects which should probably receive more representation in the topic text–

1. importance of upper respiratory tract outcomes – particularly allergic rhinitis and

2. increasing evidence related to the exposures presented and development of asthma. In addition, there is no mention of a rare but maximally severe outcome associated with ambient air pollution – infant mortality due to respiratory causes.

Finally, consider a mention to emerging exposures of concern for which the evidence base is preliminary (phthalates, bisphenol A, pesticides) yet are the subject of active investigation for which there may be better understanding soon (and before the next version of ACE is published…). This provides an opportunity to demonstrate the maturity of some of the science (ambient air pollutants) in contrast to the need to continue to understand complex, emerging environmental factors.

Here are some specific suggestions related to these points and a few additional wordsmithing suggestions:

1. Include more emphasis on upper resp tract problems, particularly allergic rhinitis.
The text focuses largely on lower respiratory tract disease, particularly asthma, which reflects a longer history of research investigation on this outcome. Clearly, this is a key outcome and is appropriately selected as a focus for the indicators. However, I think it is important to convey the more recent but increasingly robust evidence base linking environmental contaminants to upper airway disease, particularly allergic rhinitis. Like asthma, this is a chronic condition and is responsible for a large public health and medical burden for society, children and their families. (From American Academy of Allergy, Asthma, and Immunology Statistics)

There were more than 12 million physician office visits because of allergic rhinitis in 2006.[3]

Allergic rhinitis affects between 10% and 30% of all adults and as many as 40% of children.[4]

From 2000 to 2005, the cost of treating allergic rhinitis almost doubled from $6.1 billion (in 2005 dollars) to $11.2 billion. More than half of that was spent on prescription medications.[10]

Allergic Rhinitis is estimated to affect approximately 60 million people in the United States, and its prevalence is increasing.[27]

Sinusitis is one of the leading forms of chronic disease, with an estimated 18 million cases and at least 30 million courses of antibiotics per year.[22]

Specifically, in the very first opening sentence, I would suggest including "***allergic rhinitis***" and "***sinusitis***" among the list of respiratory health outcomes that can greatly impair a child's ability to function, etc. The list previously included only examples of disorders affecting the lower respiratory tract.

2. Represent the increasing evidence base regarding air pollutants and incident asthma (and/or allergies). Similarly, the sentence that begins on line 13, page 1 "Some studies" – should be modified. I suggest (***bold italics= suggested changes***): "Some studies suggest that environmental contaminants can cause the onset of ***chronic conditions such as*** asthma *or* ***upper airway allergies***, although studies relating to the exacerbation of pre-existing asthma or allergy are more prevalent because they are easier to conduct. [10,11,]

For this statement can add citation ***32***, also:

Parker JD, Akinbami LJ, Woodruff TJ, 2008 Air Pollution and Childhood Respiratory Allergies in the United States. Environ Health Perspect 117(1): doi:10.1289/ehp.11497
Morgenstern, V., A. Zutavern, et al. (2008). "Atopic Diseases, Allergic Sensitization, and Exposure to Traffic-related Air Pollution in Children." Am. J. Respir. Crit. Care Med. 177(12): 1331-1337

Line 25, page 1, last sentence of paragraph 4, add, development of asthma and upper airway allergic disease and reference number 32, and Morgenstern 2008 provided above.
For the ozone paragraph starting on line 27, page 1, in first sentence include reference to association with development of new disease, reference 11.

Line 42, page 1 – can include reference 32 alongside ref 15 in support of link between NO2 and incident asthma.

3. Impact on infant mortality due to respiratory causes:

The 2nd paragraph on page 1 would be a natural place to add mention of data linking increased air pollution to respiratory related mortality in the postneonatal period in an infant's life. (age 2-13 months).

Some key references on this topic, the latter a systematic review: Woodruff TJ, Parker JD, Schoendorf KC, 2006 Fine Particulate Matter (PM2.5) Air Pollution and Selected Causes of Postneonatal Infant Mortality in California. Environ Health Perspect 2006;114(5):786-790. Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Does Particulate Air Pollution Contribute to Infant Death? A Systematic Review. Environ Health Perspect. 2004; 112:1365–1370.)

4. Other comments re: text.

Line 32, page 1 – remove emphysema. This is almost exclusively an adult condition/disease. This is a very rare diagnosis in children. Emphysema is only seen in rare genetic conditions or congenital lung anomalies in children.

Line 43, page 1 – reference 16 supports the sentence components regarding susceptibility to respiratory infections but regf 16 did not assess bronchial reactivity per se. Was another reference intended for this component of the sentence?

Line 24, page 2, the word decreased is misspelled.

Line 32, page 2. The sentence beginning "Indoor allergens …" should start as "Other indoor allergens and irritants (because previous sentence examples includes allergens and irritant).

Line 35, page 2, "Combustion byproducts" is a term that may not be understandable to more general, lay audiences such as parents, educators (consider a parenthetical with examples, such as constituents of smoke from woodburning stoves, etc.).

Line 36, page 2– the list doesn't make sense – lower respiratory tract infections, bronchitis, pneumonia, and impaired lung function (bronchitis, pneumonia are lower respiratory tract infections – perhaps meant to put those in parentheses?). Might also add ear infections – not specifically respiratory tract but major complication of upper respiratory tract infections and major morbidity of childhood in terms of prevalence, clinical utilization…(can cite American Academy of Pediatrics Technical Report—Secondhand and Prenatal Tobacco
Smoke Exposure. Pediatrics 2009;124:e1017–e1044)

Line 5 page 3, reference 32 also provides evidence on this issue of exposure during pregnancy and development of asthma.

Consider summarizing the information provided in the text on outcomes and exposures as a table. This would provide a readily understandable/digestible synthesis of key points made in this text. For example could organize to illustrate links to both chronic disease vs acute effects. Can summarize and organize key exposures in ambient and/or indoor setting. Could try to incorporate general "strength of evidence" by font size or other symbolic representation. Below are examples of potential headers for rows/columns of exposures/outcomes.

<u>Exposures:</u>
Ambient - Criteria Air Pollutants, "Traffic", Hazardous Air Pollutants, Woodsmoke
Indoor – ETS, dustmite allergen, cockroach allergen, mold/dampness, VOCs, cat allergen, dog allergen, mouse allergen, (include : emerging concerns ? – bpa, phthalates, pesticides)

<u>Outcomes:</u>
Development of chronic disease – asthma, upper airway allergy (rhinitis)
Acute exacerbation of respiratory conditions – lower and upper respiratory tract infections, asthma or allergy attack, infant respiratory mortality

Page 3, line 13. The definition of asthma could use some tweaking to improve accuracy. The air flow problem from inflammation and bronchoconstriction is largely one of air trapping – poor air flow out of the lungs – versus the description in the text which notes" less air flow into the lungs." This is why asthma is characterized as an obstructive lung disease.

Consider some rewording such as -- Asthma is a chronic inflammatory disease of the airways. When children with asthma are exposed to an asthma trigger, airway walls become inflamed, secrete more mucus and the muscles around the airways tighten. ***This exaggerates the normal airway constriction that occurs on exhalation, trapping air in the lungs and compromising normal oxygen exchange.*** The physiologic changes can result in wheezing, coughing, difficulty breathing, chest tightness, pain, ***and poor oxygenation***.

I didn't see mention of the fact that children still die from asthma – rare event fortunately, but sobering statistics nonetheless. Consider including that in the discussion of symptoms, etc. Perhaps along with insertion of comment about infant mortality due to respiratory causes in paragraph number 2 (see comments above).

Page 3, Line 26 – Consider an opening statement to capture the essence of what is the consensus understanding about asthma etiology (complexity, multifactorial) ***It is increasingly appreciated that asthma is a complex disease with many factors, including genetic factors and environmental factors, that interact to influence it's development and severity.***
Consider dropping sentence on line 24, page 3 regarding "The tendency to develop" and simply inserting "family history of asthma and allergies" to the list of risk factors in the sentence that begins on line 26, page 3.

Line 12, page 4 – change the parenthetical to (such as asthma, upper ***and lower respiratory infections such as bronchiolitis and pneumonia****)*

Line 14, p 4 add ***"and bronchiolitis is the leading cause of acute illness and hospitalization in infants."***

(Zorc, JJ, Hall CB. Bronchiolitis: Recent Evidence on Diagnosis and Management Pediatrics 2010;125;342-349.)

Reviewer 3:

Does the topic text appropriately and clearly describe the topic and its importance for children's environmental health?

In general, the topic text appropriately and clearly describes the topic and its importance for children's environmental health. However, there are a number of issues that should be better stated and/or clarified. These are:

Page 1, line 17: change "Most" to "Four". Lead and CO have not been linked to respiratory diseases, although acute CO exposure can lead to respiratory insufficiency.

Page 1, line 21: delete "and lead".

Page 1, line 30: cite McDonnell et al. (2002 – Your Ref. # 11) for O_3 causing incident asthma.

Page 1, line 32: cite Thurston et al. (1997) for O_3 increasing use of medication. [Thurston GD, Lippmann M, Scott MB, Fine JM. Summertime haze air pollution and children with asthma. Am J Respir Crit Care Med. 155:654-660 (1997)].

Page 1, lines 41 through page 2. Line 2: The attribution of these effects to NO_2 is inappropriate. Rather, the associations are primarily with exposure to traffic pollution, which has often been indexed by an elevation in NO_2 concentration.

Page 2, line 2: Chronic NO_2 exposure has been shown to be strongly associated with reduced lung growth in childhood (Gauderman et al. 2007 – Your Ref. # 19).

Are there additional aspects of the topic's importance for children's environmental health that should be included?

Yes. There is no guidance provided on respiratory disease prevention for children. The efficacy of exposure prevention via use of :1) dust covers on bedding; 2) air humidifiers and dehumidifiers; and 3)indoor air cleaners should be discussed, as well as their limitations. For example, some devices that are sold as air cleaners also function as O_3 generators, and some air cleaners have collection efficiencies too low to be effective.

Is the relevant literature appropriately summarized? Are there other important references that should be added?

The literature cited was appropriately summarized only in part. Some additional literature that should have been cited is mentioned above.

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Yes. In addition to providing a more complete listing of the literature supporting the statements being made, a background bibliography should be provided to EPA and other documents that provide further support for the brief descriptions in the Overview statements.

Question 2 – Indicator Text

Reviewer 1:

For Indicators D1 and D2:
The indicator text does provide sufficient information about the data set and the indicator calculation to enable an understanding of the indicator. The text should be understandable by audiences with varying levels of existing knowledge. It is not clear, why Table 2a is not mentioned in the paragraph on page 6, lines 14-19.

For Indicator D3:
I would recommend changing the end of the "Overview" to be more descriptive. Rather than simply stating that they have changed over time, have they increased or decreased? Otherwise the indicator text does provide sufficient information about the data set and the calculation enable an understanding of the indicators. The text should be understandable by audiences with varying levels of existing knowledge.

Reviewer 2:

Overall, the indicator text is very well written and clear. A few suggestions to improve clarify of specific components.

Presumably the data ends in 2008 because this is most recent data available? Might consider indicating this explicitly.

Overview paragraph after line 6, page 5, insert "**each year**" at the end of the second sentence.

Line 21, page 6, please insert "***telephone-based***" in front of the word survey in the sentence that begins "A survey conducted…" (This helps briefly provide some suggestion of some of the key differences/considerations when viewing these data versus the NHIS survey data which are conducted as in person, in household interviews).

Reviewer 3:

Do the indicator texts provide sufficient information about the data set and the indicator calculation to enable an understanding of the indicators?

For reasons that are not explicitly described, the presentation is divided into three specific indicators and for different periods of years, i.e.:

D1 - % of children ages 0 to 17 years with asthma, 1997-2008;

D2 - % of children ages 0 to 17 years reported to have current asthma, by race/ethnicity and family income, 2005-2008;

D3 – Children's emergency room visits and hospital admissions for asthma and other respiratory causes, ages 0 to 17 years, 1996-2008.

It is troubling that the temporal changes in D1 and D3 that are illustrated in the Figures on pages 8 & 14 seem to be inconsistent. D1 shows no temporal trend in either asthma prevalence or asthma attack prevalence, while D3 shows a substantial transient bump up in both ER visits and hospital admissions for pediatric asthma and other respiratory causes in 2001 and 2002, followed by declines to pre-2001 levels in 2004 and beyond. During the same interval, hospital admissions for pediatric asthma and other respiratory causes fell during 2000 – 2003, and then began a continuing decline in the years that followed. What changes in medical practice or data category reporting could account for these very differences in temporal trends of asthma prevalence and asthma management? Were there other reasons for these temporal fluctuations? What do public health professionals and/or caregivers need to know to help them interpret these data?

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Yes. By discussing: 1) the questions raised above; 2) information explaining these trends that are already known to the authors; and 3) the research that needs to be undertaken to develop the answers to those questions that cannot now be satisfactorily answered.

Question 3 – Indicator Presentation

Reviewer 1:

The current template for the indicator graphs is hard to read when printed out in black and white.

For Indicator D1:
The y-axis should list all years. It is awkward and confusing to have 1997 as the only odd year. For the second bullet point, where the statistical significant trends in asthma attack prevalence when stratified by gender and/or race even if there wasn't in the overall data set? If not it would still be important to document as part of the indicator. It would be better to present the sub-bullet without the heading "statistical note." Comparisons should also be made by urban vs rural populations in addition to gender, race/ethnicity, and income. This indicator should be adequately understandable by multiple audiences.

For Indicator D2:
The gridlines and poverty labels are extremely hard to read. The wording of the second bullet point on page 11 is very awkward. Should the Table referred to in the 3rd and 4th bullet points on page 11 be D2a and not D2b. I'm not clear what we learn from the 4th bullet point. Wouldn't older children be more likely to be diagnosed with asthma? I do think this indicator should also consider reporting current asthma by urban vs. rural environments. With the improvements made above, the text should be understandable by a wide audience.

For Indicator D3:
The line and label for asthma is difficult to see. Under bullet point#2, did the rate of emergency room visits for all respiratory causes other than asthma change over time? Was it significant? It would be clearer to reorder Table D3c and Table D3b so that they are in the order they are discussed in the indicator. This indicator should be adequately understandable by multiple audiences.

Reviewer 2:

Graphics and points made are appropriate, clear and understandable. A few suggestions:

Page 8, line 11, rephrase, "In 2008, an estimated 6% ***of children with current asthma*** had one…

Statistical testing results are provided for some comparisons. In addition, consider providing confidence limits on the estimates in the data tables. Particularly, for more technical audiences (scientific, medical community) who might appreciate having the 95% confidence intervals provided at least in the tables. (I recognize that deeper in the methods documentation there are statistical significance testing p values provided. I still think that confidence intervals would be more helpful especially in the initial data tables.) This would help getting perspective on differences not explicitly presented with statistical testing – for example what appear to be "big" drop/rise in ED visit rates for 2003-2005, etc. I can see an argument for keeping the main graphs as straightforward as possible and not including error bars there.

Reviewer 3:

Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data?

Yes. For the descriptive data that have been collected, illustrated in the Figures, and summarized for levels and temporal changes in the bullet points, the presentations seem reasonable and appropriate.

Are there ways in which the presentation and description of the indicator values could be improved?

Yes. There needs to be more rationalization of the reasons for the selection of the indicators, and how the values presented can or should be interpreted.

Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Yes. Objective reasons for at least some of the unexplained temporal variations in the indices of respiratory tract morbidity should be offered. The text needs to discuss the underlying causes for the trends and their significance to the management and control of the patients' health.

Please comment on the appropriateness of the comparisons made in the indicator(s) and whether other comparison populations and/or benchmarks may be informative to the public.

The issue is not the comparisons that were made of the indicators, but whether there were any changes in the definitions of the indicators, and if so, what did that mean to the temporal changes in the underlying morbidity.

Question 4 – Context and Utility

Reviewer 1:

Please note that some of the responses under question 3, may also be appropriate here.
I do think that for policymakers and the public to better understand the ways to minimize the potential impacts of environmental impacts on children's health, it would also be important to examine how these rates differ by urban versus rural environments. If rates are different this might help policymakers identify key environmental contaminants or policies that need to be enacted based upon a child's unique environment. This is especially important when considering indicators for respiratory disease. This is the key limitation for all three indicators. Otherwise these indicators meet all of the criteria laid out by the principles of ACE. They are an excellent resource for understanding children's respiratory diseases in the US.

Reviewer 2:

These indicators are concrete, quantifiable and relevant and context provided is appropriate. Clearly the limitations of looking at the outcomes in isolation are the fact that each has multiple influences – some of which are not "environmental", which are described briefly in the fourth paragraph on page 4.

Another limitation that concerns me more, and I struggle with how best to incorporate it here is the averaging/simplification effect of looking at the asthma prevalence data from a national perspective, when there are suspected large subgroup differences. These are somewhat explored by demonstrating differences by age and ethnic groupings, as well as the brief discussion of "other estimates of prevalence" on page 6 – but this only touches the surface of what is probably very large variability by geography, culture, etc.

For example, it is very useful that the data tables show the much higher prevalence of asthma among Puerto Rican Americans compared to Mexican Americans – groups that are often classified together in the "Hispanic" classification. However, reported prevalence of asthma in the data sources used for the indicators D1,D2 are based on family report of a health care provider diagnosis of asthma which requires access to care. I have seen comment on the problems with such data in the literature - the proportion of children lacking health insurance was 11.4% for Puerto Ricans participating in the national Health Interview Survey and 30.4% for Mexican (Scott, 2004). Substantial language effects on asthma management practices and outcomes have also been demonstrated (Chan 2005). To what extent these factors explain differences are not known and likely vary by region, underscoring the importance of addressing prevalence in specific populations that can go beyond being based on solely on heath care provider diagnosis.

I would suggest considering some mention of this problem of the assessing prevalence based on "diagnosed by a heath care provider" and complexity of disentangling issues related to access to care, recognition of disease among subgroups in the section "other estimates of asthma prevalence". Perhaps something as simple as a statement "Of note these prevalence data are based on report of a health care provider diagnosis of asthma, which may vary among population subgroups. More comprehensive population based assessment of asthma prevalence that does not rely heavily on contact with the health care system are not routinely available." This could serve to highlight to policymakers and the public the importance of efforts to characterize asthma prevalence more adequately as well as improve health care access.

(Chan KS, Keeler E, Schonlau M, Rosen M, Mangione-Smith R. How do ethnicity and primary language spoken at home affect management practices and outcomes in children and adolescents with asthma? Arch Pediatr Adolesc Med 2005;159:283-289. Scott G, Ni H. Access to health care among Hispanic/Latino children: United States, 1998-2001. Adv Data 2004;344:1-20.)

Lastly, given the clearly large magnitude impact of age on D3 – and the increased recognition overall of life stage differences in susceptibility, risk factors etc for children's environmental health topics, consider portraying these age differences graphically (for example, just as D2 is a refinement of D1 to highlight important differences across ethnic subgroups – D3 could be augmented with a D4 that highlights importance of these outcomes among age groups – could use breakdown as in table D3c or perhaps some collapsing (< 1, 1-3, 4-6, 6-11, >11)? This would make it more at the forefront than as provided in accessory data tables.

Reviewer 3:

For D1, the data summary presentation in the Figure on page 8 is informative, showing that there were no significant temporal trends in the prevalence of asthma or asthma attacks.

For D2, the data summary presentation in the Figure on page 10 is informative, showing that: 1) ethnicity is a major factor accounting for the variability of childhood asthma prevalence; and 2) family income is a lesser, but still significant factor.

For D3, the hospital admissions data indicate there has been a substantial and continuing decline in admissions for both asthma and other respiratory diseases beginning in 2004. This is great for the nation's health care budget. What we need to know is whether the declines are due to the substantial and continuing decline in the concentration of ambient air $PM_{2.5}$ and/or the modest and continuing decline in ambient air O_3? If the declines are not due to the reductions in pollution, what other temporal changes could account for this welcome trend? This reviewer cannot answer these important questions, and suggests that an expert Workshop Panel be convened to deal with the issues.

Question 5 – Documentation

Reviewer 1:

The documentation is very thorough and transparent. It would be possible for someone to replicate all calculations.

Reviewer 2:

The documentation is complete and transparent. I have one small suggestion -
Under table D1a page 16 – here provide the question used in the old survey cycle. This will allow reader to understand how differs from more recent cycle/data. (The latter is very clearly provided on the bottom of page 5.)

Reviewer 3:

Yes.

4.0 SPECIAL FEATURES

4.1 Birth Defects

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Julianne Collins
- Peter Langlois
- Dawn Misra

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

1-1. Does the topic text appropriately and clearly describe the topic and its importance for children's environmental health?

1-2. Are there additional aspects of the topic's importance for children's environmental health that should be included?

1-3. Is the relevant literature appropriately summarized?

1-4. Are there other important references that should be added?

1-5. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Response to Questions:
1-1. Yes, this is an appropriate and clear description of the topic of birth defects and its relationship with environmental health in children. I have only suggested a few changes below.

1-2. I recommend that a sentence on the cost of birth defects in monetary terms and to society be inserted on line 13 of page 1. Also, some information on variation by race/ethnicity may be helpful since this is presented in a supplemental table of the indicator S5. This may need to be a stand-alone paragraph.

1-3. The relevant literature appears to be summarized appropriately.

1-4. A reference or two on the topic of the cost of birth defects (see response 1-2) should be added. Also, a reference or two on variation by race/ethnicity may be useful since this is presented in a supplemental table of the indicator S5 (such as Canfield et al. 2006 in BDRA 76:747–756).

1-5. In general, I believe that the text should be understandable for researchers, government workers, healthcare professionals, and parents. However, I do not like the use of the word "influenced" in the sentence on page 1, lines 18 and 19. I suggest that "but research suggests that defects could be influenced by environmental factors" be changed to "but research suggests that defects may also be modified or caused by environmental factors, possibly in conjunction with genetic factors"

Reviewer 2:

1. Does the topic text appropriately and clearly describe the topic and its importance for children's environmental health? 2. Are there additional aspects of the topic's importance for children's environmental health that should be included? 3. Is the relevant literature appropriately summarized? 4. Are there other important references that should be added? 5. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Response to Questions:

1.1. Yes, generally. It clearly introduces birth defects (BDs), their public health importance, and the links between certain exposures and certain BDs. I feel the text would be strengthened by discussing somewhere the problem of artifactual clusters and trends due to diagnostic variability. I'll revisit this under "Context and Utility" below.

1.2. The draft seems to have covered most of the important topics from a chemical agent viewpoint (e.g. solvents, disinfection byproducts). This makes sense given what I understand is EPA's responsibility to regulate individual chemicals. Thus I assume the draft intentionally did not summarize the literature relating to such things as residential proximity to hazardous waste sites, industrial facilities / Toxic Release Inventory sites, or incinerators. If the authors decide to incorporate a paragraph or two on those topics, I would be happy to provide some references.

There wasn't much mention of metals. For example, risk of neural tube defects increased among mothers occupationally exposed to lead (Irgens et al., 1998), and living in an area heavily polluted with lead was associated with higher rates of cardiovascular birth defects, oral clefts, and musculoskeletal anomalies (Vinceti et al., 2001).

I did not find a discussion of nitrate, though it is one of the most ubiquitous contaminants in food and water. Several epidemiologic studies report an association of prenatal exposure to nitrates in water or food and birth defects in offspring (Scragg et al., 1982; Arbuckle et al., 1993; Croen et al.,

2001), though some report a weak but nonsignificant effect (Cedergren et al., 2002; Brender et al., 2004) and others reported no association (Ericson et al., 1988; Aschengrau et al., 1993).

If the authors decide to include mention of metals or nitrates, I recommend doing a literature search; the above articles were simply the ones I had in my files.

1.3. Yes, nice job of concisely summarizing some complex human studies. I noted that the draft left out discussion of the very considerable literature based on non-human animal studies, and will assume that was intentional.

1.4. I understand the purpose was not to provide an exhaustive literature review, but to capture the most relevant papers. I believe that has been accomplished. I have added the references mentioned above to the end of this review if you decide to use them although I still recommend doing a literature review of those areas and not relying solely on the references I have provided.

1.5. The organization of this section good but might be further improved. As it currently reads, the major idea of each paragraph seems to be:
Par 1: Definition of BDs

Par 2: Public health importance of BDs

Par 3: Causes of birth defects: inheritance, drugs, high levels of environmental contaminants

Par 4: Epi studies of BDs associated with occupational exposure to solvents, of drinking water exposure to solvents

Par 5: Epi studies of job title, parental exposures to dioxins and solvents, review article of several exposures

Par 6-9: Epi studies of BDs associated with pesticides, disinfection byproducts, air pollutants, endocrine disrupting chemicals

Par 10: Additional considerations due to the process of fetal development

Par 11: Monitoring for BDs in the USA

Par 12: The Texas birth defects registry

Paragraphs 4 and 5 seem somewhat out of place, and the section might be improved by reorganizing them. Perhaps the following would help?:
Delete the last 2 sentences of par 4. Move them after current par 5, to their own paragraph (a solvents/dioxins paragraph).

Move the 2nd sentence of par 5 (with "An extensive review…paternal exposures to dioxins and solvents…") to that new solvent/dioxins paragraph. You might have to revise it slightly to make it flow, perhaps not.

Create the new par 4 from the current 1st sentence of par 4 (beginning with "A number of…"), the remaining sentences of par 5 (beginning with "Studies have found…", and "The same review…").

Revise that last sentence to read "An extensive review of the literature concluded that there is not enough evidence to determine if there are associations between birth defects aside from neural tube defects and paternal exposures to dioxin, solvents, pesticides, and outdoor air pollutants".

This way the new organization would be:
Par 4: Epi studies of BDs associated with a variety of exposures
Par 5: Epi studies of BDs associated with solvents

The first sentence of the first paragraph, as currently written sounds like only those examples qualify as birth defects. I recommend changing it to something like the following: "The term "birth defects" covers a range of structural and chromosomal abnormalities that occur while the baby is developing in the mother's body." If you want to give examples, you can list some of the birth defects already in the first paragraph.

(Par 3, sentence 3): Suggest changing "…but research suggests that defects could be influenced…" to "…but research suggests that some birth defects could be influenced…"; that is somewhat more precise.

Reviewer 3:

Generally an excellent overview of birth defects is provided. However, it could be disputed that birth defects are the leading cause of infant mortality. These defects are often intrinsically linked with preterm birth and preterm birth is usually considered the primary reason for death. I would suggest rewording to highlight birth defects as a leading cause of death in infancy, both due to strong associations with preterm birth and growth restriction as well as conditions that are incompatible with life.

The discussion of particular toxicants and birth defects appears to be up to date and considers factors more recently of interest (e.g. phthalates, BPA).

The text also provides a well written description of the state of birth defects surveillance within the U.S. This is important information to present prior to discussion of particular indicators and trends. Also, these data limitations provide the rationale for birth defects being in the special topics rather than a regular indicator at this time. The text is also well written with regard to putting the selected Texas data in context.

While the issues are complex, the presentation of the topic seems understandable for a wide range of audiences. The synthesis of past work on this topic is particularly well written with regard to the issue of understandability.

Question 2 – Indicator Text

Reviewer 1:

2-1. Does the indicator text provide sufficient information about the data set and the indicator calculation to enable an understanding of the indicator?
2-2. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and

nurses, concerned parents and educators)?

Response to Questions:
2-1. Since the indicator S5 shows how rates vary by race/ethnicity in a supplemental table, some text about this could be helpful in the understanding of these rates by the readers. This is something that could be added to line 17 of page 4, as it would help explain how rates can vary by state due to differences in the racial/ethnic composition of states. It can also be added as a new paragraph in the next section on page 4.

2-2. The sentence of the paragraph on lines 16 and 17 of page 4 is confusing, since the following paragraph also addresses this topic. I suggest that the words "or the nation as a whole" be removed from the end of the sentence.
I would suggest that the "of the Texas Department of State Health Services" be inserted on line 6 of page 4 after the word "Branch."

Also, the description of the Texas registry is a little confusing, as it is referred to as both a surveillance program, a monitoring program, and a registry (capitalized and not capitalized). It might help the comprehension by the readers if this is looked at carefully and made consistent in the overview, text, graph, and tables.

Reviewer 2:

1. Does the indicator text provide sufficient information about the data set and the indicator calculation to enable an understanding of the indicator? 2. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

Response to Questions:

2.1. Yes.

2.2. (Par 2, 1st sentence) Suggest changing "…from the Texas Birth Defects Epidemiology and Surveillance Branch" to "…from the Birth Defects Epidemiology and Surveillance Branch of the Texas Department of State Health Services", so that people know where to go for further information if they want.

(Stylistic suggestion only, Par 2 and 3, several places): Suggest changing "The Texas monitoring program…" to "The Texas Birth Defects Registry" or "the Registry" thereafter.

(Par 2, 2nd sentence) To be more precise, recommend changing this to: "The Texas Birth Defects Registry began monitoring the Houston/Galveston and South Texas areas in 1995, and gradually expanded so that beginning with births in 1999, it covered the entire state.

(Par 3, 3rd sentence) Suggest changing to: The Texas Registry staff routinely visit all hospitals and birthing centers where affected babies are delivered or treated. There they review logs and discharge lists to find potential cases, and then review medical records of the potential cases to identify actual cases with birth defects.

(Par 7, 1st sentence) Suggest adding to the end: ", called birth defect prevalence rates or birth defect rates below". Right now, it's just implied that "number of birth defects per 10,000 live births" is the same as birth defect rates.

(Par 7) I would change the 2nd sentence to "……when there is no more than a 5% chance that the observed change over time occurred by random variation from year to year if the underlying occurrence was in fact staying the same". It might help a little to replace the word "probability" with "likelihood" in the last sentence.

Reviewer 3:

The indicators are well described.

Each indicator will be also be presented for each race/ethnicity group in supplemental tables, which is important to do, given the considerable disparities in both outcomes and exposures. The indicators will also be done separately by singleton/multiple status in supplemental tables; again, this is important because of baseline differences in risk for these two groups.

The rationale for applying statistical testing seems appropriate given the evidence of underreporting.

Question 3 – Indicator Presentation

Reviewer 1:

3-1. Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data?

3-2. Are there ways in which the presentation and description of the indicator values could be improved?

3-3. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)?

3-4. Please comment on the appropriateness of the comparisons made in the indicator(s) and whether other comparison populations and/or benchmarks may be informative to the public.

Response to Questions:
3-1. Yes, in general, the figures, tables and text are appropriate. However, I have made some recommendations below.

3-2. The statistical test used for the comparison of the prevalence data should be noted in either the statistical testing section on page 5 or the statistical note on page 6. I see this is mentioned at the end of the document, and maybe the reader can be referred to that section.

The internet reference for the Texas Registry (http://www.dshs.state.tx.us/birthdefects/default.shtm) should be added to the footnote for both tables and the figure.

The orientation of the labels of the horizontal axis of the figure could be changed such that the text could fit better in the labels without the use of hyphens.

I would change the width of the columns in the tables such that each row only uses one line.

3-3. Since the table by race/ethnicity is included, it would be nice to add a descriptive paragraph and whether or not these differences are statistically significant. Otherwise, you may want to consider deleting that table and all mentions of race/ethnicity in the document.

3-4. Unfortunately, there is not a lot of population data on birth defect rates. This leads to a paucity of data that could be used for further comparisons or benchmarks. Birth defect surveillance is underfunded, and it would certainly help research and prevention efforts if there was better funding for more complete ascertainment of state birth defect data.

Reviewer 2:

1. Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data? 2. Are there ways in which the presentation and description of the indicator values could be improved? 3. Are there ways that this text could be made more understandable for audiences with varying levels of existing knowledge (including researchers, government officials, medical doctors and nurses, concerned parents and educators)? 4. Please comment on the appropriateness of the comparisons made in the indicator(s) and whether other comparison populations and/or benchmarks may be informative to the public.

Response to Questions:

3.1 Yes, nice job. Very clear with respect to time trends. However, I am unclear why the draft presents a table by race/ethnicity (Table S5a) and then doesn't say anything about it in the text. Is it mainly to justify adjusting by race/ethnicity when determining statistical significance of time trends? Do you want to make a statement about environmental justice issues and birth defects? Anyway, I recommend adding some text to cover it or putting it in the Methods section only.

3.2 Suggestion: Since there is so much room in the data table S5, why not add the 2 columns of p values from Table 1 in your Methods section? That way readers wouldn't need to refer to a more distant section in order to see the p-values summarized in the text. Not a big deal either way.

The graph for Indicator S5 doesn't have an X axis label like "Birth Defect Categories". But it's so evident that I don't know if that is really necessary.

3.3 No suggestions for improvement; good job.

3.4 I believe the comparisons are appropriate; investigators examine time trends in birth defects frequently. It's the inferences from those comparisons that give me pause; I'll discuss those more below.

It is surprising that the most common type of birth defect is musculoskeletal. When we do analyses of individual birth defects using Texas Birth Defects Registry data, the most common ones are several heart defects and among males, hypospadias. On the other hand, I can understand how the draft's grouping into large anatomic categories could change the ranking. I checked with the Birth

Defect Registry epidemiologist who provided the data, and the correct birth defect codes were used for those anatomic groups.

Reviewer 3:

The graphs are clear and illustrative – a challenge given the very large number of categories of birth defects.

Question 4 – Context and Utility

Reviewer 1:

4-1. For each indicator, please comment on whether the text appropriately and objectively reflects the strengths and limitations of existing knowledge regarding relationships between environmental conditions and children's health that are relevant to the topic.

4-2. For each indicator, please comment its utility and appropriateness addressing the three principal objectives of ACE:

a) to presents concrete, quantifiable indicators of key factors relevant to the environment and children in the United States. These indicators are designed to offer a basis for understanding time trends for some factors and for further investigation of others.

b) to inform discussions among policymakers and the public about how to improve federal data on children and the environment.

c) to provide indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children.

Response to Questions:
4-1. Yes, I believe the text appropriately and objectively reflects the strengths and limitations of existing knowledge of how environmental factors may be involved in the causation of birth defects.

4-2a) This document presents data on birth defect rates in Texas from 1999-2007. However, even though this is a representative state, it would be nice to have more complete national data. This document should allow others to see where we are at currently and where improvements can be made.

4-2b) Yes, I would hope that this document would allow the public and policymakers to see that birth defects rates are not tracked in all states and states use differing methods of ascertainment, which makes generating national birth defect rates difficult. This document should also encourage surveillance programs to collaborate with other state programs to combine data on environmental contaminants with their birth defect rate data.

4-2c) Yes, this indicator can be used to track changes in birth defects rates in Texas. However, it would be nice to have some accompanying environmental data for the same region.

Reviewer 2:

The text appropriately and objectively reflects the strengths and limitations of existing knowledge regarding relationships between environmental conditions and some birth defects. For example, several references are cited that cast doubt on associations. Overall, the presentation seems balanced.

However, the draft seems to imply that because there are some associations between some birth defects and certain environmental exposures, time trends in birth defects may reflect increasing environmental exposures. That may be true, but I do not think it is as simple as that.

For one thing, the significant changes in such a nonspecific range of birth defects (statistically significant increases in all measured categories except for chromosomal defects and oral clefts) suggests that it is unlikely that one agent or set of agents is responsible.

Second, have environmental conditions in Texas really worsened sufficiently from 1999-2007 to correspond to the increase in birth defects?

Third, other exposures have been associated with birth defects such as diet (e.g., lack of folic acid) and medications. Could changing behaviors and available drugs explain some of the increase over time?

Finally and perhaps most importantly, birth defects are highly susceptible to variations and trends in clinical practice (Langlois et al., 2010). So the most likely explanation for time trends in birth defects is that birth defects are being better diagnosed and recorded in medical charts over time, and thus more likely to be picked up by the Texas Birth Defects Registry. Other analyses recently done by the Registry suggest that to be true. It may be due to a variety of things, such as improved prenatal and postnatal technology to detect hard-to-find birth defects such as small heart defects, increasing routine use of those diagnostic procedures and of certain therapeutic procedures, and perhaps changing health insurance reimbursement practices.

Based on that, I suggest two revisions:

(Short term): Include a paragraph somewhere in the birth defects section presenting the above issues. I would suggest at the end of the indicator presentation, but it could also be at the end of the indicator text.

(Long term, perhaps next report if too late for this report): Instead of broad anatomic categories like "cardiac and circulatory" for your indicator, choose individual birth defects that are not as susceptible to diagnostic variability and trends, such as anencephaly, spina bifida, and oral clefts. There is unfortunately no universal agreement on which defects those defects are, but research is progressing (e.g. Langlois and Scheuerle, 2007; Langlois et al., 2010).

Reviewer 3:

The overall and system specific (e.g. cardiac) indicators are appropriate and will be useful in addressing the objectives described above. It might be helpful if indicators were stratified on obesity given its trajectory in the U.S. and the potential effects and interactions with nutritional factors.

Question 5 – Documentation

Reviewer 1:

5-1. Is the documentation complete and transparent?

Response to Questions:
5-1. Yes, the documentation is transparent and is close to being complete. If the minor suggestions that I made are followed, this document would be much improved.

There is an extra period on line 13 of page 3.

Reviewer 2:

Generally this is complete. Some responses could be made more clear; suggestions follow.

Metadata

I will assume the "data source" refers to the Texas Birth Defects Registry, and not the data that were requested from the Registry (a subset of the Registry). If that is in error, please ignore/modify much of what follows.

Brief description of the data set: Suggest changing 3rd and 4th sentences to something like: "The Texas Registry staff routinely visit all hospitals and birthing centers where affected babies are delivered or treated. There they review logs and discharge lists to find potential cases, and then review medical records of the potential cases to identify actual cases with birth defects."

How are the data gathered?:
Suggest changing 2nd bullet to:
Trained program staff regularly visit medical facilities.
Have legislative authority to review all relevant records.
Review log books, hospital discharge lists, and other records to identify potential cases.
Review medical charts for potential cases to identify those with birth defects.
Suggest changing "Records in the birth defects registry WERE matched…" to "Records in the birth defects registry ARE matched…"

What is the spatial representation of the database (national or other)?
If I understand this question, I believe the answer should be "Prior to 1999: selected health service regions of Texas. 1999 onward: entire state of Texas."

Are raw data (individual measurements or survey responses) available?
As currently written, it doesn't make sense as a response to that question. I would leave "Raw data for 1996-2007 are available through special request" and delete the rest. Other questions address access to the data that are not raw data.

How are database files obtained?
I would reorganize the current response to the following:
"Routinely published tabulations of data for 1995-2007 (by birth defect, overall and broken down by selected demographic factors) can be accessed at:
http://www.dshs.state.tx.us/birthdefects/Data/reports.shtm.
A queriable database of data for 1999-2006, where users can design their own tabulations, can be found at: http://soupfin.tdh.state.tx.us/bdefdoc.htm.

Other tabulations or raw data are also available through 2007, by written request. Go to http://www.dshs.state.tx.us/birthdefects/Data/reports.shtm and click on "Birth Defects Data Request and Access Policy".

Can data be stratified by race/ethnicity, income, and location (region, state, county or other geographic unit)?

Change "mother's race/ethnicity" to "mother's race/ethnicity, mother's age group, or infant gender".

Suggest changing "geographical unit" list to the following:
geographical unit:
statewide;
public health region;
border residence status; and
county (crosstabulation by mother's characteristics not available at this resolution to protect confidentiality).

Methods

(Summary, 2nd sentence):
To be more precise, recommend changing this to: "The Texas Birth Defects Registry began monitoring the Houston/Galveston and South Texas areas in 1995, and gradually expanded so that beginning with births in 1999, it covered the entire state."

(Calculation of Indicator):
Did the EPA data requestor specifically request only cases of birth defects among live births? I ask because we, like most birth defects registries in the National Birth Defects Prevention Network, usually calculate birth prevalence rates as:
number of cases of birth defect X in an area and time period x 10,000 number of live births in that area and time period but for the number of cases, we take every case, regardless of whether it was a live birth, spontaneous fetal death (stillbirth, miscarriage, etc) or pregnancy termination.
This actually won't make a huge difference in the actual rates for large structural categories like those used in this report.

If the EPA data requestor did specifically request only live born cases, I suggest modifying the calculation as:
Rate of birth defects per 10,000 live births =
Number of live births with birth defects in structural category and time period / Number of live births in time period x 10,000
(i.e. remove "in structural category and" from the denominator).

(Statistical Comparisons):
Birth defects are rare events and their occurrence is generally accepted to follow a Poisson probability distribution. Consequently, their rates are usually modeled using Poisson regression (technically one is modeling the number of cases and using the number of births in the denominator as an offset, but it comes to the same thing as modeling the rates). The draft used logistic regression. This is not incorrect; some registries and published papers have used this and in fact in most situations the results from Poisson regression are similar to those from logistic regression. To be really precise in doing logistic regression, all cases of birth defects should be

removed from the births. If that was done, it should be stated. If it was not done however, it won't have a large impact (since only about 4% of live births have birth defects).

For the top paragraph of page 17 (starting with "Comparisons of the trends…", it might be a little clearer if the 2nd sentence changed "…and a term for the middle year of the three-year period" to "and a term for the middle year of the three-year period considered as a continuous variable" or something like that.

Although the wording of the Statistical Comparisons part is high level, I think that is appropriate for anyone who is interested in reading it.

Potential Additional References

Arbuckle TE, Sherman GJ, Corey PN, Walters D, Lo B. 1988. Water nitrates and CNS defects: a population-based case-control study. *Archives of Environmental Health* 43: 162-167.

Aschengrau Z, Zierler S, Cohen A. 1993. Quality of community drinking water and the occurrence of late adverse pregnancy outcomes. *Archives of Environmental Health* 48: 105-113.

Brender JD, Olive JM, Felkner M, Suarez L, Marckwardt W, Hendricks KA. 2004. Dietary nitrates and nitrates, nitrosatable drugs, and neural tube defects. *Epidemiology* 15: 330-336.

Cedergren MI, Selbing AJ, Lofman O, Kallen BA. 2002. Chlorination byproducts and nitrate in drinking water and risk for congenital malformations. *Environmental Research* 89: 124-130.

Croen LA, Todoroff K, Shaw GM. 2001. Maternal exposure to nitrate from drinking water and diet and risk for neural tube defects. *American Journal of Epidemiology* 153: 325-331.

Ericson A, Kallen B, Lofkvist E. 1988. Environmental factors in the etiology of neural tube defects. A negative study. *Environmental Research* 45: 38-47.

Irgens A, Kruger K, Skorve AH, Irgens LM. 1998. Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. *American Journal of Industrial Medicine* 34: 431-437.

Langlois PH, Scheuerle A. 2007. Using registry data to suggest which birth defects may be more susceptible to artifactual clusters and trends. *Birth Defects Research (Part A)* 79: 798-805.

Langlois PH, Sheu SU, Scheuerle AE. 2010. A physician survey regarding diagnostic variability among birth defects. *American Journal of Medical Genetics Part A* 152A: 1595-1598.

Scragg RK, Dorsch MM, McMichael AJ, Baghurst PA. 1982. Birth defects and household water supply. *Medical Journal of Australia* 2: 577-579.

Vinceti M, Rovesti S, Bergomi M, Calzolari E, Candela S, Campagna A, Milan M, Vivoli G. 2001. Risk of birth defects in a population exposed to environmental lead pollution. *The Science of the Total Environment* 278: 23-30.

Reviewer 3:

Yes.

4.2 Contaminants in Schools and Child Care Facilities

Per the guidelines set forth in EPA's Peer Review Handbook, individual comments are not attributed directly to reviewers. As planned, the reviewers are as follows:

- Alan Becker
- Ardythe Morrow
- Beth Resnick

General Comments (If Any)

Reviewer 1:

None

Reviewer 2:

None

Reviewer 3:

None

Question 1 – Topic Text

Reviewer 1:

Update references:

Sexton, K, Greaves IA, Church TR, et al. (2000) A school-based strategy to assess children's environmental exposures and related health effects in economically disadvantaged urban neighborhoods. Journal of Environmental Epidemiology; 10:682-94.

Mir, DF, Finkelstein Y, Tulipano GD, (2010). Impact of integrated pest management training on reducing pesticide exposure in Illinois childcare centers. Neurotoxicology; 31(6): 765.

Wilson, NK, Chuang JC, Iachan R, (2004). Design and sampling methodology for a large study of preschool children's aggregation exposures to persistent organic pollutants in their everyday environments. Journal of Exposure Analysis Environmental Epidemiology; 2004; 14(3): 260-74.

Wilson, N.K, Chuang JC, Lyu C, (2001). Levels of persistent organic pollutants in several day care centers. Journal of Exposure Environmental Epidemiology; 11(6): 449-58.

Lambrinidou Y, Triantafylidou S, Edwards M, (2010). Failing our children: lead in U.S. school drinking water. New Solutions; 20(1):25-47.

Chiang WF, Yang HJ, Lung SC, (2008). A comparison of elementary schoolchildren's exposure to arsenic and lead. Journal of Environmental Carcinogen ecotoxicology Review; 26(3): 237-55.

Newman DM, (2010). PCBs in school: what about school maintenance workers? New Solutions; 20(2): 193-4.

Herrick RF (2010). PCBs in school-persistent chemicals, persistent problems. New Solutions; 20(1): 115-26.

Herrick RF, Lefkowitz DJ, Weymouth GA, (2007). Soil contamination from PCB-containing buildings. Environmental Health Perspectives. 115(2): 173-5.

Peper M, Klett M, Morgenstern R,(2005). Neuropsychological effects of chronic low-dose exposure to polychlorinated PCBs: A cross-sectional study. Environmental Health. 19: 4:22

The data does not seem to cover all of the issues in the chemical and pesticide exposures and do not include a data base. I would suggest the poison control data be included in the data base, especially with the sanitizers and cleaning products. They collect chlorine exposures from mixing cleaners. Why not include the NIOSH, SENSOR Pesticide Exposure Program as part of the pesticide exposure data base? Many states collect self-reporting, poison control centers, pesticide applicator and agriculture pesticide exposure.

The data set for the pesticide study in California does not consider agricultural pesticides. The reason for this is because spraying farm pesticides are restricted from being used within a certain distance of the school. Other states do not have this rule, so agricultural pesticides should be included for a national indicator related to pesticides in schools and day care centers.

Reviewer 2:

The text is a very appropriate summary of the topic and its importance to children's environmental health. The relevant literature appears to be appropriately summarized. However, there is a disconnect between the summarized literature and the indicators selected. Many of the health concerns (e.g., lead) lack an indicator. Further, contaminants in schools and child care facilities appears to lack systematic monitoring. Data for the Schools indicator are available only for California.

In general, I believe there could be a much stronger presentation of information if there was a figure or table, that linked a health concern to the indicator(s) and data source. For this topic, for example, lead, asbestos, PCBs, and insecticides, and so on would each be listed as health concerns. For lead and asbestos there would be an indication that there are no indicators for these in the school or child care setting. For PCBs, there would be an indicator.

While the indicators selected appear appropriately important, it is not clear why PCBs and insecticides would be selected as indicators while lead in schools was not selected as an indicator.

Reviewer 3:

The topic text is very choppy, hard to follow and written at a level way to advanced for the lay-person. Organization, language, flow and clarity need work. The text should "tell the story" to the

reader as to the importance of this topic and its relation to children's health. In current format, much work is required of the reader to put all the disjointed pieces together.

The introductory paragraph does not adequately emphasize the importance of the topic and connection to children's health and well-being. Apart from the first sentence, the introductory paragraph is one long sentence (line 5 to line 10) listing contaminants, but does not relay any information about the potential dangers of these contaminants. This sentence should be broken into two or three sentences. Furthermore, the contaminants should be in a logical order, such as outdoor contaminants, building materials and maintenance then furnishings, then learning environments and then hobbies.

There is not a smooth transition from the first paragraph to the second. The second paragraph is very disjointed, addressing multiple topics, without clear explanations. The opening sentence (lines 12-14) is long and confusing. The example of schools housing more occupants that office buildings includes no explanation of why this would present an environmental health challenge. Pest problems are added in at the end of the paragraph without a transition and again no explanation as to why the conditions listed might create a pest problem.

The third paragraph is unclear. The first sentence (line 20-22) does not provide any explanation as to what child care and school environment characteristics are shared. For a lay reader, there needs to be an explanation as to why a wide variety of child care settings would create any concerns. Similarly, further explanation of an independently owned child care center versus a centrally operated school is needed.

Paragraph four should be the second paragraph, as it provides some context as to the relevance of indoor environment contaminants to children's health, although a bit more information on the types of indoor contaminants they are referring to would be helpful. Language in this paragraph is far too technical for a lay reader (i.e., reproductive toxicity, hormone disruption, and immature metabolic pathways). The last sentence about children having more years of future life to develop a disease would be clearer if it included a specific example.

An additional overview paragraph about outdoor contaminants would be helpful to provide context.

There is no flow from paragraph four to paragraph five (staring line 42). As the preceding paragraph focuses in on environmental contaminants and then this paragraph highlights indoor air pollutants. Additionally, no explanation of the difference between an environmental contaminant and air pollutant is provided. The educational performance information included is very important, but the points are lost due to the poor organization and flow of this section.

Paragraph six jumps to disparities, again without any transition language. Paragraph seven then returns to types of indoor contaminants, which were addressed originally in paragraph four. Paragraph seven contains complicated language (i.e., direct and indirect ingestion, ventilation efficiency). "Current state of schools and child care environments" needs more explanation. Additionally, explanation of the reasoning behind the banning or limited use of substances will help to reinforce the potential impact of exposure to these contaminants on children's health.

For the paragraphs highlighting specific indoor contaminants, the potential health risks to children should be at the beginning of the paragraph, rather than the conclusion. Additionally, these paragraphs should all be organized in the same way (i.e,. explain the potential health risk to children, provide information on exposure risks in schools and child care facilities, current state of

regulation, etc..). Furthermore, these paragraphs again use terms that are unfamiliar to a lay reader (i.e., insulating fluids in capacitors, joint sealants, latency period, "managed in place", benzene, propellents, rodent dander, aromatic hydrocarbons). For lead, the magnitude of the problem is not clear, additionally, there is no mention of some potential sources, such as drinking water and water coolers, etc. Asbestos need more explanation of the long latency period. It is not clear why these particular contaminants each have a full paragraph, but other contaminants, such as mercury, mold, and soil contaminants do not.

"School Siting" is very awkward terminology that might not be familiar to a lay person, perhaps use "school location." Similarly, "voluntary model guidelines" needs explanation, as well as how someone can find out if there school is built on top of or near contaminated lands in order to avoid creating unnecessary anxiety. Vapor intrusion needs to be defined.

In the pesticide paragraphs language needs to be simplified. The first two sentences contain the terms repel, mitigate, and microorganisms, fungicides, rodenticides, herbicides, and antimicrobrials. Additional technical language used in this paragraph includes degradation, residue, reservoir for direct human exposure or migrate, indirect ingestion, pathways, and air intrusion.

A concluding paragraph for the introductory section again highlighting the importance of this issue and its connection to children's health is needed.

Question 2 – Indicator Text

Reviewer 1:

I think the indicator is understandable and the information pertaining to the data set is straight forward and easy to read. I would like to see poison control data and pesticide sensor data included or considered. Exposure data would be more useful than testing for the presence of pesticides.

Reviewer 2:

The text is well written, but an important aspect that appears to me to be missing or difficult to understand is the selection of these specific indicators and not others, as well as an assessment of the years and the U.S. population for which data are available or unavailable. So, for example, there was a national survey of child care centers (one year only?). Other than that, there are monitoring data in California? Is that correct? Also, that lead is very important, but data are unavailable – is that also correct?

Reviewer 3:

There is not adequate explanation of the risk of each of the indicators. A sentence or two highlighting potential risks from exposure to these contaminants would be helpful. The CTEPP study mentions a 48 hour period in 2000-2001, but does not mention during what time of year. The First National Env. Health Survey of Child Care centers also does not include the time of year of the study.

The "data presented in the indicators" section for child care indicators 1 and 2 is very hard to follow. It would be clearer if the data explanations for each of the indicators were done separately, rather than combined.

For indicator school 1 there is mention that this data resulted from the California Healthy Schools Act of 2000, but no mention of this with regards to expanding data on a national level (which is stated as one of the three main objectives of this report). "Data Presented in the Indicator" (line 18) replace "mass of pesticides" with "amount of pesticides." There should be additional information on possible differences on pesticide use in California versus the rest of the nation with regards to climate, state regulations, etc.

Question 3 – Indicator Presentation

Reviewer 1:

Lead and asbestos and some other contaminants in the introduction do not seem to be included in the indicator graphs or bullet points. I would suggest leaving out the information which doesn't pertain to the indicator graphs. Or start a new indicator and/or mention that there is no data for this, however many state programs and CDC may have data.

Reviewer 2:

The indicators presented are clear. The issue is whether these indicators are sufficient, e.g., what about lead in day care centers and schools? The siting of schools? There are no indicators for these important domains.

Reviewer 3:

Indicator Child Care 1: Data presentation is confusing regarding both the regional and national data presented together in one graph. Perhaps these should be separated into two graphs. In the data notations on the bottom it should define specifically where the regional data is from.
For Indicator child care 2: the title should indicate that this is national data.

Question 4 – Context and Utility

Reviewer 1:

a.) Cut out all information in introduction not pertaining to indicator data. Does NHANES contain pesticide data by age. Maybe this would be the place to put the data from 1-5 year olds since most of these children would most likely be in day care. You could also include additional school age children.

b.) I did not find anything on how to improve the data. There also needs to be a section on the limitations of the data set.

c.) I am certain that these indicators do not do this.

Reviewer 2:

There are three indicators, as follows:
Indicator Child Care1: Percentage of environmental and personal media samples with detectable pesticides in child care facilities, 2001

Indicator Child Care2: Percentage of environmental and personal media samples with detectable industrial chemicals in child care facilities, 2001

Indicator School1: Pesticides used inside California schools by commercial applicators, 2002–2007

These indicators are concrete and quantifiable and represent key factors relevant to the environment and children in the United States. However, it is not clear whether the child care indicators (1 and 2) are based on single survey data sources or can be monitored over time. It is also not clear how representative the data are for the three indicators in relation to the U.S. population as a whole.

In relation to the potential to inform discussions among policymakers and the public about how to improve federal data on children and the environment – it appears that there are virtually no data on lead, asbestos, school siting and other key factors, and very little (and perhaps no ongoing data) on exposure to pesticides, and other contaminants in day care centers, and so on. What data there are is cause for great concern. But of equal concern is that there are so little data.

In relation to the need to provide indicators that can be used by policymakers and the public to track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children – there appears to be such a paucity of ongoing data sources that information or indicators for policymarkers is severely limited. It appears that data on many contaminants (e.g., lead, asbestos, radon) in child care centers and schools is not available. Also, that federal surveys to address indicators 1 and 2 in child care settings are not available in most states and may or may not be available over time, and that indicator 3 is based on data available only in California. Thus, the major point should be that data sources are needed to measure important indicators.

Reviewer 3:

The connection regarding relationships between environmental conditions and children's health should be strengthened throughout the section, as well for each indicator. As noted above, each indicator should have more specific text explaining the potential health risk of exposure to each indicator.

There is no discussion of the need for further investigation of these factors and tracking them over time, as well as improving federal data. This is a particularly glaring omission for Indicator School 1 where there is only data available from California. Lastly, there is no clear mention throughout the entire section about objective c (tracking and understanding potential environmental contaminants on children's health or identifying or evaluating ways to minimize environmental impacts on children).

Question 5 – Documentation

Reviewer 1:

A new section is needed on limitations to the current data and general recommendations on improving future data collection analysis and including additional data.

Reviewer 2:

The documentation appears adequate for the indicators.

Reviewer 3:

Although I am not familiar with all of the literature in these topic areas, the documentation seems to be the strongest component of this section. References are extensive and meta data tables appear to be complete and transparent.