U.S. EPA's Responses to Peer Review Comments Submitted on Draft Indicator Documents for America's Children and the Environment, Third Edition

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Environments and Contaminants

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Environments and Contaminants

Topic: Criteria Air Pollutants

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P2, L20 (Particulate Matter section)	**Comment:** 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.
		Response: We have incorporated clarifying text.
1/1	P2, L7 (Ground-level Ozone section)	**Comment:** 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.
		Response: We have incorporated clarifying text.
1/1	P1, L27-29	**Comment:** 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.
		Response: We have not changed the text on page 1, as our focus is on children. Additional subpopulations (including the elderly) are noted elsewhere in this text.
1/1	P10, L11-12	**Comment:** 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.
		Response: The text has been revised.
1/1	P1 P12, L23-26	**Comment:** 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.
		Response: We believe this is clear on page 1.

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1/1	P12, L16	**Comment:** Instead of "intensity of pollution" consider "degree of air pollution" or something related to "air quality." I'm concerned that readers may misinterpret "intensity."
		Response: The text has been revised to "concentrations for all pollutants for which an AQI has been established."
1/1	P26, L32	**Comment:** 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.
		Response: No response necessary.
1/1	P2, L20 (Particulate Matter section)	**Comment:** 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.
		Response: We have further clarified the difference between fine and thoracic coarse particles. We believe further discussion regarding the chemical composition of particles is not necessary for this text.
1/1	P1-4	**Comment:** 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.
		Response: We believe this is appropriately addressed in the pollutant-specific paragraphs on pp. 2-3.
1/1	P5-10 (Indicator E2)	**Comment:** 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."
		Response: The title has been changed to: "Percentage of children ages 0 to 17 years living in counties with 8-hour ozone and 24-hour $PM_{2.5}$ concentrations above the levels of air quality standards, by frequency of occurrence, 2009."
1/1	P1-4	**Comment:** 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.
		Response: We have added clarifying text noting natural sources of ozone precursors.

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1/1	P2, L28-29	**Comment:** 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.
		Response: The text has been revised to improve clarity.
1/1	N/A Throughout document	**Comment:** Explicitly note that $PM_{2.5}$ is a subset of PM_{10}.
		Response: The text has been revised.
1/1	P9, L17-L22	**Comment:** 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).
		Response: The text has been changed to: "In each year since 1999, between 1 and 5% of children lived in counties…"
1/1	P12	**Comment:** The limitations text on the AQI (E3) indicator (page 12) is helpful.
		Response: No response necessary.
1/1	P14-P15	**Comment:** 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.
		Response: This bullet has been removed.
1/2	P2, L24 P2, L32	**Comment:** 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".

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		Response: The text has been revised.
1/2	P1-4 (Topic Text)	**Comment:** 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.
		Response: Text relevant to the traffic proximity literature has been added.
1/2	P2, L19	**Comment:** 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)
		Response: Text has been added citing the recommended study and two more recent publications from the same research group: Islam, T., K. Berhane, R. McConnell, W.J. Gauderman, E. Avol, J.M. Peters, and F.D. Gilliland. 2009. Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children. *Thorax* 64 (3):197-202. Islam, T., R. McConnell, W.J. Gauderman, E. Avol, J.M. Peters, and F.D. Gilliland. 2008. Ozone, oxidant defense genes, and risk of asthma during adolescence. *American Journal of Respiratory and Critical Care Medicine* 177 (4):388-95.
1/2	P20 (References section)	**Comment:** 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.

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		Response: The Clark and Gehring studies have been referenced in the new text on effects of traffic-related pollution. The Kajekar paper had already been cited in the text – reference 21 in the review draft.
1/2	P3, L37	**Comment:** 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.
		Response: We decided not to include this text; the summary information presented in this section for each of the criteria pollutants focuses on effects with stronger evidence that have served as basis for the NAAQS. The two referenced studies are cited in the draft ACE3document for Birth Defects.
1/2	P3, L7-9	**Comment:** Page 3, line 7-9 sentence regarding suggestive evidence, add "and development of asthma. "
		Response: We chose not to add this statement, since the PM ISA does not make strong conclusions regarding development of asthma. Elsewhere in the text, we mention the limited evidence on prenatal exposure to PM and other air pollutants and its association to the development of asthma.
1/3	P2, L19	**Comment:** 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: 1) Page 2, line 19: insert "daily" before "mortality".
		Response: We have instead further clarified that this outcome is related to short term exposure.
1/3	P2, L31	**Comment:** 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: 2) Page 2, line 31: insert "into" after "penetrate".

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		Response: The text has been revised.
1/3	P2, L33	**Comment:** 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: **3)** Page 2, line 33: insert "maximum" before "diameter".
		Response: The text has been revised.
1/3	P2, L34	**Comment:** 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: **4)** Page 2, line 34: change "produced" to "formed"
		Response: The text has been revised.
1/3	P2, L35	**Comment:** 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: 5) Page 2, line 35: change "chiefly by combustion processes (including" to "chiefly of combustion products from".
		Response: The text has been revised.
1/3	P2, L37	**Comment:** 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: 6) Page 2, line 37: change "PM_{10}" to "Thoracic coarse particles". (Note: PM_{10} includes both coarse and fine particles)
		Response: The text has been edited to clarify coarse and fine fractions of PM_{10}.
1/3	P2, L40	**Comment:** 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: 7) Page 2, line 40: insert "excess" before "mortality".

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		Response: The text has been revised.
1/3	P3, L13	**Comment:** 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: 8) Page 3, line 13: change the 2nd "in" to "by".
		Response: The text has been revised.
1/3	P3, L27	**Comment:** 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: 9) Page 3, line 27: change "sulfur dioxide" to "sulfate particles".
		Response: The text was not revised. The ISA for Sulfur Oxides is clear that the findings regarding emergency department visits and hospital admissions are for short-term exposures to SO2.
1/3	P3, L39	**Comment:** 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: 10) Page 3, line 39: change "Nitrogen dioxide" to "Nitric oxide (NO) and nitrogen dioxide (NO_2) are".
		Response: The text has been revised.
1/3	P3, L40	**Comment:** 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: 11) Page 3, line 40: after "equipment" insert ", and NO is oxidized to NO_2 in the atmosphere".
		Response: The text has been revised.
1/3	P1-4 (Topic Text)	**Comment:** 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,

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		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.
		Response: A new paragraph to address this issue has been inserted in the Indicator text.
1/3	P20 (References section)	**Comment:** 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.
		Response: We generally rely on findings from EPA's Integrated Science Assessments (ISA) and Criteria Documents (CD) to characterize the literature, rather than citations of individual studies. We have added a limited number of references for selected key findings of interest, particularly in cases where there are important findings published since the most recent ISA/CD.
1/3	P20 (References section)	**Comment:** 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.
		Response: The ACE3 website will provide links to ISA/CDs and other key resources.
2/1	P7, L19 (Statistical Testing section) P12-13, L32 (Statistical Testing section)	**Comment:** 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.
		Response: •The text has been revised to clarify that statistical testing is applied to the annual indicator values, i.e. the percentage of children living in counties with pollutant concentrations greater than the level of each standard in each year •We do not think revision to the bullet points as suggested is necessary; the structure of the bullets provides the necessary reference to the particular trend. The points quoted by the reviewer are sub-bullets, where the immediately preceding text specifies the trend in question. For example, it

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		is clear that the "trends for sulfur dioxide and nitrogen dioxide" on page 9 are referring to the bullet point that reported statistics for these pollutants spanning the years 1999-2009. " •We believe the statistical significance results are important, and provide the analytic basis for saying whether or not an indicator value decreased over time. Reviewers of other topics were supportive of the addition of statistical testing for ACE3.
2/1	P5 (Indicator E1, and Indicator E2) P7, L30	**Comment:** 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.
		Response: The denominator of these calculations is all children in the U.S. We believe this approach, with the text statement regarding treatment of unmonitored counties, is preferable to a denominator of children in monitored counties only – which would imply that the percentage of children affected will be the same in unmonitored counties as it is in monitored counties.
2/1	P5 (Indicator E1 and Indicator E2)	**Comment:** 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.
		Response: Clarifications have been added to the indicator text. Regarding E1, EPA revoked the SO2 24 hour and annual standards in the last NAAQS revision, when the one-hour standard was adopted. For CO, only the 8-hour standard is included, because the 1-hour standard is rarely exceeded. For NO2 only the 1-hour standard is included, because the annual standard is rarely exceeded.
2/2	P5 (Indicator E1 and Indicator E2)	**Comment:** The indicator text is very well written and clearly understandable for broad audiences.
		Response: No response necessary.
2/3	P5 (Indicator E1, Indicator E2, Indicator E3)	**Comment:** For reasons that are not explicitly described, the presentation is divided into three specific indicators, i.e.: 1) E1 - % of children ages 0 to 17 years living in counties in which NAAQS were exceeded, 1999-2009;

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		2) 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; 3) 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: 1) the NAAQS are only partially relevant to children's risks, with some driven more by risks to adults; 2) 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; 3) the concentration limits have changed over time as NAAQS revisions have been promulgated; 4) they do not reflect risk factors other than central monitoring site concentrations that will affect a child's exposure, such as: a) Age; b) Pre-existing disease, such as asthma; c) Extent of physical activity, which affects breathing rates and volumes; d) Proximity to local pollution sources, such as traffic and other combustion sources.
		Response: Point 1- we added text regarding the extent to which children's health effects motivated the standard for each pollutant. Point 2 – all of the primary NAAQS are set in the judgment of the administrator and are requisite to provide public health protection with an adequate margin of safety. Point 3 – as stated in the text, the indicators use the same concentration (i.e. the level of the current standard) for all years shown. Point 4 – these considerations are all relevant to a risk assessment, but environmental indicators need not incorporate all of these elements. Indicators are preferably based on measured data; incorporation of many of these issues would require modeling and adopting a number of assumptions.
2/3	P5 (Indicator E1, Indicator E2, Indicator E3)	**Comment:** 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.

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		Response: Clarification of the focus in E2 on O3 and PM2.5 has been added.
2/3	P5-19 (Indicator Text)	**Comment:** 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.
		Response: We added a statement that many effects can be reduced by limiting outdoor activities on high pollution days.
3/1	P10 (Figure)	**Comment:** 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.).
		Response: We prepared a version of the figure in the suggested format, but concluded that it would be more difficult to interpret for non-scientific audiences.
3/1	P16 (Table E1, Table E1a)	**Comment:** • 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).
		Response: The reviewer's interpretation of 40.9% is correct. The note has been corrected. For comparisons of indicator values by race/ethnicity, ACE3 generally relies on the most current data available – in this case, 2009. Providing the data for additional years would not substantially increase the information provided, but would substantially increase resource requirements.
3/1	P17-18 (Table E2)	**Comment:** Why does Table E2 group years 1999-2005, and then 2006-2009?
		Response: This is due to how many columns can be fit in the width of a page.
3/1	P6-7	**Comment:** 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.

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		Response: This would require a separate map for each pollutant (and each year if one wanted to trace it over time). Resolution of a county-level map on a page is not sufficient to clearly identify particular counties. We believe our current presentation captures the critical information, which is the percentage of children nationally in counties without monitors.
3/1	P11, L1-2 P14 (Figure) P14, L2	**Comment:** 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)?
		Response: We have clarified the text. Calculation of this indicator uses day-by-day AQI values for each county, weighted by the number of children in each county. The denominator of the indicator calculation is: the number of children per county*365 days per year, summed over all counties. The numerator is the same, except that it considers number of days per year in each county with good, moderate, etc. air quality.
3/2	P17, L11 (Table E1B) P19, L4 (Table E3B)	**Comment:** 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.
		Response: The poverty level definition is presented in the report introduction.
3/2	P17-18 (Table E2)	**Comment:** 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.
		Response: We agree and will avoid such breaks in the final printed version.
3/3	P5-19 (Indicator Text)	**Comment:** *Do the indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data?* Yes.
		Response: No response necessary.

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3/3	P5-19 (Indicator Text)	**Comment:** *Are there ways in which the presentation and description of the indicator values could be improved?* No.
		Response: No response necessary.
3/3	P5-19 (Indicator Text)	**Comment:** 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 children's outdoor activities can reduce the effects of pollution, it can also limit the health benefits of such activities.
		Response: 1- We consider this more detail than needed for this report. 2 - We have added this point to the indicator text. 3 - We have added this point to the topic text.
3/3	P5-19 (Indicator Text)	**Comment:** 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.
		Response: We have added text noting that not all individuals will experience effects when the level of the standard is exceeded. We are not concerned only with chronic effects; and further, as stated in the text, for PM2.5 "annual and 24-hour standards work together to provide protection against effects associated with long- and short-term exposures."
4/1	P5-19 (Indicator Text)	**Comment:** 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.
		Response: Text has been added emphasizing that some individuals may experience effects at concentrations below the levels of the NAAQS. Text included in the review draft addressed the point that the indicator does not distinguish by magnitude of the concentration above the standard.

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4/1	P5-19 (Indicator Text)	**Comment:** 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.
		Response: The review draft addressed this with the statement that indicator E1 "is based on exceedances of individual standards and does not reflect any combined effect of multiple pollutants." This statement has been revised to "The indicator is based on concentrations of individual pollutants compared with individual standard levels, and does not reflect any combined effect of exposure to multiple criteria pollutants."
4/1	P10 (Figure) P17-18 (Table E2)	**Comment:** 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 frequency 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.
		Response: The indicator represents the number of days per year in which measurements greater than the level of the NAAQS were recorded. We have added text regarding frequency of monitoring, noting that the figure will likely understate the number of days of exceedances since measurements are not collected each day. We have also changed the title to "Percentage of children ages 0 to 17 years living in counties with 8-hour ozone and 24-hour PM2.5 concentrations above the levels of air quality standards, by frequency of occurrence, 2009." The indicator remains valuable for demonstrating that many children live in counties where exceedances occur on multiple days during the year.
4/2	P5-19 (Indicator Text)	**Comment:** 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.
		Response: No response necessary.
4/3	P8 (Figure)	**Comment:** 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 exceedances 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

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		percentages in recent years have reached very low levels.
		Response: No response necessary.
4/3	P10 (Figure)	**Comment:** 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.).
		Response: No response necessary.
4/3	P11 (Indicator E3) P14 (Figure)	**Comment:** 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.
		Response: The Air Quality Index is a widely used EPA calculation. We believe the three indicators are complementary.
5/1	P22-23 (Metadata section)	**Comment:** 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).
		Response: The metadata table has been revised as suggested.
5/1	N/A (Overall Text)	**Comment:** All of the indicators that are not based on the whole U.S. need to state the number of counties included.
		Response: We provide percentage of children in counties without monitors, which is more relevant than the number of counties.

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5/1	P12, L11-12	**Comment:** 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.
		Response: We have clarified the text. Percentage of children's days with no monitoring data is shown in E3 (it is the lack of data that is tracked in this particular instance).
5/1	N/A (Overall Text)	**Comment:** How was poor data quality addressed for the air pollutant measurements (e.g., measurement flagged with lab issues by EPA, etc.)?
		Response: For most of the criteria air pollutants, except for the PM2.5 annual standard and lead standard, data were obtained from EPA's AQS DataMart and no adjustments were made for incomplete data or data from "exceptional events." Data submitted by tribal, state, and local agencies must pass several quality assurance tests before they are saved in AQS and the AQS DataMart and each submitting agency annually certifies that the data they submit is correct. Data up to 2009 were not retrieved until January 2011 to allow sufficient time for annual quality assurance tests to be applied by submitting agencies. For the PM2.5 annual standard and lead standard, high quality AQS data were analyzed by EPA OAQPS and the annual summary statistics calculated using data completeness requirements and averaging rules were obtained from EPA OAQPS.
5/2	N/A (Overall Text)	**Comment:** The documentation is complete and transparent. See small comment under 3 above.
		Response: No response necessary.
5/3	N/A (Overall Text)	**Comment:** Yes.
		Response: No response necessary.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Environments and Contaminants

Topic: Hazardous Air Pollutants

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1		**Comment:** 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.
		Response: We have expanded the discussion of non-cancer health effects.
1/2	P1 (Topic Text) P8-9 (References section)	**Comment:** 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.
		Response: We have added an explanation for the separation of HAPs in indoor environments and referenced the related sections.
1/3	P1, L25-27	**Comment:** 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.
		Response: The mention of the indicator in the topic text is for introduction and justification for why the indicator is appropriate is more fully explained in the indicator text.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/3	P1 (Topic Text) P8-9 (References section)	**Comment:** 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.
		Response: We have added text on recent epidemiological studies of PAHs and adverse effects in children and of formaldehyde and childhood asthma. There are few other epidemiological studies of specific air toxics and children's health effects. Effects observed in studies of proximity to traffic are difficult to attribute to air toxics, because criteria pollutants are also part of the mixture and frequently have separate studies finding associations with the same outcomes. We have added text discussing traffic proximity findings in the ACE3 Criteria Pollutants topic, while noting that HAPs are part of the mix of traffic-related pollutants.
1/3	P1 (Topic Text)	**Comment:** 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.
		Response: We have expanded text on the nature of non-cancer health effects associated with some HAPs.
1/3	P2-7 (Indicator E4)	**Comment:** 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.
		Response: We have added additional material regarding the uncertainty of NATA: "NATA's computer modeling approach has the advantage of allowing estimation of HAP concentrations at locations throughout the United States, rather than in just those locations that have HAP monitors. However, compared with monitoring, the

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		computer model requires estimating quantities of HAP emissions, estimating locations of HAP emissions sources, and modeling the dispersion of HAPs in the atmosphere after they have been emitted." We also cited data showing that modeled data are generally consistent with the few existing monitors or lower and stated as a limitation that ambient concentrations of HAPs will change over time due to sources. NATA uses modeling because monitoring is insufficient due to the variation of HAP concentration within metropolitan areas or regions.
1/3	P2-7 (Indicator E4)	**Comment:** 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.
		Response: We have made additions to the text to provide more information about this limitation. The text now states: "Benchmarks for non-cancer effects incorporate assumptions that are based on adult respiratory physiology (i.e., breathing rates and lung structure); benchmarks for some HAPs would be lower if they were adjusted for children's respiratory physiology." We have also added text describing adjustments of risk estimates for certain carcinogens with adequate data to account for exposure in early life but note that there is not adequate data to adjust for all HAPs.
1/3	P2, L26-28	**Comment:** 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.
		Response: We believe this is sufficiently addressed by saying, "…with three health benchmark concentrations derived from scientific assessments conducted by EPA and other environmental agencies." Details for how different sources of benchmark values were prioritized are not necessary for this text, and are provided in the NATA document that we cite as the source of the benchmark values. We have also made an addition regarding updating the benchmarks, "Finally, the benchmark values for HAP s are uncertain to varying degrees, due to data limitations and the lag in time between when new studies become available and the completion of updated assessments by EPA and other government agencies."
2/1	P14, L5	**Comment:** 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?
		Response: The remainder of this paragraph on page 14 provided the explanation for the difference in the count of HAPs – due to the multiple groups included in the HAP Polycyclic Organic Matter.

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2/1	P2, L18	**Comment:** 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.
		Response: Indicator E4 is based on modeled data from NATA which does not provide data for some HAPs. The text has been updated to show results from 2005 for which NATA provides estimated concentrations of 179 HAPs in ambient air. The methods documentation provides more information on the count of HAPs included in calculating the indicator.
2/1	P3, L6-7	**Comment:** 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.
		Response: Specific examples of non-cancer effects have been added to the topic text for clarity.
2/1	P5, L2-9	**Comment:** 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)?
		Response: We have added text in the benchmark description regarding the potential levels, "The comparison to the cancer risk benchmark incorporates data for all HAPs considered carcinogenic to humans, likely carcinogenic to humans, or with suggestive evidence of carcinogenicity. The majority of HAPs included in the comparison to the cancer risk benchmarks are considered "carcinogenic to humans" or "likely carcinogenic to humans.""
2/1	P5, L5-9	**Comment:** 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).
		Response: This would be of minimal utility because a small proportion of the risk is from HAPs with "suggestive evidence of carcinogenicity."
2/1	P2-7 (Indicator E4)	**Comment:** 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

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		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.
		Response: The indicator has been revised to use the census tract-level estimates instead of the county-level estimates.
2/1	P14, L18-19	**Comment:** Chromium's valence states affect its toxicity, so the combination of all chromium compounds to Chromium VI compounds (page 14) is an odd choice.
		Response: We have revised the analysis of chromium compounds. We previously used the value for chromium compounds, which represented the summed concentrations for several different chromium species – both trivalent and hexavalent. We obtained files from OAQPS with ambient concentrations for the individual chromium species. Concentrations of hexavalent chromium species were summed together, and the benchmarks for Chromium VI were applied to this new sum.
2/1	P16, L20-38	**Comment:** Does the Private University School Survey contain information for all private schools in the U.S.?
		Response: That is the target population and they have a record of every private school in the US.
2/1	P17-18, L38-	**Comment:** 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.
		Response: We believe this is clear when we say the total school populations. It is noted earlier that the schools used are public and private schools.
2/1	P14	**Comment:** 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.
		Response: The differences in the two files for 2-chloroacetophenone had negligible effects on the results. With the update to NATA 2005, this text has been removed.
2/2	P2, L5	**Comment:** 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.

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		Response: This error has been corrected.
2/2	P2, L19-22	**Comment:** (Lines 19-22, page 2) Are any modeled values statistically significantly lower than measured values?
		Response: The model- to- monitor comparisons do not use statistical hypothesis testing. Comparisons are ratios comparing the annual average monitor concentration to the modeled concentration.
2/2	P3, L4-7	**Comment:** (Lines 4-7, page 3) This sentence is confusing. Is the third benchmark for minimal risk or for risk for other health effects?
		Response: The text has been revised to say "minimal risk for adverse non-cancer health effects."
2/2	P3, L13-14	**Comment:** (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…"
		Response: This text has been revised.
2/2	N/A Overall text	**Comment:** Text is understandable to an educated person.
		Response: No response necessary.
2/2	P3, L15-19	**Comment:** 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.
		Response: The text has been revised for clarity and addresses the justification for adult benchmarks as well as limitations.
2/3	P2-7 (Indicator E4)	**Comment:** 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.
		Response: No response necessary.

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3/1	P5-6	**Comment:** 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.
		Response: The bullet points directly after the figure for Indicator E4 are meant to be in direct reference to the figure for ease of viewing. Later bullet points highlight other key points from the data tables or other analyses.
3/1	P10 (Table, Row 6)	**Comment:** 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.
		Response: We address spatial resolution elsewhere in the metadata.
3/1	P10-11 (Metadata section)	**Comment:** 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.
		Response: Metadata are intended to describe the data source, not the indicator.
3/1	P3, L15-16	**Comment:** 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?
		Response: Text has been revised to say "Because they are typically based on studies of adults or mature laboratory animals, the three benchmarks generally reflect health risks to adults…"
3/1	P11 (Table, Row second from bottom)	**Comment:** 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.
		Response: We do not think such text is necessary. The statement in the metadata indicates that there may be spatial variability in quality of the emissions estimates or performance of the dispersion model. The indicator does not present results for any geographic level/division other than nationwide.
3/2	P5-7 (Indicator E4)	**Comment:** Graph, bullet points and data tables are all simple and easy to grasp. They generally summarize the data well.

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		Response: No response necessary.
3/2	P5-7 (Indicator E4)	**Comment:** Although they would be long, tables giving the indicators for each HAP might be a helpful adjunct, as an appendix, perhaps.
		Response: We may consider this addition in future work, for select HAPs that contribute the most to benchmark exceedances.
3/2	P5-7 (Indicator E4)	**Comment:** 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.
		Response: No response necessary.
3/2	P5-7 (Indicator E4)	**Comment:** 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.
		Response: The current version of the indicator uses NATA 2005 data, and the updated set of benchmarks compiled by EPA for the release of NATA 2005 in 2011.
3/3	P5-7 (Indicator E4)	**Comment:** 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.
		Response: We have added data tables with indicator values (calculated at the census tract level) by race/ethnicity and by income group. The metadata statement has been revised.
3/3	P5-7 (Indicator E4)	**Comment:** I also think it would useful to present a graph or table showing the results if diesel particles were included in the analysis.
		Response: EPA has made the decision not to integrate Diesel PM cancer risks with other HAP risks. The basis for this decision is feedback from Science Advisory Board

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		reviews on estimation of cancer potency for Diesel PM.
3/3	P5-6, L6-	**Comment:** 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.
		Response: An additional graph could provide useful information, but it is not possible to include all figures of interest for ACE3. The number of HAPs exceeding cancer benchmarks per tract would not capture situations where a number of HAPs are just below a benchmark but combine to exceed the benchmark. Since drivers are likely to differ by location, it is not clear how this information could be captured in a figure appropriate for this report.
4/1	P2-7 (Indicator E4)	**Comment:** Overall, I think the indicators are useful, with the caveats of the limitations described above, especially regarding the usefulness of the non-cancer indicator.
		Response: No response necessary.
4/1	P2-7 (Indicator E4)	**Comment:** 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.
		Response: These limitations in understanding of the effects of environmental contaminants in general are discussed in the introduction to the report, and we have expanded the text regarding limitations of the HAP benchmarks. We have added text to address the threshold limitation by saying, "To the extent that underestimation occurs, the percentage of children living in census tracts exceeding the benchmark levels may be understated. In addition, the indicator does not differentiate between census tracts in which the benchmarks are exceeded by a large margin and those in which estimated HAP concentrations are just above the benchmark concentrations." This issue is partially addressed by the use of two different risk levels for the cancer

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		benchmarks.
4/1	P2-7 (Indicator E4)	**Comment:** 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.
		Response: Individual sensitivity is addressed in the report introduction. Limitations are addressed uniformly throughout ACE3 and we believe the current method is appropriate. We think the limitations are expressed more clearly in the context of describing the indicator generally, and an attempt to separate them into a limitations section would be confusing. We have added text addressing the limitation regarding variation in response in the indicator text: "Due to variation in human response to HAP exposure and uncertainty in the benchmark values, it is not necessarily the case that a person living in a location where this benchmark is exceeded will experience adverse effects. It is also possible that individuals may experience effects at levels below the benchmark level."
4/2	P2-7 (Indicator E4)	**Comment:** 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. a) 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.

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		Response: We have added text explaining our handling of indoor air, "In addition to their presence in ambient air, many HAPs have indoor sources, and the indoor sources may frequently result in greater exposure than the presence of HAPs in ambient concentrations. Sufficient data are not available to develop an indicator considering the combined exposure to HAPs from both indoor and outdoor sources; therefore the following indicator considers only levels of HAPs in ambient air." There is also a footnote linked to this statement explaining that indoor HAPs are further discussed in other topics.
4/2	P2-7 (Indicator E4)	**Comment:** b) 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.
		Response: No response necessary.
4/2	P2-7 (Indicator E4)	**Comment:** c) 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.
		Response: The text discusses the limitations in looking at NATA over time. Current risk benchmarks compiled for NATA 2005 are used in the current analysis.
4/3	P2-7 (Indicator E4)	**Comment:** 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.
		Response: The indicator has been updated to 2005 and the census tract level estimates are now used.
4/3	P6, L3-9	**Comment:** 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

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		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.
		Response: Based on the scope of this report and the available data, we believe we have sufficiently introduced the potential risks of diesel particles.
4/3	P2-7 (Indicator E4)	**Comment:** 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.
		Response: Text has been added to the description of the benchmarks to address this issue, "Further, the benchmarks reflect risks of continuous exposure over the course of a lifetime. Potential risks from higher concentrations experienced over a short amount of time (one day, one hour, or less) may in some cases trigger immediate responses, such as asthma attacks or effects on the central nervous system are not addressed by these benchmarks."
4/3	P2-7 (Indicator E4)	**Comment:** 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.
		Response: We agree that changes over time are an important aspect of health exposures; however the best available data was used and feel that we address these limitations. We appreciate the suggestions and will consider them for future editions of ACE.
5/1	P1, L7-8	**Comment:** 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.
		Response: The introduction to the Environments and Contaminants section describes the various topics covered and we believe this will be evident to the reader. We have also added a footnote in regards to this, "Lead is an exception: it is regulated as a criteria pollutant and "lead compounds" are included on the list of HAPs. Note that criteria pollutants are discussed further in the *Criteria Air Pollutants* topic."

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
5/1	P1, L23-24	**Comment:** • 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?
		Response: We believe this is phrased to be factually accurate and explain the necessity of modeling. We have also added an explanation of NATA's computer modeling approach in the indicator text to be more descriptive.
5/1	P3, L31-35	**Comment:** • 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.
		Response: We have made additions in the topic text to provide more information about indoor exposures. We have added an example of formaldehyde exposure in indoor environments as well adding, "In addition to their presence in ambient air, many HAPs also have indoor sources, and the indoor sources may frequently result in greater exposure than the presence of HAPs in ambient air. Sufficient data are not available to develop an indicator considering the combined exposure to HAPs from both indoor and outdoor sources; therefore the following indicator considers only levels of HAPs in ambient air." There is also a footnote linked to this statement explaining that indoor HAPs are further discussed in other topics.
5/1	P13, L39-40	**Comment:** • 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.
		Response: With the update to NATA 2005 concentrations and documentation, this point no longer applies and is not included in the revised draft.
5/2	N/A Overall	**Comment:** The write up is generally very clear and concise. The mathematics are simply and straightforwardly described and easy to follow.
		Response: No response necessary.
5/2	P12, L16-18	**Comment:** (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.
		Response: We believe the reference to the NATA document on health benchmarks is sufficient.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
5/3	P8-9 (References section)	**Comment:** The citations in the document are good, but should be supplemented as indicated in response #1.
		Response: We have added a number of citations in our expanded discussion of HAPs health effects findings.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Environments and Contaminants

Topic: Indoor Environments

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P1-4 (Topic Text)	**Comment:** The topic text appropriately and clearly describes the topic and its importance for children's environmental health.
		Response: No response necessary.
1/1	P1-4 (Topic Text)	**Comment:** There are a few additional aspects of the topic that would be appropriate to include for this audience. 1) 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)
		Response: We have added new text on third-hand exposures to ETS in buildings and automobiles.
1/1	P1-4 (Topic Text)	**Comment:** There are a few additional aspects of the topic that would be appropriate to include for this audience. 2) 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: (Need some references)
		Response: While we were able to find several studies showing differences in soil lead levels between rural and urban environments, the only references we have found for urban-rural differences in blood lead levels are from NHANES III. [Brody, D.J., J.L. Pirkle, R.A. Kramer, K.M. Flegal, T.D. Matte, E.W. Gunter, and D.C. Paschal. 1994. Blood lead levels in the US population. Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991). *Journal of the American Medical Association* 272 (4):277-83.] These may not reflect the current

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		situation, given the substantial decline in blood lead levels since NHANES III, so we chose not to incorporate this information.
1/1	P1, L7	**Comment:** 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
		Response: Toys have been added to this sentence.
1/1	P1, L20	**Comment:** Consider the following edits as ways to make the text more readable to a variety of audiences. - 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.
		Response: The text has been removed.
1/1	P1, L39-40	**Comment:** Consider the following edits as ways to make the text more readable to a variety of audiences. - page 1, line 39-40, please rewrite as "higher nicotine concentrations in air"
		Response: This sentence has been revised to: "Adult smoking in personal cars can have a significant impact on children's environmental tobacco smoke exposures, as the air in smokers' cars tends to have significantly higher nicotine concentrations than that in non-smokers' cars."
1/1	P2, L13	**Comment:** Consider the following edits as ways to make the text more readable to a variety of audiences. - page 2, line 13, please rewrite as "based on national survey data of homes"
		Response: This edit has been made.
1/1	P2, L29	**Comment:** Consider the following edits as ways to make the text more readable to a variety of audiences. - page 2, line 29, "wheezing" illnesses would be clearer
		Response: This text has been revised.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P2, L30	**Comment:** Consider the following edits as ways to make the text more readable to a variety of audiences. - page 2, line 30, are you sure ETS is a known "cause" or just a known "risk factor" of SIDS
		Response: The Surgeon General's report concludes on page 155 that ETS "causes SIDS."
1/1	P2, L34-35	**Comment:** Consider the following edits as ways to make the text more readable to a variety of audiences. - 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
		Response: The sentence has been revised to clarify that exposure of pregnant women to ETS has been linked to a reduction in **mean** birth weight.
1/1	P2, L38	**Comment:** Consider the following edits as ways to make the text more readable to a variety of audiences. - page 2, line 38, please add "in children" after asthma
		Response: This text has been removed.
1/1	P3, L39-41	**Comment:** Consider the following edits as ways to make the text more readable to a variety of audiences. - page 3, line 39-41, seems like there should be a citation for this statement
		Response: A reference has been added, citing EPA's lead and home renovations page.
1/2	P1-4 (Topic Text)	**Comment:** • 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.
		Response: No response necessary.
1/2	P1-4 (Topic Text)	**Comment:** • 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.
		Response: Text has been added to explain this point.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	P1-4 (Topic Text)	**Comment:** • 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.
		Response: Arsenic, pesticides, and mold were measured only in the American Healthy Homes Survey (2005-2006) and not in the National Survey of Lead and Allergens in Housing (1998-1999). The allergens measured in NSLAH were cockroach allergens, dust mite allergens, cat allergen, dog allergen, rodent allergens, allergens of the fungus Alternaria alternata, and endotoxin. NSLAH did ask residents if they smelled mildew in the house, but mold was not measured. Text has been added explaining that lead was selected because data are available to represent more than one point in time.
1/3	P1-4 (Topic Text)	**Comment:** 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.
		Response: The last paragraph of the topic overview has been revised to read: "The following indicators present data on environmental tobacco smoke and lead dust hazards in children's homes, because they are well-established indoor hazards to children's health and because they have nationally representative data available for more than one point in time. Other indoor environmental hazards in children's homes generally lack nationally representative data necessary for development of indicators that can identify any changes over time. Unlike many outdoor pollutants, indoor pollutants are not regulated or systematically monitored in residential settings, and data collection for indoor pollutants is much more limited"
1/3	P1-4 (Topic Text)	**Comment:** 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 that74% of children who did not report a smoker in the household had detectable cotinine levels (Braun J, et al. EHP 2008).
		Response: We have added text on underestimation, referencing Braun et al, Kalkbrenner et al., and the Surgeon General report. Indicators of serum cotinine levels are presented separately in the ACE Biomonitoring section.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/1	P5, L12	**Comment:** Indicator E5 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"
		Response: We use "ages" throughout ACE3 to describe age ranges.
2/1	P5, L18	**Comment:** Indicator E5 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 18, should be "NHIS only in"
		Response: This edit has been made (we assume this refers to line 14 in the PDF, not line 18).
2/1	P5, L26-27	**Comment:** Indicator E5 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 26-27, should be "researchers have used these data to associate ETS exposure with adverse effects on childhood lung function and other health outcomes.
		Response: This edit has been made.
2/1	P6, L1	**Comment:** Indicator E5 The text for this indicator is not as clearly written as for others and should be closely edited. Consider the following edits. - page 6, line 1, should be "Children age 6 years"
		Response: We use "ages" throughout ACE3 when referring to age ranges.
2/1	P5-8 (Indicator E5) P5, L17	**Comment:** 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."
		Response: The text has been clarified to note that if the answer to the first question was positive, participants were asked how many days per week smoking usually occurred anywhere inside the home.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/1	P9-13 (Indicator Dust1) P9, L7 P9, L18-19	**Comment:** Indicators Dust1 1. 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. 2. 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.
		Response: 1. We revised the text on page 9 to clarify: "Samples collected from the housing units surveyed in NSLAH and AHHS were analyzed to determine their lead content. HUD then compared these measured lead levels to federal guidelines to identify homes with lead-contaminated dust, deteriorated lead-based paint, and lead-contaminated soil hazards." 2. We have adopted the convention of "children ages 0 to 5 years" throughout ACE3 when referring to age ranges, and we believe this is clear.
2/2	P2, L10-17	**Comment:** 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.
		Response: The following text now appears at the end of the topic introduction: "The following indicators present data on environmental tobacco smoke and lead dust hazards in children's homes, because they are well-established indoor hazards to

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		children's health and because they have nationally representative data available for more than one point in time. Other indoor environmental hazards in children's homes generally lack nationally representative data necessary for development of indicators that can identify any changes over time. Unlike many outdoor pollutants, indoor pollutants are not regulated or systematically monitored in residential settings, and data collection for indoor pollutants is much more limited."
2/2	P2, L10-17	**Comment:** 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.
		Response: The following text now appears at the end of the topic introduction: "The following indicators present data on environmental tobacco smoke and lead dust hazards in children's homes, because they are well-established indoor hazards to children's health and because they have nationally representative data available for more than one point in time. Other indoor environmental hazards in children's homes generally lack nationally representative data necessary for development of indicators that can identify any changes over time. Unlike many outdoor pollutants, indoor pollutants are not regulated or systematically monitored in residential settings, and data collection for indoor pollutants is much more limited."
2/2	P5, L10-13 P20 (Metadata section)	**Comment:** 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.
		Response: The text has been clarified.
2/2	P5-13 (Indicator E5, Indicator Dust1) P5, L4-5 (Overview section)	**Comment:** 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)?
		Response: This information is provided in the overview box for the indicator and the discussion of the data source. For ETS, 1994 and 2005 were the only years with comparable data from the NHIS (1998 is not comparable, and the question was not asked in NHIS in other years). Comparable data for 2010 are now available and have been added to the indicator.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/2	P9-13 (Indicator Dust1)	**Comment:** The discussion of lead should further emphasize that the measure is exposure in homes not measures of lead in children, although biomarkers do exist.
		Response: We believe the text is clear on this point; see especially the sentence on page 10, line 22: "This indicator represents the potential for children's indoor exposure to lead based solely on the percentage of children ages 0 to 5 years living in homes with levels of lead-based paint and dust above federal standards." Indicators of blood lead levels are also presented separately in the ACE Biomonitoring section.
2/2	P5-8 (Indicator E5)	**Comment:** 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.
		Response: We have added a sentence on underestimation (referencing the Surgeon General's report).
2/2	P5-8 (Indicator E5) P9-13 (Indicator Dust1)	**Comment:** 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.
		Response: We have added text to the ETS and lead indicator sections of Indoor Environments highlighting these distinctions.
2/2	P26-36	**Comment:** 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.
		Response: This comment pertains to the detailed documentation of the indicator calculation, which is intended for more technical audiences. We believe the indicator text in the main report provides sufficient detail for general audiences to understand the indicator.
2/2	N/A (Indicator text)	**Comment:** • Please clarify how observations for persons of multiple races were processed in calculation of the indicators by racial group.
		Response: This is discussed in the Race/Ethnicity and Family Income section of the Methods documentation. In general, survey respondents indicating multiple races are considered in the "All Other Races/Ethnicities" grouping.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/2	N/A (Indicator E5)	**Comment:** • 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).
		Response: We provide the actual NHIS questions, which lump cigarettes, cigars, and pipes together, so we believe this is implicit.
2/2	P34	**Comment:** • 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).
		Response: This is discussed in the Statistical Comparisons area of the Methods section. In cases where both the adjusted and unadjusted comparisons provide the same conclusion, we do not believe it is necessary to specify adjusted or unadjusted.
2/2	P22, L3	**Comment:** • Define primary sampling unit, or use alternate phrasing (page 22).
		Response: This term has been defined in the metadata table.
2/2	P25, L17	**Comment:** • It's unclear what is meant by "supplementary files" on page 25.
		Response: We have deleted this sentence from the Methods summary, since the files used to develop the indicator are described in detail in the Overview of Data Files section.
2/2	P 34, L14-L15	**Comment:** • 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".
		Response: These changes have been made.
2/3	P25-43 (Methods section)	**Comment:** 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.
		Response: The methods sections for all indicators will be available only online for reference, and not included in the printed edition of ACE3.
2/3	P5-8 (Indicator E5)	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
	P12, L8 (Table E5a)	large underestimate of children's SHS exposure. It also results in several empty cells in Table E5a.
		Response: We have added text discussing the issue of underestimates. Note that there are separate indicators in the Biomonitoring section on cotinine levels in children and women of childbearing age.
3/1	P5-8 (Indicator E5) P7 (Figure)	**Comment:** 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.
		Response: We will ensure that the word "level" is included the first time that the term "poverty level" is used in the text under each graph; we believe the full meaning is clearly implied in subsequent instances under the same graph.
3/1	P5-8 (Indicator E5) P7 (Figure)	**Comment:** Indicator E5 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.
		Response: There are differences for the other income groups – but the differences are much greater for children below poverty, and we therefore considered those to be of greatest interest.
3/1	P5-8 (Indicator E5) P7 (Figure)	**Comment:** Indicator E5 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.
		Response: In 2005, the difference in rates for Puerto Rican children below poverty level compared with Mexican-Americans below poverty level was statistically significant. However, with the update to 2010 data the difference was not statistically significant, and estimates for Puerto Rican children were more uncertain (high relative standard errors). We therefore did not include this comparison in the bullet points.
3/1		**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We are using a common color scheme and design for all ACE3 graphs to be used on the website and report. We believe these are clear and legible and they meet the requirements for both print publication and web publication.
3/1		**Comment:** Indicator Dust1 The text should be understandable to a wide variety of audiences.
		Response: No response necessary.
3/2	P5-8 (Indicator E5)	**Comment:** 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).
		Response: We agree, however it is not feasible to include all data of interest in figures in ACE3.
3/2	P9-13 (Indicator Dust1)	**Comment:** 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).
		Response: The Methods section describes this point in more detail; we do not feel it is necessary to include detailed discussion of these types of issues in the main indicator text. We try to limit analytic and methodological details in the main text to keep the report accessible for broad audiences. Note that the survey was designed to be representative of housing in the United States – not housing with children or housing with lead hazards.
3/2	P5-13 (Indicator E5 and Indicator Dust1)	**Comment:** 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.
		Response: This type of presentation is beyond the scope of ACE. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
3/3	P12, L2 (Table E5)	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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.
		Response: The Biomonitoring section includes an indicator on cotinine levels in children and women of child-bearing age. We have added text to the Indoor Environments ETS indicator text explaining that questionnaires are likely to result in underestimates of exposure.
3/3	P9-13 (Indicator Dust1)	**Comment:** 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.
		Response: Serum cotinine and blood lead data are presented in the ACE3 Biomonitoring section.
3/3	P9-13 (Indicator Dust1)	**Comment:** 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.
		Response: We have added text (citing Wilson et al.) about ETS exposure in multi-unit dwellings.
3/3	N/A (Overall Text)	**Comment:** 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.
		Response: We believe the current report organization is preferable.
4/1	P5-8 (Indicator E5)	**Comment:** 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.

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		Response: As noted above, with the update of the indicator to incorporate data from the 2010 NHIS, some of these results changed. In the 2010 data, the most pertinent differences by race/ethnicity were for children in homes below poverty level, so we focused on that finding.
4/1	P9-13 (Indicator Dust1)	**Comment:** 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.
		Response: Because of the relatively small number of surveyed homes with lead hazards and young children, stratified values may not be reliable.
4/2	N/A (Overall Text)	**Comment:** 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: 1. 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? 2. 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. 3. These indicators do not group children into "safe" and "unsafe" levels of

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		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.
		Response: The text at the end of the topic introduction states that "The following indicators present data on environmental tobacco smoke and lead dust hazards in children's homes, because they are well-established indoor hazards to children's health and because they have nationally representative data available for more than one point in time. Other indoor environmental hazards in children's homes generally lack nationally representative data necessary for development of indicators that can identify any changes over time. Unlike many outdoor pollutants, indoor pollutants are not regulated or systematically monitored in residential settings, and data collection for indoor pollutants is much more limited." Ages used are discussed in the overview of each indicator. We have added text to the introductions of both indicators explaining that older children can also be at risk. We have also added text clarifying that there is no "safe" level of exposure to ETS or to lead.
4/3	P5-8 (Indicator E5)	**Comment:** 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.
		Response: We have added text and references on the likelihood that parental questionnaires underestimate exposure. Note that the Biomonitoring section includes indicators for cotinine levels in children and women of child-bearing age.
4/3	P9-13 (Indicator Dust1)	**Comment:** 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.
		Response: Our approach is to discuss statutes and regulations pertinent to understanding a particular topic in the text for that topic; thus, for example, we discuss federal requirements relevant to lead hazards in housing in the Indoor Environments topic. If this text were moved elsewhere, it would make this indicator more difficult to understand. Other lead requirements are not pertinent to this indicator, and their inclusion here would be confusing to the reader.
4/3	P2-3 (Environmental Tobacco Smoke) P5-8 (Indicator E5)	**Comment:** This document should emphasize the reasons for the decline in SHS exposure, including bans on public smoking.

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		Response: We have added text on the reasons for the decline, including smoking bans.
4/3	P2-3 (Environmental Tobacco Smoke) P5-8 (Indicator E5)	**Comment:** 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.
		Response: We have added text on smoking bans in offices and other public places and cited the recommended references.
5/1	N/A (Overall Text)	**Comment:** The documentation is very thorough and transparent. It would be possible for someone to replicate all calculations.
		Response: No response necessary.
5/2	P6, L18-24	**Comment:** 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.
		Response: For the Environments and Contaminants section, we decided to retain discussion of statistical testing for each indicator where it is applied, because statistical testing is not applied to several of the indicators in this section. For the Biomonitoring and Health sections, where statistical testing is applied to each indicator, we decided to move the relevant text to the section introduction.
5/3	N/A (Overall Text)	**Comment:** Yes, with exceptions noted above.
		Response: No response necessary.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Environments and Contaminants

Topic: Drinking Water Contaminants

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1/1	P1-4 (Topic Text)	**Comment:** 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).
		Response: No response necessary.
1/1	P1-4 (Topic Text)	**Comment:** 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.
		Response: We have added a brief section summarizing the literature on prenatal and childhood Mn exposure and associated neurobehavioral impairments: "Manganese is a naturally occurring mineral that can enter drinking water sources from rocks and soil or from human activities. While manganese is an essential nutrient at low doses, chronic exposure to high doses may be harmful, particularly to the nervous system. Many of the reports on adverse effects from manganese exposure are based on inhalation exposures in occupational settings. Fewer studies have examined health effects associated with oral exposure to manganese. However, some recent epidemiological studies have reported associations between long-term exposure to high levels of manganese in drinking water during prenatal development or childhood and intellectual impairment; decreased non-verbal memory, attention, and motor skills; hyperactivity; and other behavioral effects. Most studies on the health effects of manganese have been conducted in countries where manganese exposure is generally higher than in the United States. However, two studies conducted in specific areas of high manganese contamination in the United States reported associations between prenatal or childhood manganese exposure and problems with general intelligence, memory, and behavior. Although there is no health-based regulatory standard for manganese in drinking water, EPA has set a voluntary standard for manganese as a guideline to assist public water systems in managing their drinking water for aesthetic considerations, such as

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		taste, color and odor."
		Comment: 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.
		Response: We mentioned cognitive function as an effect associated with arsenic exposure in the review draft, but in order to address the comment more specifically we have added a separate sentence on arsenic and cognitive function. The sentence reads "These include studies of associations between high levels of exposure to arsenic and abnormal pregnancy outcomes, such as spontaneous abortion, still-births, reduced birth weight, and infant mortality, as well as associations between early-life exposure to arsenic and increased incidence of childhood cancer and reduced cognitive function."
1/1	P1-4 (Topic Text)	**Comment:** 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.
		Response: We have a biomonitoring section dedicated to perfluorochemicals where we discuss associations between prenatal exposure and impaired fetal growth.
1/1	P1-4 (Topic Text)	**Comment:** 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
		Response: We have added more information to the discussion of lead in drinking water, although we think that including details on sampling methods is beyond the scope of this introductory text. In the ACE Biomonitoring section, there is a separate section dedicated to discussion of lead. We have added information to the sentences here on lead to read "Drinking water is a known source of lead exposure among children in the United States, particularly from corrosion of pipes and other elements of the drinking water distribution systems. Exposure to lead via drinking water may be particularly high among very young children who consume baby formula prepared with drinking water that is contaminated by leaching lead pipes. The National Toxicology Program has concluded that childhood lead exposure is associated with reduced cognitive function, reduced academic achievement, and increased attention-related behavioral problems."

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1/2	P1-4 (Topic Text)	**Comment:** 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.
		Response: We have emphasized that the arsenic studies were performed in other countries where exposures are much greater than in the U.S. The following statement was moved earlier in the paragraph, before the study descriptions: "Population studies of health effects associated with arsenic exposure have been conducted primarily in countries such as Bangladesh, Taiwan, and Chile, where arsenic levels in drinking water are generally much higher than in the United States due to high levels of naturally occurring arsenic in groundwater." We have added more information to the discussion of lead in drinking water. In the ACE Biomonitoring section, there is a separate section dedicated to discussion of lead that goes into much more detail and includes some discussion of the interaction with nutritional status. We have added information to the sentences here on lead to read "Drinking water is a known source of lead exposure among children in the United States, particularly from corrosion of pipes and other elements of the drinking water distribution systems. Exposure to lead via drinking water may be particularly high among very young children who consume baby formula prepared with drinking water that is contaminated by leaching lead pipes. The National Toxicology Program has concluded that childhood lead exposure is associated with reduced cognitive function, reduced academic achievement, and increased attention-related behavioral problems."
1/2	P1-4 (Topic Text)	**Comment:** 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.
		Response: The text states that EPA has standards to control levels of these contaminants in drinking water, so we believe it is clear that steps are in place to protect against high exposures. We have added qualitative clarifications of the exposure levels in

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		the studies where these had been omitted. We inserted language to clarify that it is high levels of nitrates and nitrites that are associated with health effects to read: "High levels of nitrates and nitrites can cause the blood disorder methemoglobinemia (blue baby syndrome) and have been associated with thyroid dysfunction in children and pregnant women." Similarly, we clarified the exposure levels for disinfection byproducts-associated health effects. The sentence reads "Consumption of drinking water from systems in the United States and other industrialized countries with relatively high levels of disinfection byproducts has been associated with bladder cancer and developmental effects in some studies."
1/2	P1-4 (Topic Text)	**Comment:** 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.
		Response: We include text about the challenges in extrapolating animal data to humans in the introduction to the report.
1/2	P1-4 (Topic Text)	**Comment:** 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)
		Response: The topic text is meant to give an overview of the issue and how it is relevant for children's health. We provide a qualitative characterization of the exposure levels in the cited studies (see above) and have links to the EPA website that has all MCLs. As explained in the text, actual contaminant levels occurring during reported violations are not available.
1/2	P1, L1	**Comment:** 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.
		Response: We have made this revision. The sentence now reads "Drinking water sources may contain a variety of contaminants that, at elevated levels, have been associated with increased risk of a range of diseases in children, including acute diseases such as gastrointestinal illness, developmental effects such as learning disorders, endocrine disruption, and cancer."

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1/2	P1, L6	**Comment:** Page 1, line six : should say "dose" rather than "exposure"
		Response: We believe that "exposure" is adequate since it commonly refers to intake for body weight (mg/kg/day).
1/2	P1, L24	**Comment:** 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.
		Response: We have added more information to the discussion of lead in drinking water, although we think that including details on water regulations is beyond the scope of this introductory text. In the ACE Biomonitoring section, there is a separate section dedicated to discussion of lead. We have added information to the sentences here on lead to read "Drinking water is a known source of lead exposure among children in the United States, particularly from corrosion of pipes and other elements of the drinking water distribution systems. Exposure to lead via drinking water may be particularly high among very young children who consume baby formula prepared with drinking water that is contaminated by leaching lead pipes. The National Toxicology Program has concluded that childhood lead exposure is associated with reduced cognitive function, reduced academic achievement, and increased attention-related behavioral problems."
1/2		**Comment:** 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?)
		Response: The topic text is meant to give an overview of the issue and how it is relevant for children's health. We have tried to give basic information about whether exposure levels are high or at levels currently found in some U.S. drinking water systems and if the exposures are long-term or short-term, where we are able. Adding details about exposure and duration for each study might make the report difficult to understand for non-researchers. Studies use different exposure metrics, have different designs and other details that cannot be described briefly. We inserted language to clarify that it is high levels of nitrates and nitrites that are associated with health effects to read "High levels of nitrates and nitrites can cause the blood disorder methemoglobinemia (blue baby syndrome) and have been linked to thyroid dysfunction in children and pregnant women." Similarly, we clarified the exposure levels for disinfection byproducts-associated

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		health effects. The sentence reads "Consumption of drinking water from systems in the United States and other industrialized countries with relatively high levels of disinfection byproducts has been associated with bladder cancer and developmental effects in some studies." We also moved the sentence about arsenic levels in the U.S. vs. other countries further up in the paragraph in order to communicate to readers that arsenic levels in the U.S. are much lower than in some of the countries where studies characterizing health effects have been conducted. The sentence reads "Population studies of health effects associated with arsenic exposure have been conducted primarily in countries such as Bangladesh, Taiwan, and Chile, where arsenic levels in drinking water are generally much higher than in the United States due to high levels of naturally occurring arsenic in groundwater."
1/2	P1, L38	**Comment:** 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".
		Response: We moved the sentence about arsenic levels in the U.S. vs. other countries further up in the paragraph in order to communicate to readers that arsenic levels in the U.S. are much lower than in some of the countries where studies are being conducted. The sentence reads "Population studies of health effects associated with arsenic exposure have been conducted primarily in countries such as Bangladesh, Taiwan, and Chile, where arsenic levels in drinking water are generally much higher than in the United States due to high levels of naturally occurring arsenic in groundwater."
1/2	P2, L7-8	**Comment:** 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.
		Response: While the study is interesting, we feel that including discussion of a unique health outcome based on only one study is premature at this time – particularly given the

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		much more extensive findings for other endpoints associated with arsenic.
1/2	P2, L19-25	**Comment:** 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.
		Response: The topic text is meant to give an overview of the issue and how it is relevant for children's health. We have tried to give basic information about whether exposure levels are high or at levels currently found in some U.S. drinking water systems and if the exposures are long-term or short-term, where we are able. Adding details about exposure and duration for each study might make the report difficult to understand for non-researchers. Studies use different exposure metrics, have different designs and other details that cannot be described briefly. The sentences on disinfection byproducts have been changed to "Consumption of drinking water from systems in the United States and other industrialized countries with relatively high levels of disinfection byproducts has been associated with bladder cancer and developmental effects in some studies. Some individual epidemiological studies have reported associations between the presence of disinfection byproducts in drinking water and increased risk of birth defects, especially neural tube defects and oral clefts; however, recent articles reviewing the body of literature determined that the evidence is too limited to make conclusions about a possible association between exposure to disinfection byproducts and birth defects."
1/2	P3, 11-60	**Comment:** 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.
		Response: Please see above response. We have changed the sentences to the following "A study conducted in Massachusetts reported associations between birth defects and maternal exposure to drinking water contaminated with high levels of tetrachloroethylene around the time of conception. An additional study reported that older mothers or mothers who had previously miscarried, and who were exposed to high levels of tetrachloroethylene in contaminated drinking water, had a higher risk of delivering a baby with reduced birth weight. However, other studies did not find associations between maternal exposure to tetrachloroethyene and pregnancy loss, gestational age, or birth weight. Studies in laboratory animals indicate that mothers exposed to high levels of tetrachloroethylene can have spontaneous abortion, and their fetuses can suffer from altered growth and birth defects."
1/2	P3, L33	**Comment:** 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

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		Response: Please see above response. We have changed the sentences to the following "Exposure to elevated levels of perchlorate inhibits iodide uptake into the thyroid gland, possibly disrupting the functions of the thyroid and potentially leading to a reduction in the production of thyroid hormone."
1/2	P5, L7 (Overview section)	**Comment:** Page 5 OVERVIEW paragraph- how often are the data compiled?
		Response: We added this information. The sentence now reads "Indicator E7 shows the estimated percentage of children served by community water systems that did not meet health-based drinking water standards in each year from 1993 to 2009. Indicator E8 shows the estimated percentage of children served by community water systems that did not adhere to monitoring and reporting requirements in each year."
1/2	P6, L43	**Comment:** 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?
		Response: The EPA has performed audits on water systems to determine what percentage of health based violations that occurred were actually reported. This issue is discussed in the indicator because we want to explain to the reader that violations of health-based standards may be under-reported in the indicator. Further discussion of reporting issues is beyond the scope of this report.
1/2	P7, L5-6	**Comment:** 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.
		Response: As stated in the text, SDWIS does not provide contaminant concentrations and these data are not available; we have added a statement that the indicator does not reflect the extent to which a standard was exceeded. If a violation continues for multiple calendar years, it is counted as a violation for each year presented in the indicator, but the duration of a violation within a year is not captured. Any violation is treated as a potential concern, although the importance of the violation does depend on the particular contaminant, the magnitude and duration of the violation, and the extent of the violation within a system. Indicators are intended to give a graphical view that provides a brief, readily understood national summary of an extensive collection of underlying data (for example, a quick view of whether the measure is improving, worsening, or static; areas for attention and further investigation).

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1/2	P7, L33	**Comment:** 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.
		Response: We have added a footnote to explain that FDA regulates bottled water.
1/2	P9-12 (Tables and Figures)	**Comment:** The tables and figures on pages 9-12 are well done.
		Response: No response necessary.
1/3	P1-4 (Topic Text)	**Comment:** 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.
		Response: These are addressed with responses below.
1/3	P1, L4	**Comment:** 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
		Response: We have added "endocrine disruption" to the sentence and added a reference. The sentence now reads "Drinking water sources may contain a variety of contaminants that, at elevated levels, are associated with increased risk of a range of diseases in children, including acute diseases such as gastrointestinal illness, developmental effects such as learning disorders, endocrine disruption, and cancer."
1/3	P1, L11	**Comment:** P1, l 11 what about both microbial and chemical emerging contaminants? These should be listed in the "Several types of drinking water contaminant examples."
		Response: We have organized the topic text to first discuss contaminants for which EPA has set limits, and have included emerging contaminants, such as personal care products, in the following paragraphs.

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1/3	P1, L12	**Comment:** 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)"
		Response: We have added as suggested to read "Examples include microorganisms, (e.g., *E. coli, Norovirus, and Giardia)*…" We have also added information and a reference about *Norovirus* to our discussion of microbial contaminants to read "Children are particularly sensitive to microbial contaminants, such as *Giardia, Cryptosporidium, Norovirus* and *E. coli*, because their immune systems are less developed than those of most adults."
1/3	P1, L18-21	**Comment:** P 1, l 18-21 The order of these two sentences should be switched
		Response: We have changed the text as suggested.
1/3	P1, L22-24	**Comment:** P1, l 22-24 This short introduction on lead should be expanded especially since the Washington DC lead issue received so much attention
		Response: We have added information to the sentences on lead to read "Drinking water is a known source of lead exposure among children in the United States, particularly from corrosion of pipes and other elements of the drinking water distribution systems. Exposure to lead via drinking water may be particularly high among very young children who consume baby formula prepared with drinking water that is contaminated by leaching lead pipes. The National Toxicology Program has concluded that childhood lead exposure is associated with reduced cognitive function, reduced academic achievement, and increased attention-related behavioral problems."
1/3	P1, L28	**Comment:** P1, l 28 How is the disinfectant by products reference (#30) connected to nitrates?
		Response: We have removed reference 30 as a citation for this sentence.
1/3	P1, L28-30	**Comment:** P1, l 28-30 Thyroid hormone levels are affected by many substances not just nitrates. I would separate this section from a specific compound
		Response: We agree that thyroid hormone levels are affected by many substances. ACE3 includes indicators for some of these other substances. For each of these substances, we have included a discussion, similar to this one for nitrates. As nitrates and nitrites have been associated with thyroid disruption and are relevant for drinking water, we think it is important to include this discussion. It is also important to briefly explain the importance of thyroid disruption for children's

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		health, since many readers may not be aware of this issue.
1/3	P1, L32	**Comment:** 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
		Response: We have revised the sentence to read "Arsenic enters drinking water sources from natural deposits in the earth, which vary widely from one region to another, or from agricultural and industrial sources where it is used as a wood preservative and a component of fertilizers, animal feed, and a variety of industrial products."
1/3	P1, L35	**Comment:** P1, l 35 With respect to referencing this and other sentences (e.g. ref 32 in this case) why not cite peer-reviewed literature?
		Response: Because the aim of the topic text is to provide an overview about why the topic is important for children's health, we try to cite sources that summarize data, particularly if the literature on the issue is expansive, as is the case with arsenic. We have added a literature review as a citation for the sentence regarding health outcomes associated with arsenic exposure that reads "Long-term consumption of arsenic-contaminated water has been associated with the development of skin conditions and circulatory system problems, as well as increased risk of cancer of the bladder, lungs, skin, kidney, nasal passages, liver, and prostate."
1/3	P2, L5-8	**Comment:** P 2 l 5-8 So what does this mean for U.S. health? This should be explained
		Response: We include text in the introduction that discusses interpretation of epidemiology studies with exposure levels greater than those in the U.S. The specific meaning of arsenic exposures for U.S. health is unknown and beyond the scope of this report.
1/3	P2, L9-25	**Comment:** 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 (a) P2 l 11 replace "deactivated" with "inactivated"
		Response: We have made this change as suggested.
1/3	P2, L11	**Comment:** P2 l 9-25 --disinfection of drinking water -- (b) P2 l 11 add "the volume of water to be treated" at the end of the sentence
		Response: We have added this as suggested.

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1/3	P2, L13-15	**Comment:** P2 l 9-25 --disinfection of drinking water -- (c) 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.
		Response: We feel that including technical language regarding treatment methods may be inappropriate for our audience, but we understand the reviewer's concern. We have changed the sentence to be "Surface and groundwater systems use filtration and other treatment methods to physically remove particles. Disinfectants, such as chlorine and chloramine, ultraviolet radiation, and ozone are added to drinking water provided by public water systems to kill or neutralize microbial contaminants."
1/3	P2, L15	**Comment:** P2 l 9-25 --disinfection of drinking water -- (d) P2, l 15 add ozone and ultraviolet radiation to the list of disinfectants
		Response: The change was made as suggested.
1/3	P2, L16	**Comment:** P2 l 9-25 --disinfection of drinking water -- (e) 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).
		Response: We have deleted this phrase from the sentence. It now reads "However, this process can produce disinfection byproducts, which form when chemical disinfectants react with naturally occurring organic matter in water."
1/3	P2, L27-28	**Comment:** • P2 l 27-28 add " and enter groundwater through abandoned wells on farms." to the end of the sentence.
		Response: We have added this phrase as suggested.
1/3	P3, L17-25	**Comment:** • P3 l 17-25 This section on personal care products should be expanded
		Response: We feel that our discussion of personal care products is sufficient for this overview since it is meant to explain why a drinking water indicator is important for children's health.
1/3	P3, L18	**Comment:** • P3 l 18 add "and triclosan and triclocarban" after veterinary medications

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		Response: We do not think it is necessary to mention these specific chemicals since we do not mention specific pharmaceuticals, cosmetics, etc.
1/3	P4, L3	**Comment:** • 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
		Response: We include information on how indicators were selected in the introduction to the Environments and Contaminants section. The remainder of the drinking water text goes into some detail on defining the indicators.
1/3	P4, L6-12	**Comment:** • P4 l 6-12 This paragraph needs additional development
		Response: We provide the expanded description of the data and the indicators in the Indicator text on the pages that follow.
1/3	P4, L10-12	**Comment:** • P4 l 10-12 The last sentence needs expanding. What are the percentages referring to?
		Response: We explain what the percentages are for E6 (now E7) in the first sentence of that paragraph.
2/1	P6, L41-	**Comment:** 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?
		Response: Correlating health measures with exposure measures is beyond the scope of this report. The indicator presented is meant to provide information about the extent to which contaminants in community water systems reach levels that may be of concern for children, not to suggest any particular frequency of health effects or conclusions regarding causation. We agree that measured contaminant concentrations would be preferable, and would support the development of improved indicators.
2/1	P6, L41-	**Comment:** The significance of the time related increase in violations for nitrate/nitrite, disinfectants, chemicals and radionuclides should be discussed.

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		Response: Violations for these standards do not have substantial changes for the years shown.
2/2	P5 (Indicator E6, Indicator E7)	**Comment:** 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.
		Response: As stated in the text, SDWIS does not provide contaminant concentrations and these data are not available; we have added a statement that the indicator does not reflect the extent to which a standard was exceeded. If a violation continues for multiple calendar years, it is counted as a violation for each year presented in the indicator, but the duration of a violation within a year is not captured. Any violation is treated as a potential concern, although the importance of the violation does depend on the particular contaminant, the magnitude and duration of the violation, and the extent of the violation within a system. Indicators are intended to give a graphical view that provides a brief, readily understood national summary of an extensive collection of underlying data (for example, a quick view of whether the measure is improving, worsening, or static; areas for attention and further investigation), and are not intended to represent a risk assessment.
2/3	P5-12 (Indicator E6 and Indicator E7)	**Comment:** 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.
		Response: Any violation is treated as a potential concern. The indicator presented is meant to provide information about the extent to which contaminants in community water systems reach levels that may be of concern for children.
2/3	P7, L 4-26	**Comment:** 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

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		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.")?
		Response: Any violation is treated as a potential concern, although the importance of the violation does depend on the particular contaminant, the magnitude and duration of the violation, and the extent of the violation within a system. Indicators are intended to give a graphical view that provides a brief, readily understood national summary of an extensive collection of underlying data (for example, a quick view of whether the measure is improving, worsening, or static; areas for attention and further investigation).
2/3	P7, L 4-26	**Comment:** 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.
		Response: The indicators are not intended to be extrapolated for determining children's environmental health, but to highlight violations of standards that may represent a concern for children's health. While detailed analysis about the trend is limited by the changing standards, interpretations can be made, such as lower percentages correlate with greater compliance to standards, regardless of how the standards have changed. In order to highlight regulatory standards that may have had large impacts on the data, we have included a break in the data line at the time the standard was put in place.
2/3	P5, L7	**Comment:** 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
		Response: Any violation is treated as a potential concern. The indicator presented is meant to provide information about the extent to which contaminants in community water systems reach levels that may be of concern for children.
2/3	P5, L11	**Comment:** P5 l 11 "These indicators.." this needs to be more specific. Define which indicators
		Response: We have rephrased to read "EPA's Safe Drinking Water Information System, Federal Version (SDWIS/FED) provides information on violations of drinking water standards." We address the specific indicators in later sentences—the phrase "these indicators" is no longer included.

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2/3	P5, L24-26	**Comment:** P5 l 24-26 The complete definition for community water systems should be included
		Response: We believe that the definition we have included, in addition to other information in the indicator text, provides sufficient explanation to orient readers as to the nature of these systems.
2/3	P6, L29-35	**Comment:** P6 l 29-35 How are these data temporally justified to predict children's health risks?
		Response: The indicators are not meant to provide a prediction of children's health risks, but rather to show how the measure has changed over past years. They are intended to give a graphical view that provides a brief, readily understood national summary of an extensive collection of underlying data (for example, a quick view of whether the measure is improving, worsening, or static; areas for attention and further investigation).
2/3	P7, L4-8	**Comment:** P 7 l 4-8 If the statements in this paragraph are correct, why use this indicator system at all?
		Response: Any violation is treated as a potential concern, although the importance of the violation does depend on the particular contaminant, the magnitude and duration of the violation, and the extent of the violation within a system. Indicators are intended to give a graphical view that provides a brief, readily understood national summary of an extensive collection of underlying data (for example, a quick view of whether the measure is improving, worsening, or static; areas for attention and further investigation).
2/3	P7, L10-16	**Comment:** 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?
		Response: Any violation is treated as a potential concern, although the importance of the violation does depend on the particular contaminant, the magnitude and duration of the violation, and the extent of the violation within a system. Correlating health measures with exposure measures is beyond the scope of this report. The indicator presented is meant to provide information about the extent to which contaminants in community water systems reach levels that may be of concern for children, not to suggest any particular frequency of health effects or conclusions regarding causation. We agree that measured contaminant concentrations would be preferable, and would support the development of improved indicators.
2/3	P7, L24-26	**Comment:** P7 l 24-26 Why use the indicators at all if changes over time cannot be assessed?

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		Response: While detailed analysis about the trend is limited by the changing standards, interpretations can be made, such as lower percentages correlate with greater compliance to standards, regardless of how the standards have changed.
3/1	P9-12	**Comment:** By and large, 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.
		Response: The indicator displays violation data for all health-based drinking water standards.
3/2	P5-12 (Indicator E6 and Indicator E7)	**Comment:** 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.
		Response: While we think the suggested approach is interesting, adding these types of comparisons is not within the scope of this report.
3/3	P5-12 (Indicator E6 and Indicator E7)	**Comment:** 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?
		Response: SDWIS does have a number of limitations that have been articulated in our text. As stated in the text, SDWIS does not provide contaminant concentrations and these data are not available; we have added a statement that the indicator does not reflect the extent to which a standard was exceeded. If a violation continues for multiple calendar years, it is counted as a violation for each year presented in the indicator, but the duration of a violation within a year is not captured. Any violation is treated as a potential concern, although the importance of the violation does depend on the particular contaminant, the magnitude and duration of the violation, and the extent of the violation within a system. Indicators are intended to give a graphical view that provides a brief, readily understood national summary of an extensive collection of underlying data (for example, a quick view of whether the measure is improving, worsening, or static; areas for attention and further investigation), and are not intended to represent a

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		risk assessment. Some of the details suggested for inclusion could not be easily captured in an indicator graphic, even if concentration and duration data were available, but would be more likely captured in a risk assessment or in an expanded set of indicators dedicated to drinking water data.
4/1	P5-12 (Indicator E6 and Indicator E7)	**Comment:** 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.
		Response: Some of the details suggested for inclusion could not be easily captured in an indicator graphic, but would be more likely captured in a risk assessment or in an expanded set of indicators dedicated to drinking water data. Correlating health measures with exposure measures is beyond the scope of this report; discussion of this issue has been added to the report introduction. The indicator presented is meant to provide information about the extent to which contaminants in community water systems reach levels that may be of concern for children, not to suggest any particular frequency of health effects or conclusions regarding causation. We agree that measured contaminant concentrations would be preferable, and would support the development of improved indicators. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
4/1	P5-12 (Indicator E6 and Indicator E7)	**Comment:** 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
		Response: Please see response to previous comment.
4/1	P5-12 (Indicator E6 and Indicator E7)	**Comment:** 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.
		Response: Please see response to previous comment.
4/1	P5-12 (Indicator E6 and Indicator E7)	**Comment:** 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.

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		Response: We will evaluate data for individual standards or subsets of standards in this category the next time we calculate indicator updates. However, the presentation in ACE3 is an indicator rather than a risk assessment, so grouping chemicals with different effects is not inherently problematic.
4/2	P5-12 (Indicator E6)	**Comment:** 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?
		Response: As stated in the text, SDWIS does not provide contaminant concentrations and these data are not available; we have added a statement that the indicator does not reflect the extent to which a standard was exceeded. If a violation continues for multiple calendar years, it is counted as a violation for each year presented in the indicator, but the duration of a violation within a year is not captured. Any violation is treated as a potential concern, although the importance of the violation does depend on the particular contaminant, the magnitude and duration of the violation, and the extent of the violation within a system. The indicators are not intended to represent a risk assessment or provide the type of data necessary to perform risk assessment calculations.
4/2	P5-12 (Indicator E6)	**Comment:** Indicator E6 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.
		Response: Indicators are intended to give a graphical view that provides a brief, readily understood national summary of an extensive collection of underlying data (for example, a quick view of whether the measure is improving, worsening, or static; areas for attention and further investigation), and are not intended to represent a risk assessment or provide the type of data necessary to perform risk assessment calculations.
4/2	P5-12 (Indicator E6)	**Comment:** Indicator E6 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-

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		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.
		Response: Correlating health measures with exposure measures is beyond the scope of this report. The indicator presented is meant to provide information about the extent to which contaminants in community water systems reach levels that may be of concern for children, not to suggest any particular frequency of health effects or conclusions regarding causation. We agree that measured contaminant concentrations would be preferable, and would support the development of improved indicators. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
4/2	P5-12 (Indicator E7)	**Comment:** 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.
		Response: No response necessary.
4/2	P5-12 (Indicator E7)	**Comment:** Indicator E7 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
		Response: Please see above response.
4/2	P5-12 (Indicator E7)	**Comment:** Indicator E7 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

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		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.
		Response: Please see above response.
4/3	P5-12 (Indicator E6 and Indicator E7)	**Comment:** 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.
		Response: Please see above responses.
5/1	N/A (Overall Text)	**Comment:** As indicated above, the documentation is incomplete without separation of different environmental contaminants for use in risk assessment
		Response: Indicators are intended to give a graphical view that provides a brief, readily understood national summary of an extensive collection of underlying data (for example, a quick view of whether the measure is improving, worsening, or static; areas for attention and further investigation), and are not intended to represent a risk assessment or provide the type of data necessary to perform risk assessment calculations.
5/2	N/A (Overall Text)	**Comment:** The 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

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		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.
		Response: We have added information about arsenic exposure levels to the topic text and have included a review reference that we use for other arsenic-associated health effects, rather than additional references representing individual studies. We have removed discussion about disinfection byproduct-associated reproductive endpoints from our topic text and have expanded the discussion about health effects for which there are more studies.
5/3	P20-21 (Metadata section)	**Comment:** 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?
		Response: Raw data regarding contaminant levels are not available, as stated in the metadata. A separate entry for each violation, which is a form of raw data concerning violations, is available in SDWIS.
5/3	P20-21 (Metadata section)	**Comment:** 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.
		Response: The indicators are not intended to be extrapolated for determining children's environmental health, but to highlight violations of standards that may represent a concern for children's health. While detailed analysis about the trend is limited by the changing standards, interpretations can be made, such as lower percentages correlate with greater compliance to standards, regardless of how the standards have changed. In order to highlight regulatory standards that may have had large impacts on the data, we have included a break in the data line at the time the standard was put in place.

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Section: Environment and Contaminants

Topic: Food Contaminants

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1/1	P1-5 (Topic Text)	**Comment:** 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, phthalates, 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 organochlorine insecticides, or other brominated compounds) that are often found as contaminants.
		Response: While there are many other chemicals of concern that could be included in a food contaminants discussion, this text is not intended to be comprehensive. We chose several contaminants relevant to children's health that we believe will be of interest to ACE readers.
1/1	P1-5 (Topic Text)	**Comment:** 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.
		Response: Discussion of endogenous chemicals formed during cooking is beyond the scope of this text.
1/1	P1-5 (Topic Text)	**Comment:** 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).
		Response: The PBDE toxicity discussion has been clarified to specifically denote endocrine disruption, and the suggested reference has been incorporated. Breast milk as an exposure pathway for infants has also been added to the text.
1/1	P1-5 (Topic Text)	**Comment:** 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).

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		Response: We have chosen to use the broader classification of pesticide since some of the compounds utilized may have been used to control for non-insect pests (e.g. carbophenothion can be used as an insecticide as well as for ticks and mites, which are not insects). While there are many other chemicals of concern and other pesticides/fungicides that could be included in a food contaminants discussion, many of these chemicals lack sufficient data to create reliable, nationally representative indicators.
1/2	P1-5 (Topic Text)	**Comment:** 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.
		Response: While there are many other chemicals of concern that could be included in a food contaminants discussion, this text is not intended to be comprehensive. We chose several contaminants relevant to children's health that we believe will be of interest to ACE readers.
1/3	P1-5 (Topic Text)	**Comment:** 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.
		Response: No response necessary.
1/3	P1-5 (Topic Text)	**Comment:** Were any other chemicals considered for inclusion in the topic text, or was it simply limited to the chemicals included as biomarker indicators?
		Response: We chose to limit discussion to brief summaries of chemicals included as other Biomarker topics. Since we could only provide a summary of information relevant to a chemical's role as a food contaminant, we selected chemicals included in the Biomonitoring section so that readers could easily refer to the more extensive topic text associated with each chemical.
1/3	P1-5 (Topic Text)	**Comment:** Also, wondering if it would be of interest to discern between organophosphate "pesticides" or "insecticides"?
		Response: We have chosen to use the broader classification of pesticide since some of the compounds utilized may have been used to control for non-insect pests (e.g. carbophenothion can be used as an insecticide but also for ticks and mites, which are not insects).

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2/1	P6-9 (Indicator E8)	**Comment:** 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.
		Response: We revised the sentences which indicate how we chose the 4 food items presented. Indicator text was expanded to further address interpretation of the results for the selected fruits and vegetables. While adding information on additional fruits and vegetables would be informative, space constraints limited our ability to present additional fruits or vegetables, and each of these fruits or vegetables would also have missing years due to the data collection methods of the PDP. However, we did choose the fruits and vegetables that had data for the most years.
2/2	P6-9 (Indicator E8)	**Comment:** 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.
		Response: We revised the sentences which indicate how we chose the 4 food items presented. Peaches and nectarines are also not on the list of the most-consumed foods.
2/2	P6-9 (Indicator E8)	**Comment:** 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.
		Response: Based on information available at the time of writing, we chose to select 4 commonly consumed items by children. We acknowledge in the indicator text that other foods may have greater or lower levels of OP residues than the 4 foods presented here. In selecting the 4 foods shown, we balanced the availability of data from multiple years with the expected consumption by children. In future editions, additional fruits and vegetables may be reported.
2/3	P6-9 (Indicator E8)	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		detection rates are going down when this only represents a fraction of what may be in these foods.
		Response: In the indicator text of the peer-review draft, we originally stated, "Some aspects of trends in organophosphate residues could be missed by the indicator if any organophosphates other than the 43 considered in the indicator had substantial changes in use on the four selected foods during the years 1998–2008." We have added language to the text to address the concern of residue detection rates being misinterpreted as equivalent to no OP (or alternative) residues.
2/3	P21, L1 (Table)	**Comment:** 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?
		Response: The FDA Total Diet Study has been considered for ACE, but the USDA PDP has historically been used in ACE to address pesticide residues, and provides information suitable to the analyses performed in ACE. TDS also analyzes only four samples for each type of food (each a composite of foods collected from three cities) annually.
3/1	P8-9	**Comment:** 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.
		Response: No response necessary.
3/2	P7, L10-11	**Comment:** 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.
		Response: Pg 7 (lines 15-17) state that detection gaps in a given year are due to missing data, and not necessarily the absence of pesticide residues. A note has been added to the figure on this point; and the horizontal axis labels now include only those years for which data are available.
3/3	P8-9	**Comment:** 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?
		Response: Sample size inclusion was considered, but we determined that it would make the indicator more difficult to understand for a broad audience. Sample sizes are provided in the methods documentation included in the review document and that will be available online.

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		Comment: 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.
		Response: A note has been added to the figure. Also, the horizontal axis labels in the figure have been revised to only show years where data are present.
4/1	P6-9 (Indicator E8)	**Comment:** 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?
		Response: An indicator of percent detected has greater ability to capture any changes over time and to track trends.
4/1	P6-9 (Indicator E8)	**Comment:** Also, other food contaminants may have been reported with perhaps more relevance to potential adverse health effects in children.
		Response: The Pesticide Data Program matches ACE3 criteria better than any other data set, and from the PDP we believe that organophosphate pesticides are a reasonable selection for this report, given the research on OPs and children's health. Continuing data collection programs are lacking for many food contaminants of interest.
4/2	P8 (Figure)	**Comment:** The reviewer believes that the indicator text and the presentation would mislead the policymakers and the public on the aspect of pesticide residues in foods. According to the graphs presented, it is intuitive for the public 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.
		Response: Language has been added to more clearly define the limitations of the indicator, and to emphasize the focus on organophosphate pesticides. Interpretation of decreases in OP detections would be speculative; however, the topic text does note that restrictions on food crop uses of OPs have been adopted since 1999.
4/3	P6-9 (Indicator E8)	**Comment:** 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

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		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.
		Response: No response necessary.
5/1	N/A (Overall Text)	**Comment:** This appears to be adequate and is presented transparently.
		Response: No response necessary.
5/2	N/A (Overall Text)	**Comment:** Except for the comments made for Question 4, this document is complete and transparent.
		Response: No response necessary. See response above to the previous concern regarding limitations of presenting data only on OP pesticides.
5/3	P6-9 (Indicator E8)	**Comment:** 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.
		Response: All 4 foods were tested for all 43 pesticides in each year they were sampled from 1998-2009. The PDP measured additional OPs in one or more years over the same time frame, but these OPs were not included in our analysis. Language has been added to the text stating that potential substitution with other OP or non-OP pesticides is not accounted for in this indicator.

Peer Review of February 2011 Draft ACE3 Indicator Documents
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Section: Environments and Contaminants

Topic: Contaminated Lands

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P1, L5-8	**Comment:** *Page 1* 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.
		Response: We chose not to give examples here so that this introductory paragraph would remain brief; however, we agree that clarification of "naturally occurring substances" is useful and added asbestos as an example in this case.
1/1	P1, L14-15	**Comment:** *Page 1* 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".
		Response: The text has been revised to say "or residing on or near to contaminated land."
1/1	P1, L18	**Comment:** *Page 1* 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.
		Response: This phrase has been removed.
1/1	P1, L21-23	**Comment:** *Page 1* 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).

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		Response: The text has been simplified to state "Soil dust may be carried on the wind and inhaled into the lungs where it can be very damaging." Potential risks of inhaled particles are addressed in more detail elsewhere in the ACE report.
1/1	P1, L23	**Comment:** *Page 1* Line 23: Replace "most crucial step" with "the optimal approach" to convey a technique rather than a series of steps within a single technique.
		Response: The text has been changed.
1/1	P1, L27-30	**Comment:** *Page 1* Line 27 – 30: This sentence is too long and contains too much information and hypothetical situations. Consider breaking up into several sentences.
		Response: The text has been revised to say "For example, consumption of fish caught at or near a contaminated site may increase risk of exposure to contaminants from the site. The same is true of drinking water from contaminated ground- or surface water sources. "
1/1	P1, L37	**Comment:** *Page 1* 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.
		Response: We believe this is important as a reference for the readers; however the text has been revised to "nearly 1%". We do not think that most readers would consider approximately 1% to be trivial.
1/1	P2, L9	**Comment:** *Page 2:* 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.
		Response: The text regarding PFP has been revised for clarification and ease of understanding. The terminology in this text has been revised; PFP has replaced with "human health protective measures in place."
1/1	P2, L34	**Comment:** 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.
		Response: The subject is addressed in more detail in the introduction to the report. We have also added text regarding magnitude, duration, and route of exposure along with stage of development, genetic, and sociologic factors that may influence the effect

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		of an environmental exposure.
1/1	P2, L38-39	**Comment:** 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.
		Response This text has been revised for clarity. However, due to the nature of the indicators in this section, we believe it is important to introduce the concept of social disparities at this point. The indicator data combined with the influence of socio-cultural factors show the potential for adverse outcomes specific to certain groups of children and we believe it is important for this concept to be introduced here.
1/1	P2, L42	**Comment:** 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.
		Response: Genetic susceptibility is addressed in the introduction to ACE. The text has also been modified to briefly mention genetics and not detract too much attention from the overall topic.
1/1	P1, L5-6	**Comment:** *Page 1* Line 5 – 6: "Common categories of land contaminants …." – Change to "These contaminants commonly include …."
		Response: The text has been revised.
1/1	P1, L27	**Comment:** *Page 1* Line 27: Delete "potential"
		Response: We retained "potential" because pollution of ground water, surface water, etc. does not necessarily cause human exposure.
1/1	P1, L30-32	**Comment:** *Page 1* Lines 30 -32: Delete the last sentence. Not needed. Does not add to the paragraph and document.

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		Response: The original phrasing was retained due to its help in explaining the process and the potential for exposure.
1/1	P1, L35	**Comment:** *Page 1* Line 35 : Delete "company"
		Response: Company has been deleted.
1/1	P1, L39	**Comment:** *Page 1* Line 39: Delete "some of" – too tentative.
		Response: The original phrasing was retained. Superfund only cleans up a subset of contaminated sites. Some of the most contaminated are not placed on the Superfund National Priorities List: states or potentially responsible parties are dealing with them on their own.
1/1	P1, L43	**Comment:** *Page 1* Line 43: With the sentence beginning "Other", insert the following phrase "The EPA is also responsible for …".
		Response: The text has been revised.
1/1	P2, L5	**Comment:** *Page 2:* Line 5: Delete "The focus" and replace with "The EPA's priority"
		Response: The text has been changed to "EPA's primary concern is to…"
1/1	P2, L11-12	**Comment:** *Page 2:* Lines 11 – 12 : Delete the first sentences.
		Response: We have retained this text.
1/1	P2, L25-32	**Comment:** *Page 2:* Lines 25 – 32 : This paragraph is very wordy. I'm not sure how to fix it.
		Response: This paragraph has been revised.
1/1	P2, L37-38	**Comment:** *Page 2:* Lines 37 – 38: Delete the sentence starting with "Some populations". It is

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		redundant.
		Response: This paragraph has been revised.
1/2	P1-3 (Topic Text)	**Comment:** 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)). 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.
		Response: These references have been added.
1/2	P5-6	**Comment:** 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. 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
		Response: The introduction to this report addresses the issue of social disparities in much greater detail. We have chosen not to incorporate this reference because it is

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		beyond the scope of the report but we have added an additional reference by Gee (2002).
1/2	P1-3 (Topic Text)	**Comment:** 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.
		Response: Social disparities are discussed in the introduction and throughout the report in more detail. We believe after our revisions that this concept has been clearly and succinctly described in reference to contaminated lands. We have added citations for contaminated lands that have been directly linked to actual exposures. This issue is further described in the indicator text as well and describes the limitations in estimating the extent to which children are actually exposed.
1/3	P12, All	**Comment:** 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.
		Response: We have added a number of peer-reviewed references.
2/1	P4, L5	**Comment:** *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).
		Response: Family income is the measure used throughout ACE, and is imbedded in many of the data sets used. The government's official policy for determining poverty status is based on family income.
2/1	P4, L16	**Comment:** 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.
		Response: We believe that we address these limitations by stating that "these areas are not the actual site boundaries, and are not expected to reflect the actual area of contamination." We believe these to be reasonable approximations of the site based on the best available information.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/1	P5, L11	**Comment:** *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.
		Response: The 2005-2009 ACS does not contain all of the block group level data elements that were used in this analysis. In particular, there is no current census data source that provides population proportions above and below poverty at the block group level. Five-year ACS data provide this information at the census tract level. We plan to re-do the analyses using Census 2010 data for block populations in 2010 by age/race (not previously available) combined with ACS 2006-2010 (or later) data for census tract populations by age/race/poverty level. ACS 2006-2010 is preferable to ACS 2005-2009 because it uses the same geography (boundaries) and the 2010 decennial census. ACS census-tract level data on population proportions above and below poverty at the census tract level will be used in the same way that block group level income grouping data were used in the previous analysis.
2/2	P4-11 (Indicator Text)	**Comment:** 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.)
		Response: 2010 census data were not released prior to preparation of the indicator; at the time that indicator calculations for ACE3 were finalized, data at the highest level of geographic resolution were not released for all states. We believe that the current text is clear regarding the census data used. We do not believe the details of data provided by the Census Bureau are necessary for this text, and that most readers will understand that much of the data from the 2010 census was released after 2010.
2/2	P4 (Corrective Action and Superfund Sites Section)	**Comment:** 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.
		Response: A map has been added to the appendix as well as a breakdown by state, race and income.
2/2	P5, L38- P6	**Comment:** 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?

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The indicator text is meant to describe the data and limitations but interpretation of the data and further conclusions are beyond the scope of this report.
2/2	P5, L25	**Comment:** Line 25 on page 5: add "national": "…indicators at the national and state level…
		Response: The indicator is currently at the national level and the appendix adds state level values.
2/3	P5, L16	**Comment:** 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.
		Response: No response necessary.
2/3	P5, L27-33	**Comment:** 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.
		Response: Unfortunately the racial/ethnic groups are dictated by the census data available at the local level, which do not allow for estimation of (for example) "Black non-Hispanic" rather than "Black." While in many other topics with other data sources we do separate Hispanics into an independent category, this particular source does not make such a separation.
3/1	P7, L6	**Comment:** *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.

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		Response: While we agree this is a very interesting question, we are unaware of an explanation for these results. Analysis to identify possible explanations would be a significant effort beyond the scope of this report.
3/1	P9 (Figure)	**Comment:** *Page 9* The figure is too busy and confusing. Please revise.
		Response: We considered possible revisions, but concluded that it is important to include all of the data displayed.
3/2	P7 (Figure) P9 (Figure) P10 (Table E9) P10-11 (Table E10)	**Comment:** 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."
		Response: The text has been revised to say "Approximately 6% of all children in the United States lived within one mile of a Corrective Action or Superfund site that may not have had all human health protective measures in place as of 2009."
3/2	P7 (Figure) P9 (Figure) P10 (Table E9) P10-11 (Table E10)	**Comment:** The two figures and the data tables give the reference to EPA after "DATA" but should also include "2000 U.S. Census".
		Response: We generally credit the source of the environmental/health data and not the census under the figures and tables; the indicator text and methods documentation make clear that Census data are also used.
3/2	P4, L1-7	**Comment:** 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.
		Response: The title is now "Percentage of children ages 0 to 17 years living within one mile of Superfund and Corrective Action sites that may not have all human health protective measures in place, 2009."
3/2	P4, L1-7	**Comment:** 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 change.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We have made this change (substituting "race/ethnicity" for "age/ethnicity").
3/2	P9 (Figure)	**Comment:** 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.
		Response: We chose not to add further features to the figure.
3/2	P7, L11 (Also Overall Text)	**Comment:** "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.
		Response: We have added a map to the appendix. We include indicator values by state, race/ethnicity, and income in the appendix. Further localized information is beyond the scope of this report, which focuses on national indicators. We believe most readers will understand that there is variability within national values.
3/2	P7, L1-15 P9, L1-13	**Comment:** The bullet points for both indicators are appropriate and clear as related to the displayed data.
		Response: No response necessary.
3/3	P4 (Indicator E9 and Indicator E10)	**Comment:** 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?
		Response: The suggested figure appears to correspond to the current Indicator E9.
4/1	P4 (Indicator E9)	**Comment:** Indicator - % of children 0-17 years living within one mile of Superfund or Corrective Action sites that were not PFP, 2009

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		a. 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.
		Response: We agree, and will be using ACS 2006-2010 (or later) values to recalculate the indicators for future updates. Updates of the 5-year ACS values can be used for future indicator updates in comparable fashion. However, some use of the decennial census (now using 2010) remains necessary to implement the methodology, due to limitations of the ACS.
4/1	P4 (Indicator E9)	**Comment:** Indicator - % of children 0-17 years living within one mile of Superfund or Corrective Action sites that were not PFP, 2009 b. 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).
		Response: Although not included in the report, data from our analyses are available at the county level.
4/1	P4 (Indicator E9)	**Comment:** Indicator - % of children 0-17 years living within one mile of Superfund or Corrective Action sites that were not PFP, 2009 c. 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.
		Response: Please see the above response.
4/1	P4 (Indicator E10)	**Comment:** 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 a. I find this indicator redundant and not needed. Much of the detail needed is provided by the first indicator.
		Response: We believe that it is important to show the percentages of each race among the exposed children and the racial distribution in the general population of U.S. children to show possible excess burden among different demographic groups, along with the additional details for children below poverty level.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/1	P4 (Indicator E10)	**Comment:** 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 b. 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).
		Response: Please see the response above.
4/1	P4 (Indicator E10)	**Comment:** 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 c. 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.
		Response: Please see the response above.
4/2	P4-11 (Indicator Text)	**Comment:** 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).
		Response: Please see the response above.
4/2	P4-11 (Indicator Text)	**Comment:** 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

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		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.
		Response: In all of the topics of the Environments and Contaminants section, we have focused on potentially harmful aspects of the environment that may be associated with health risks in children. In this topic we discuss the percentage of children who are potentially exposed to Contaminated Lands and therefore the success would be to reduce this number. The ideal success is to reduce this number in all racial groups and especially those with a larger percentage of exposed children to reduce disparities among these groups. As a general matter, we agree that indicators may frequently lead to further investigation to provide a basis for follow-up.
4/3	P4 (Indicator E9 and Indicator E10)	**Comment:** 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.
		Response: Please see responses above.
5/1	P22-25 (Table A1, Table A2, Table A3)	**Comment:** *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.
		Response: We have added a footnote indicating that these are cases in which there are no non-PFP sites.
5/2	P16 (Methods section)	**Comment:** 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.
		Response: We have added metadata for the Census data sets.
5/2	P16 (Methods section)	**Comment:** The description of the methods used to generate the data seemed clear and detailed, although I did not attempt to recreate the data myself.
		Response: No response necessary.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
5/3	P22-25 (Table A1, Table A2, Table A3)	**Comment:** 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."
		Response: The table has been revised to say "All children in proximity" etc. We believe Tables A2 and A3 are clear.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Environment and Contaminants

Topic: Climate Change

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1/1	P1-3 (Topic Text)	**Comment:** 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.
		Response: We have added language earlier in the text about how climate change may increase children's exposure to environmental conditions that can affect their health. The sentence reads "Climate change may increase children's exposure to extreme temperatures, polluted air and water, extreme weather events, wildfires, infectious disease, allergens, pesticides, and other chemicals. These exposures may affect children's health in a number of direct and indirect ways."
1/1	P1-3 (Topic Text)	**Comment:** 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.
		Response: We believe the reviewer is referring to the study by Drayna et al. We have added language and the suggested reference about the association between increased rainfall and GI illness. The sentence reads "One study found that periods of heavy rainfall were associated with increased emergency room visits for gastrointestinal illness among children."
1/1	P1, L11	**Comment:** 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.
		Response: We have added language early in the text to explain how climate change may affect children. The added sentence reads "Climate change may increase children's exposure to extreme temperatures, polluted air and water, extreme weather events, wildfires, infectious disease, allergens, pesticides, and other chemicals. These exposures may affect children's health in a number of direct and indirect ways."
1/1	P2, L14-23	**Comment:** 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

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		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.
		Response: We have added the following sentence for consistency, "Children may be at greater risk for these types of infectious diseases as they spend more time outdoors compared with adults, where they might contact disease-carrying organisms, and they have less-developed immune systems."
1/1	P2, L25-29	**Comment:** 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….)
		Response: We have added language to address this issue, "Exposure to weed and grass pollen has been associated with exacerbation of children's asthma, emergency room visits, and hospitalizations."
1/1	P2, L34	**Comment:** 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.
		Response: We have added a sentence about how climate change may increase children's exposure to harmful contaminants to read "Through various indirect pathways, climate change may lead to increasing levels and/or frequencies of childhood exposure to harmful contaminants." We address many of these contaminants in other ACE indicators.
1/1	P1-3 (Topic Text)	**Comment:** 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.
		Response: EPA has decided to defer publication of an ACE3 indicator for climate change, and to conduct further evaluation of indicator design issues. Many of the indirect impacts are captured in other ACE indicators, e.g. air quality, respiratory effects.

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1/1	P3, L8	**Comment:** Also page 3 line 8 – how is "unusually high" defined? You do this on the next page, but some redundancy may be OK.
		Response: Comment is no longer applicable, as presentation of a climate change indicator was removed from the report for now, pending further development.
1/1	P5, L7-9	**Comment:** Page 5 – line 7-9 this sentence should be in the topic area and be part of the intro---
		Response: We have added information and an additional reference about infants to the topic text as follows "Infants may be especially vulnerable to heat events in part because they depend on adults for care and are unable to communicate thirst and discomfort."
1/2	P1-3 (Topic Text)	**Comment:** 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.
		Response: We agree that heat related illness is an important point of discussion. We have added sentences and additional references to address these issues to read "Heat exposure can result in heat rashes, heat stroke, heat exhaustion, and even death; children may be especially at risk because they often spend more time outside than adults do. Children's bodies are less effective at adapting to heat compared with those of adults. Also, children may not feel the need to drink as urgently, which can lead to severe dehydration and electrolyte imbalance. Humidity can further exacerbate heat stress in children. Infants may be especially vulnerable to heat events in part because they depend on adults for care and are unable to communicate thirst and discomfort. Caregivers can help protect children from heat-related health effects." The topic text is meant to be a general overview in order to convey the importance of the topic for inclusion, so a figure on health effects vs. temperature is outside the scope of this report. Using temperature measurements is a more direct way to represent climate change as compared to health indicators such as heat-related ER visits. Both approaches will be considered in future work.

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1/3	P1, L18-26	Comment: 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).
		Response: We have added sentences and additional references (including the suggested reference) to address these issues to read "Heat exposure can result in heat rashes, heat stroke, heat exhaustion, and even death; children may be especially at risk because they often spend more time outside than adults do. Children's bodies are less effective at adapting to heat compared with those of adults. Also, children may not feel the need to drink as urgently, which can lead to severe dehydration and electrolyte imbalance. Humidity can further exacerbate heat stress in children."
1/3	P2, L11-12	**Comment:** 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.
		Response: We have added a sentence regarding GI illness and rainfall and included the suggested citation. The section now reads "Extreme weather events are also associated with increased risk of food- and water-borne illnesses as sanitation, hygiene, and safe food and water supplies are often compromised after these types of events. One study found that periods of heavy rainfall were associated with increased emergency room visits for gastrointestinal illness among children."
1/3	P2, L22-23	**Comment:** 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.
		Response: We have added Lyme disease to the sentence to read "Changes in the geographic distribution of disease-carrying organisms may alter the spread of vector-borne diseases such as Lyme disease, West Nile virus and Dengue fever."
1/3	P2, L25-29	**Comment:** 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).

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		Response: We have included mention of the lengthened ragweed season and included the suggested reference. The sentence now reads "Climate change has already caused an earlier onset of the U.S. spring pollen season and a lengthened ragweed season."
1/3	P3, L7-8	**Comment:** Last paragraph, page 3. The indicator is 3 or more days not one or more.
		Response: This text has been removed.
2/1	P4-7 (Indicator Text)	**Comment:** 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?
		Response: EPA has decided to defer publication of an ACE3 indicator for climate change, and to conduct further evaluation of indicator design issues.
2/1	P4-7 (Indicator Text)	**Comment:** 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?
		Response: EPA has decided to defer publication of an ACE3 indicator for climate change, and to conduct further evaluation of indicator design issues.
2/1	P4-7 (Indicator Text)	**Comment:** 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.
		Response: . EPA has decided to defer publication of an ACE3 indicator for climate change, and to conduct further evaluation of indicator design issues.
2/1	P4-7 (Indicator Text)	**Comment:** 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.
		Response: For the ACE indicators, we prefer to use measured data when it is available, rather than modeled data.
2/1	P4-7 (Indicator Text)	**Comment:** Are there plans in subsequent reports to add additional climate measures?

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		Response: We will consider additional climate measures in future editions of ACE.
2/2	P4 (Indicator CL1)	**Comment:** 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.

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		Response: There is evidence that location can have an impact on a population's vulnerability to adverse health effects. Studies have shown that the minimum mortality temperature varies from one location to another. We have added references and additional text to address this comment. The references detail studies that show mortality occurs at different temperatures in different locations, both in the United States and the European Union. We have added "Studies have shown that the temperature at which mortality and morbidity (e.g., respiratory hospital admissions) can occur from heat exposure varies based on location. Extreme heat exposure may have a greater impact on populations living in regions that experience high temperatures less frequently, such as the Northwest and Midwest United States. In warmer climates such as those in the South and Southwest United States, the population may be acclimated to heat and area infrastructure is better designed to accommodate high temperatures." This evidence suggests that it is appropriate for the indicator to be based on temperatures that are extreme for a particular county.
2/3	P5, L5	**Comment:** 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."
		Response: EPA has decided to defer publication of an ACE3 indicator for climate change, and to conduct further evaluation of indicator design issues.
2/3	P5, L9	**Comment:** 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**

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		examine children as a sub-group.
		Response: We have added more explanation and an additional reference about why infants may be vulnerable to heat events to read "Infants may be especially vulnerable to heat events in part because they depend on adults for care and are unable to communicate thirst and discomfort."
2/3	P5, L9	**Comment:** 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.**
		Response: We have added the suggested reference and a sentence and reference about how caregivers can protect children from heat to read "Caregivers can help protect children from heat-related health effects."
3/1	P6, L3-5	**Comment:** *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*
		Response: This text has been removed. EPA has decided to defer publication of an ACE3 indicator for climate change, and to conduct further evaluation of indicator design issues.
3/1	P6, L3-5	**Comment:** 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.
		Response: We will consider this comment in designing the indicator, but in general, we are unable to speculate about unexplained events.
3/1	P6, L3-5	**Comment:** 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?

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		Response: We will consider this comment in designing the indicator but we think it is important to focus initially on a time trend of national data. We will consider additional climate measures in future editions of ACE.
3/1	P6, L3-5	**Comment:** 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.
		Response: We think it is important to focus initially on a time trend of national data. We look forward to expanding our presentation in future editions of ACE.
3/2	P4 (Indicator CL1)	**Comment:** 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.
		Response: EPA has decided to defer publication of an ACE3 indicator for climate change, and to conduct further evaluation of indicator design issues.
3/3	P5-6 (Graph and Table)	**Comment:** The graph and table are clear though somewhat redundant.
		Response: In general, we feel that it is important to include both presentations of the data. For all ACE indicators, we report the values depicted in the graph in a separate data table - in the printed report, data tables are collected in an appendix.
3/3	P4 (Indicator CL1)	**Comment:** 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.
		Response: EPA has decided to defer publication of an ACE3 indicator for climate change, and to conduct further evaluation of indicator design issues.
4/1	P4-7 (Indicator Text)	**Comment:** a) 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.
		Response: Our initial focus is to capture climate change in the most direct manner, through temperature change. Drinking water and air quality indicators capture climate change impacts indirectly. We reference the relevance of climate change for air quality and asthma in the topic text. We will consider additional climate change indicators in future editions of ACE.

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4/1	P4-7 (Indicator Text)	**Comment:** b) 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?
		Response: We will consider this comment in designing the indicator. We are hopeful that we can include additional climate indicators in future editions of ACE. Many of the indirect impacts are captured in other ACE indicators, e.g. air quality, respiratory effects.
4/1	P6, L4 P6 (Graph)	**Comment:** c) 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 0.4% annual increase really translates into would be helpful.
		Response: We will consider this comment in designing the indicator.
4/1	P4 (Indicator CL1)	**Comment:** d) 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.
		Response: ACE generally focuses on presentation of national-level indicators.
4/2	P4 (Indicator CL1)	**Comment:** 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.
		Response: There is evidence that location can have an impact on a population's vulnerability to adverse health effects. Studies have shown that the minimum mortality temperature varies from one location to another. We have added references and additional text to address this comment. The references detail studies that show mortality and morbidity occurs at different temperatures in different locations, both in the United States and the European Union. We have added "Studies have shown that the temperature at which mortality and morbidity (e.g., respiratory hospital admissions) can occur from heat exposure varies based on location. Extreme heat exposure may have a greater impact on populations living in regions that experience high temperatures less frequently, such as the Northwest and Midwest United States. In

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		warmer climates such as those in the South and Southwest United States, the population may be acclimated to heat and area infrastructure is better designed to accommodate high temperatures." This evidence suggests that it is appropriate for the indicator to be based on temperatures that are extreme for a particular county.
4/2	P4 (Indicator CL1)	**Comment:** 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.
		Response: These data would be useful for development of a separate health indicator. We will consider additional indicators for future editions of ACE.
4/3	P4-7 (Indicator Text)	**Comment:** 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.
		Response: No response necessary.
4/3	P4-7 (Indicator Text)	**Comment:** 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.
		Response: We have added information about the connection between precipitation and gastrointestinal illness to the topic text and will consider additional indicators for climate change in the future. The additional language in the topic text reads "One study found that periods of heavy rainfall were associated with increased emergency room visits for gastrointestinal illness among children."
5/1	P5, L24	**Comment:** Yes- I think addition of a reference at the end of the sentence line 24 page 5 would improve the documentation for references.
		Response: References have been added for these sentences.
5/1	P5, L24	**Comment:** In terms of understanding how the indicator was calculated the documentation looks good.
		Response: No response necessary.
5/2	N/A	**Comment:** [No comment was provided by the reviewer]

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: No response necessary.
5/3	P15, L6	**Comment:** 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.
		Response: Documentation will be revised with development of the revised climate change indicator.
5/3	P18, L5	**Comment:** 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?
		Response: The reviewer is correct; this was an error in the documentation.

Biomonitoring

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Biomonitoring

Topic: Lead

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P1, L26-L28	**Comment:** 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.
		Response: The text has been revised.
1/1	P3, L11-L12	**Comment:** 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).
		Response: We have modified the paragraph in question and moved it to an earlier section in the text.
1/1	P3, L32-L34	**Comment:** SUGGESTED CHANGE: Page 2, 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.
		Response: We have added this text.
1/2	P 14, References	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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. NeurotoxicolTeratol. 2004 May-Jun;26(3):359-71.
		Response: Conduct disorders were already discussed in the previous sentence, with the Braun, et al. reference. We have moved the discussion of conduct disorders to the sentence suggested, and added this reference: Marcus, D.K., J.J. Fulton, and E.J. Clarke. 2010. Lead and conduct problems: a meta-analysis. *Journal of Clinical Child and Adolescent Psychology* 39 (2):234-41. We did not include the Chiodo et al. reference here because this study only discusses "withdrawn behaviors" and not distinct conduct disorders. However Chiodo et al. was added in reference to decreased attention.
	N/A Overall text	**Comment:** 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).
		Response: The text has been rearranged accordingly.
1/2	N/A Overall text	**Comment:** 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?
		Response: The pertinent regulatory measures are discussed in the lead topic text. A full description of lead regulation is outside the scope of ACE.
1/2	N/A – In document edits	**Comment:** 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.
		Response: No response necessary.
1/2	N/A Overall text	**Comment:** 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.
		Response: The pertinent regulatory measures are discussed in the lead topic text. A full description of lead regulation is outside the scope of ACE.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/3	P1, L36	**Comment:** 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.
		Response: After careful consideration of this revision, we decided that the text as-is best captures the message we are trying to convey regarding lead-contaminated tap water intake.
1/3	P1, L41	**Comment:** Page 1, line 41. Include vinyl mini-blinds, keys etc often from foreign sources where controls for lead content are lax.
		Response: We included discussion related to vinyl mini-blinds, based on information found on the CDC website and in a referenced article from Levin et al. The referenced article also cites the Denver Post in regards to Mattel Inc. toys manufactured in China being recalled due to lead-contamination. However, we did not feel that there was enough evidence to substantiate the claim that lead-contaminated products are primarily from foreign sources.
1/3	P2, L20	**Comment:** 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.
		Response: We were unable to find confirmation of this information on the CDC website or in the Levin et al. reference; therefore, we did not include this information.
1/3	P2, L31	**Comment:** Page 2, line 31. Consider adding the following: It should be mentioned that these behavioral changes could also be influenced by socio-economic status.
		Response: The text has been revised.
1/3	P2, L32	**Comment:** Page 2, line 32. Might want to add that lead from mother exposure before birth can be transferred to the infant through breast milk.
		Response: The text has been revised and an additional reference included. Source: Ettinger, et al. Levels of lead in breast milk and their relation to maternal blood and bone lead levels at one month postpartum. Environ Health Perspect. 2004 June; 112(8): 926–931.
2/1	P5, L24-L25	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: For all Biomonitoring topics, we have streamlined the race/ethnicity and income data tables, removing the following columns: unknown incomes, 100-200% of poverty, and >200% of poverty.
2/1	P8, L6-L9	**Comment:** 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
		Response: This information was stated in the first bullet.
2/2	P4, starting L7	**Comment:** 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.
		Response: The detailed documentation will be provided online for interested readers, but will not be included in the published report.
2/2	N/A description of dataset	**Comment:** 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.
		Response: We have revised the indicator text. Much of the description is now provided once in the Biomonitoring section introduction. The current content of the indicator text is standardized across ACE for each indicator, with a few indicator-specific exceptions.
2/3	P4, L7	**Comment:** 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.
		Response: This data is representative of the population of the US based on NHANES sampling techniques.
3/1	P7, Indicator B1 Graph	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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.
		Response: We did consider this, but ultimately decided it is not necessary because we provide the definition of the median and 95th percentile in the text.
3/1	P7 & P9, Graphs	**Comment:** The two figures shown are simple and well done. The text is helpful in providing a detailed explanation of what is being shown.
		Response: No response necessary.
3/2	Starting P11 (Data Tables)	**Comment:** 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.
		Response: The childhood blood lead data are represented in just two figures in ACE3, with supporting and additional information provided in the data tables. We believe the tables efficiently display the relevant information; however, some columns have been removed from tables stratifying by income group. We use a standard table design for all NHANES comparisons by race/ethnicity and income, which we believe will be clearer to readers than an approach that provides a different focus for each chemical presented.
3/2	N/A Addition to text	**Comment:** 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.
		Response: We provide a separate indicator on indoor lead hazards in the Indoor Environments topic. Stratification of indicator values by race/ethnicity and income is an important element of this report, which has been strongly encouraged by the Children's Health Protection Advisory Committee and other reviewers.
3/2	N/A Addition to text	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We believe the figures efficiently display the relevant information. This is an appealing suggestion, but goes beyond the scope of this report.
3/3	N/A Overall data presentation	**Comment:** 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: (*inserted as separate comments below)*
		Response: Our approach is to calculate a consistent set of statistics for each biomonitoring indicator, and to provide consistent information in the indicator graphs (either a time series, or a fixed set of demographic comparisons), and then to note the items of greatest interest in the bullet points. Text would become unnecessarily lengthy and tedious if each data point is noted.
3/3	P7, L5 & L8	**Comment:** Page 7 lines 5 and 8. Add (see table B1) to be consistent with bullet points on page 8.
		Response: Our format is to cross-reference a data table only for values not shown in the indicator figure.
3/3	P9, Chart for Indicator B2	**Comment:** 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.
		Response: Our format is to cross-reference a data table only for values not shown in the indicator figure. It is logical to state the overall median before discussing medians by group.
3/3	P9, L8	**Comment:** Page 9, line 8. The next bullet talks about black-non Hispanics again without reference to Table B2
		Response: The value for Black non-Hispanics appears in the figure. Our format is to cross-reference a data table only for values not shown in the indicator figure.
3/3	P11, Table for Indicator B2	**Comment:** 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.
		Response: We have noted the items of greatest interest in the bullet points. Text would become unnecessarily lengthy and tedious if each data point is noted. The figure has been rearranged and is now consistent with the data table.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/3	P10, L6-L13	**Comment:** 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.
		Response: Please see above.
4/1	N/A Overall indicator text	**Comment:** B1: I think this is well done. Please see my comment above regarding B1.
		Response: No response necessary.
4/1	N/A Overall indicator text	**Comment:** B2: I think the figure and text are well done and give the key points in the figure. a) 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.
		Response: No response necessary.
4/1	N/A Overall indicator text	**Comment:** b) 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.
		Response: No response necessary.
4/1	N/A Overall indicator text	**Comment:** 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.
		Response: While the geometric mean levels are available, we feel that the median will be best understood by our target audience.
4/2	N/A Overall indicator text	**Comment:** 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?

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The second paragraph of the review draft states "In the United States, the major current source of early childhood lead exposure is lead-contaminated house dust.... A major contributor to lead in house dust is deteriorated or disrupted lead-based paint." Other major lead sources are discussed in the subsequent paragraphs. Our approach is to discuss statutes and regulations pertinent to understanding a particular subject matter in that topic; thus, for example, we discuss federal requirements relevant to lead hazards in housing in the Indoor Environments topic. We believe there is substantial information presented that goes beyond what the CDC or American Academy of Pediatrics would report. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
4/2	N/A Overall indicator text	**Comment:** a) 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.
		Response: These issues are discussed in the topic text. Lead concentrations in ambient air are addressed in the Criteria Air Pollutants indicators; indoor lead hazards are addressed in an Indoor Environments indicator; lead in drinking water is addressed in a Drinking Water indicator. The suggested indicators cannot all be presented together in a lead-specific section, because there are many issues other than lead addressed in the Criteria Pollutants, Indoor Environments and Drinking Water topics.
4/2	N/A Overall indicator text	**Comment:** b) 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 data, then it should state this and indicate what is being done to rectify it.
		Response: This information is included. See previous response.
4/2	N/A Overall indicator text	**Comment:** c) 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.
		Response: This information is included.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/3	N/A Overall data presentation	**Comment:** As stated above, consistency between charts, bullet points and tables would clarify the presentation.
		Response: We believe a consistent approach has been applied. The figure has been rearranged and is now consistent with the data tables.
4/3	N/A Overall indicator text	**Comment:** 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.
		Response: We believe the structure of the presentation is appropriate and provides a standard approach that is effective for conveying an important public health message when applied across all 23 ACE3 topics. The topic text discusses the significance of the issue for children's environmental health, followed by presentation of the data and bullet points to highlight key findings from the data. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
5/1	P19 (Metadata section)	**Comment:** The Metadata tables seem appropriate and are understandable to an informed public and lay audience.
		Response: No response necessary.
5/1	P21, Methods section	**Comment:** The Methods section: This seems appropriate although I am not a statistician, so can't give an expert opinion on this.
		Response: No response necessary.
5/2	N/A	**Comment:** See comments above.
		Response: N/A
5/3	P14, References	**Comment:** References: Appears to be representative, not checked.
		Response: No response necessary.
5/3	P19, Metadata	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: Metadata are intended to describe a data set, not an indicator. Many ACE3 indicators make use of NHANES data, so it is appropriate to provide a general characterization. Details of the data specific to an indicator are provided in the Methods for that indicator.
5/3	P21, Methods section	**Comment:** 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?
		Response: Details of sample collection are beyond the scope of ACE. Data are appropriate for comparison over time.
5/3	P14, References	**Comment:** 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).
		Response: No response necessary.

Peer Review of February 2011 Draft ACE3 Indicator Documents

Peer Review Comments and EPA Responses

Section: Biomonitoring

Topic: Mercury

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	N/A Overall text	**Comment:** 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.*
		Response: We have reviewed the reference provided and believe the information currently in the draft provides sufficient background for our target audience.
1/1	P1, Introductory section	**Comment:** 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*
		Response: Elemental and inorganic mercury are discussed on pp. 2-3 of the review draft.
1/1	P11, References	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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., EsmailiS.,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.*\
		Response: We reviewed these references and determined that they would not add substantial new information to the text. The text is not intended to be a comprehensive review of the mercury literature.
1/2	N/A Overall topic text	**Comment:** Topic text section was well-written with only a few questions.
		Response: No response necessary.
1/3	N/A Overall text	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		from New York and Massachusetts are buried in the document amongst text pertaining to health outcomes reported in various studies.
		Response: We have expanded text on the New York and Massachusetts studies.
1/3	N/A Overall text	**Comment:** 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.
		Response: There is no consensus on a blood mercury equivalent of the EPA reference dose of 0.1 ug/kg/day. Because many would take issue with the choice of 5.8 ppb, we decided not to include such a comparison for ACE3. We have included discussion of general issues related to this point in the introduction to the Biomonitoring section.
1/3	N/A Overall text	**Comment:** 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.
		Response: We feel that an inclusion of dose levels is too technical given the scope and intended audiences of this report, particularly since the various epidemiological studies have different designs, different statistical methods, and different dose metrics.
1/3	P1, L32, L34, L36 and P2, L1, L3-L4, L5, L6	**Comment:** 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?)

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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?)
		Response: We feel that reporting specific exposure levels is too technical for some members of the report's audience. The key point to convey is whether the exposure levels are similar to those that might be commonly experienced in the U.S., or are they much higher? We have reviewed the text to ensure this is effectively conveyed and have modified where appropriate.
1/3	P2, L2-L5	**Comment:** 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.
		Response: The purpose of the text is not to either support or call into question the mercury RfD. The significance of these studies is that they find adverse effects in U.S. populations with blood mercury levels within the range of those shown in the indicator. Description of these studies has been expanded.
1/3	P4-5	**Comment:** 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.
		Response: There is no clear criterion for defining "at risk" from mercury exposure in blood mercury units and it is beyond the scope of this report to define one. The summary of the literature gives a qualitative sense of neurodevelopmental findings and how they relate to typical U.S. exposures.
1/3	P1, L8-L13	**Comment:** 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.

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		Response: We have included updated information about the contribution of coal-burning utilities to mercury emissions.
1/3	P2, L38	**Comment:** 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.
		Response: We are not aware of children's health issues associated with exposure to elemental or inorganic mercury in women of child-bearing age, so we did not expand upon this text.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: See above responses.
1/3	P1-P2	**Comment:** 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.
		Response: We have made several edits to address this concern. However, it is important to note that in many epidemiological studies of the effects of methylmercury, the exposure metric is total mercury. We have added explanation of this point.
1/3	P1-P3, headings	**Comment:** **Organization** 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 a. Lines 2-7: What is mercury?

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		b. P1: Needed: What have we learned about mercury and children's health since 2000? c. P1, L8-L17: Cite references #18-20 here for concerns about RfD, existing levels. How does mercury enter the environment? d. Lines 18-25: How does mercury enter people's bodies? Page 2 a. Lines 2-7: How does mercury affect the health of children? b. 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? e. Needed: Is mercury exposure a problem in the workplace? f. Lines 38-line 10 page 3: Is there a problem with mercury in schools? g. Lines 11-20: How is mercury measured in biomonitoring studies? h. Lines 21-31: What levels of mercury in people have been identified by biomonitoring? i. Lines 32-25: What has the federal government learned about mercury exposures and children's health since the last ACE study report in 2003?
		Response: We have chosen not to add sub-headings. We have reviewed the text and edited where appropriate to ensure a logical and consistent organization.
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: We have substantially increased the number of biomonitoring indicators for ACE3, compared with the prior version, from 5 to 13. More could be included, but we have had to place some limits on the number of indicators to make the effort manageable. Further, as discussed in the text, the scientific findings regarding adverse effects of methylmercury are much greater for prenatal exposure than for childhood exposure. Children ages 1 to 5 years are included in the data tables, and we have added bullet points that draw on the data for children.
2/1	P1, L17, L20	**Comment:** 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".
		Response: We have replaced "high" with "increased" for L17. We have retained "high" in L20 since we describe what this means in the following sentence.
2/1	P1, L19	**Comment:** 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.

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		Response: We believe the term "biota" is not understandable to the average reader and may cause confusion. We have added text to the sentence to be more inclusive.
2/2	P4, L7	**Comment:** 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.
		Response: We believe that including those of "other" race/ethnicity makes the overall sample more representative of the U.S. population, not less representative. We discuss the differences in fish consumption and blood mercury by race/ethnicity in the topic text (p.3 of the review draft).
2/2	P4, L13-L17	**Comment:** 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?
		Response: Summaries of blood mercury levels in children are provided in the data tables. We place higher priority on the levels in women of child-bearing age because of the much greater evidence for effects from prenatal exposure than for childhood exposure. The text has been revised to reflect all of the years used.
2/2	P4, L18-L25	**Comment:** 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.
		Response: We have revised the text.
2/2	P4, L26	**Comment:** Page 4, lines 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.

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		Response: The half-life of methylmercury of 158-170 hours is based on measurements in lactating and non-lactating mice and would be expected to be shorter than in humans due to their faster metabolism. ATSDR reports the methylmercury half-life in humans as between 48-65 days. CDC's biomonitoring report and several peer-reviewed articles (Tollefson and Cordle, 1986; Sherlock et al., 1984; Smith et al., 1994; Smith and Farris, 1996; Clarkson, 2002) state that the half life of methylmercury in humans is around 50-60 days. We have added this statement: "Total blood mercury is generally representative of methylmercury exposures in the past few months."
2/2	P4, overall	**Comment:** 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.
		Response: Urine tends to reflect inorganic mercury exposure, while blood is more reflective of methylmercury exposure. Based on current evidence (as summarized in the text), methylmercury appears to be the greater children's health concern. We do not agree that urine mercury better represents long-term exposure to total mercury; see above discussion of methylmercury's half-life.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: Please see above responses.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: The reference dose is in intake units (ug/kg/day); there is no reference dose in blood mercury units. There is no consensus regarding the use of 5.8 ppb blood as equivalent to the reference dose of 0.1 ug/kg/day.
2/3	N/A Overall presentation of data	**Comment:** 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

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		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.
		Response: We believe it is clearer to include the findings of the scientific studies in the topic text, and focus the indicator text on how the indicator was developed. The topic text is intended to summarize the current literature relevant to children's environmental health, but characterization/interpretation of the literature is beyond the scope of ACE. Also, note that the exposure units in both the Oken et al. and Lederman et al. studies are different than those of the NHANES data, so some translation (with attendant uncertainties) would be necessary to compare; further, selection of an appropriate level to represent "effects" in these studies would likely involve significant work that would typically be done in a risk assessment, which is beyond the scope of ACE. We have inserted additional text in the report introduction to clarify the scope and intent of ACE3.
2/3	P10, tables	**Comment:** **Content** 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?
		Response: We have added a bullet after the indicator graph discussing the increases with age and the overall increasing trend from ages 1-17 years.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: We have chosen not to add sub-headings. We have reviewed the text and edited where appropriate to ensure a logical and consistent organization. The sample sizes used have been added to the text and the sample is representative of the U.S., so the percentages reported should apply to the total U.S. population of women and newborns. Please see comments above regarding the RfD.
3/1	N/A Overall indicator text	**Comment:** I would like to see the 95^{th} percentile and race ethnicity of the 1-5 age group. Also the 95^{th} percentile of income including the 1-5 age group. Also can the data be presented by regions (coastal, Midwest, etc.)
		Response: Because of the limited health effects findings for childhood exposure, we chose not to include more detailed data tables by race/ethnicity for children. Information on the residential location of survey participants is not provided in the publicly available NHANES files.

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3/2	P5, L12	**Comment:** 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.
		Response: We have added a bullet point referencing data from this table (now renumbered as Table B3a).
3/2	P6, L4	**Comment:** 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.
		Response: We believe that including those of "other" race ethnicity makes the overall sample more representative of the U.S. population, not less representative. We mention the difference in fish consumption and blood mercury in the "other" category in the topic text (p.3 of the review draft).
3/2	P7, L28	**Comment:** 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.
		Response: We agree and have added a bullet point addressing differences by children's age groups.
3/2	P5, L8	**Comment:** Page 5, line 8. Add (see Table B4) at the end.
		Response: This comment appears to pertain to page 6, line 8. We do not include references to table numbers for values that are shown in the indicator graph.
3/3	P8, Table B4a	**Comment:** **Organization** 1) Table B4a is not discussed in the text.
		Response: A bullet point has been added discussing the differences at the median by race/ethnicity.
3/3	N/A Overall text	**Comment:** 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.
		Response: There is considerable uncertainty regarding the appropriate conversion to represent the reference dose in blood mercury units.

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3/3	N/A Overall indicator data presentation	**Comment:** 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.
		Response: Please see the responses above.
3/3	P8, table B4a	**Comment:** 1) Table B4a is not discussed in the text.
		Response: A bullet point has been added discussing the differences at the median by race/ethnicity.
3/3	N/A Multiple sections	**Comment:** 2) It is difficult to track down the Table numbers in the explanatory text.
		Response: Our general approach is to provide a table number for values not shown in the indicator figure.
3/3	N/A all data tables	**Comment:** 3) Statistical significance could be indicated in the tables with the use of (*).
		Response: This has potential to be very confusing, since the comparison referred to by an asterisk will not be obvious (e.g. is it a difference by income level, or a difference with another race/ethnicity?)
3/3	P10, Table B4d	**Comment:** 5) What does the doubling of the median concentration in B4d from 3-6 to 6-11 mean?
		Response: It would be a substantial effort, beyond the scope of this report, to identify explanatory variables. We are unaware of any publications that have evaluated this difference.
4/1	N/A data presentation	**Comment:** a.) More detailed analysis for the 1-5 age group needs to be included.
		Response: More detailed analysis is beyond the scope of this report. Table B3d indicates that there are no differences by age within this span.
4/1	N/A data presentation	**Comment:** 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

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		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.
		Response: Recommendations for data improvement are beyond the scope of this report, which is meant to inform discussion on further data needs. We have included data for children in the tables and have highlighted some key findings in the bullet points.
4/1	N/A Overall text	**Comment:** 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.
		Response: No response necessary.
4/2	N/A Overall text	**Comment:** 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?
		Response: Data for children are included in the data tables and described in the bullet points. As indicated in the text, reported associations with adverse effects in children are much greater for prenatal exposure than for childhood exposure.
4/2	N/A Overall text	**Comment:** 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.
		Response: We believe the structure of the presentation is appropriate and provides a standard approach that is effective for conveying an important public health message when applied across all 23 ACE3 topics. The topic text discusses the significance of the issue for children's environmental health, followed by presentation of the data and bullet points to highlight key findings from the data.
4/3	N/A Overall text	**Comment:** 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.
		Response: Please see above responses. We have edited the phrasing of the principal

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		objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
4/3	N/A Overall text	**Comment:** 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."
		Response: We have made a number of revisions to the text, and we believe the information clearly relates to public health, children and the environment.
4/3	N/A Overall text	**Comment:** 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.
		Response: We have included updated information about coal and appropriately describe the potential adverse effects of exposure to mercury. Further interpretation and conclusions are beyond the scope of ACE.
5/1	N/A New Section	**Comment:** A new section is needed on limitations to the current data and general recommendations on improving future data collection analysis.
		Response: Recommendations for data improvement are beyond the scope of this report.
5/2	P15, Metadata	**Comment:** 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, needs to be clarified.
		Response: Metadata are specific to a data source, not to an indicator. Years of data available for mercury are provided in the indicator text. Analytical methods are available in CDC publications and are beyond the scope of this report.
5/2	P17, Methods	**Comment:** 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

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		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.
		Response: We have reviewed this text and believe it is clear regarding what has been measured in NHANES. See above responses regarding children's mercury data.
5/2	P21, L6	**Comment:** 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.
		Response: We mention the difference in fish consumption and blood mercury in the "other" category in the topic text (p.3 of the review draft). The description of the All Other Races/Ethnicities group is also given in the introduction to the Biomonitoring section.
5/2	P8, Data Tables	**Comment:** 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.
		Response: We have included a comment on the lower mercury levels in children in a bullet under the indicator figure.
5/2	P26, Statistical Comparisons	**Comment:** 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)
		Response: No response necessary.
5/2	P11, references	**Comment:** References: Appears to be representative of the literature.
		Response: No response necessary.
5/3	N/A Overall text	**Comment:** 2) I would avoid the use of the term "environmental chemicals," which conveys the idea that mercury and other industrial pollutants are somehow

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		"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."
		Response: This term is commonly used in the field.
5/3	N/A Overall text	**Comment:** 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.
		Response: The methods section of the report will only be provided online for interested readers and is presented as it is to be detailed and transparent.
5/3	P11, references	**Comment:** 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.
		Response: We have revised the text to include more information from these studies.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Biomonitoring

Topic: Cotinine[1]

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1/1	P1, L28-29	**Comment:** 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.
		Response: We rephrased the sentence to read: "In addition, the Surgeon General concluded the evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to ETS and childhood cancer."
1/2	P1, L1-L37	**Comment:** 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.
		Response: We altered the language to appropriately represent the outcomes that have been more causally linked to ETS exposure (according to the U.S. Surgeon General) vs. the outcomes for which ETS may cause an increased risk, but for which the evidence is not sufficient to make a causal link.
1/3	P1, L1-L37	**Comment:** Overall, I think it is fine. However, it may be helpful to those outside of science of medicine if you mention that ETS exposure is commonly referred to as second-hand smoke exposure.
		Response: We added language to the first sentence of the section about second-hand smoke to read "Environmental tobacco smoke (ETS), commonly referred to as secondhand smoke, is a complex mixture of gases and particles…"

[1] In the February 2011 peer review draft, the cotinine indicators were numbered B5 (children) and B6 (women ages 16 to 49 years). As of September 2011, the cotinine indicators were renumbered to B4 and B5, respectively.

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2/1	P3, L1-L3	**Comment:** 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?
		Response: Indicator B4 reflects all data available between 1988-2010, so the indicator includes the data for 3 year olds that was available for part of that time (1999-2010). We have clarified the text.
2/1	P3, L6	**Comment:** 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.
		Response: We found no indication of cotinine measurements in children younger than age 3 years on the NHANES website. The 2007-2008 codebook says age 3+ http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/COTNAL_E.htm
2/1	P1, L1-L37	**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.
		Response: The sentences have been rephrased to "Once nicotine enters the body, it is rapidly broken down in a matter of a few hours into other chemicals. Cotinine is a primary breakdown product of nicotine, and has a longer half-life. This characteristic makes cotinine a better indicator than nicotine of an individual's exposure to ETS. Measurement of cotinine in blood serum is a marker for exposure to ETS in the previous few days."
2/1	P3, L3-L4	**Comment:** 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.
		Response: The data presentation in this report reflects the aims of the report, and does not necessarily need to match the tables and data on the NCEH website.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/2	Starting P2, Indicator text	**Comment:** 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.
		Response: We removed the language about why blood serum was used. Since only blood serum data are available from NHANES, we decided that it wasn't necessary to discuss the issue.
2/3	P2, L14-L18	**Comment:** 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.
		Response: We removed the language about why blood serum was used. Since only blood serum data are available from NHANES, we decided that it wasn't necessary to discuss the issue.
2/3	P3, L17	**Comment:** 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.
		Response: The word has been corrected to "nonsmoker" throughout the document.
2/3	P24, L24	**Comment:** Page 24, line 24, "pre-natal" should be "prenatal"
		Response: This change has been made throughout the document.
3/1	P6, L1-L10	**Comment:** 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.
		Response: These bullet points were included to provide information that may be helpful for interpreting the indicator graph. We moved the information in the bullet explaining the recent declines in active smoking into the topic text.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/1	P6, L17	**Comment:** Page 6, line 17 Why was the data set from 2005-2008 used and not other data sets or combined data sets?
		Response: We focus on the most recent data for making demographic comparisons – using the two most current NHANES cycles. We have added language to better clarify our approach to the Biomonitoring section introduction.
3/1	P6, L23	**Comment:** Page 6, lines 23. There is no discussion of the data in Tables B5b and B5c. Why present the tables and not the discussion?
		Response: The cotinine indicator tables being referred to are now B4b and B4c. We added bullet points to address findings in Tables B4b and B4c.
3/1	P8, Table B6a and B6b	**Comment:** Page 8. Comment. There was no discussion of Tables B6a or B6b. Why present the tables and not the discussion?
		Response: The cotinine indicator tables being referred to are now B5a and B5b. We added bullet points to address findings in Tables B5a and B5b.
3/1	P8, L1-L3	**Comment:** 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.
		Response: We moved the information in the bullet explaining the recent declines in active smoking into the topic text.
3/1	P5, L7 & L10	**Comment:** Page 5, lines 7 and 10. Add (see Table B5) at the end.
		Response: The format we have chosen for the report is to only reference data tables in the instance where a bullet describes data found only in the table, and not in the indicator graph.
3/1	P7, L4 & L8	**Comment:** Page 7, lines 4 and 8. Add (see Table B6)
		Response: The format we have chosen for the report is to only reference data tables in the instance where a bullet describes data found only in the table, and not in the graph.
3/2	N/A Overall data presentation P5,L1&P7,L1	**Comment:** 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?

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We have added the sample sizes for the figures to the indicator text and have included sample sizes in the tables for demographic comparisons.
3/2	N/A Overall data presentation	**Comment:** 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?
		Response: Because this report was designed for a broad audience, we feel that including the p-values or confidence intervals in the summary points is too technical. P-values are provided in the methods section and standard errors are provided online for interested readers.
3/2	N/A Overall data presentation	**Comment:** Also, did the authors consider presenting figures to display the reported race/ethnicity and poverty differences? I think those illustrations could be useful.
		Response: We considered presenting figures to display demographic comparisons; however, we decided to focus on presenting trends in figures in order to keep the report at a manageable length. The data for all demographic comparisons are included in data tables for those interested.
3/2	N/A Overall data presentation	**Comment:** Were the women's concentrations not further analyzed by race/ethnicity and income? Why not?
		Response: The concentration of cotinine in women's blood was analyzed by race/ethnicity and income and the data are included in data tables B5a and B5b. Bullets were added to discuss these findings.
3/2	N/A emphasis of data presentation	**Comment:** 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.
		Response: We added a bullet to address comment as follows: • In every time period measured, children at the 95th percentile had higher levels of cotinine in their blood than women at corresponding levels. (Compare with Indicator B5.)
3/3	P5, L2-L4	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: Because this report was designed for a broad audience, we feel that including the p-values or confidence intervals in the summary points is too technical. P-values are provided in the methods section and standard errors are provided online for interested readers.
3/3	P5-P8	**Comment:** Is it possible to present some statistics for trend over time on pages 5-8? I think the change over time is of importance.
		Response: In the bullets, we discuss whether trends are statistically significant or not. We have added language to the bullets to clarify that the statistical analysis was performed to look across the entire trend, rather than compare two time points. We also include information on all statistical analysis comparisons in the methods section.
3/3	P5-P8	**Comment:** Further, it would be helpful to compare the measures from the most current year with years other than the 1988-1991 cotinine measures.
		Response: The statistical analysis we provide looks at whether the trend over the entire time period was statistically significant. The bullets have been rephrased to emphasize that the statistical analysis was performed to look across the trend, rather than to compare two time points.
3/3	P5-P8	**Comment:** 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.
		Response: We considered presenting figures to display demographic comparisons; however, we decided to focus on presenting trends in figures in order to keep the report at a manageable length. The data for all demographic comparisons are included in data tables for those interested.
3/3	N/A Overall data tables	**Comment:** Graphical figures as opposed to large data tables are better for diverse audiences as they are generally easier to understand.
		Response: We considered presenting additional figures; however, we decided to focus on presenting trends in figures in order to keep the report at a manageable length. The data for all demographic comparisons are included in data tables for those interested.
4/1	N/A Overall text of data presentation	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: Bullets have been added underneath the indicator figures that discuss findings from each table.
4/1	N/A Overall text of data presentation	**Comment:** 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.
		Response: We believe the structure of the presentation is appropriate and provides a standard approach that is effective for conveying an important public health message when applied across all 23 ACE3 topics. The topic text discusses the significance of the issue for children's environmental health, followed by presentation of the data and bullet points to highlight key findings from the data. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
4/2	N/A Overall text	**Comment:** 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.
		Response: No response necessary.
4/3	N/A Overall Indicator parameters	**Comment:** 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.
		Response: As indicated by the comment, there is no standard definition of "women of childbearing age" and several different age groups have been used in the literature. The 16-49 age grouping was chosen for ACE3 because it represents the full age range of women of childbearing age, and has been previously used in multiple publications for presenting NHANES blood mercury data. In order to address the concern that a 49 year old woman is less likely to be pregnant as compared to a women of other ages, we performed a birth-rate adjustment according to a recently published method. Please see: Axelrad, D.A., and J. Cohen. 2011. Calculating summary statistics for population chemical biomonitoring in women of childbearing age with adjustment for age-specific natality. *Environmental*

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Research 111 (1):149-155.
4/3	P8, L1-L3	**Comment:** 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).
		Response: While we think that providing comparisons over the entire time period is important for describing trends in cotinine levels, we recognize that smoke-free laws help reduce ETS exposure and may affect cotinine levels in both women and children. Therefore, we moved information in the bullet about the reduction in active smokers into the topic text and added a discussion of smoke-free laws and their impact on children's health.
5/1	P17 (Overall metadata section)	**Comment:** 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.
		Response: The metadata section was created to explain the general source of the data (NHANES). A more detailed explanation of the data used to calculate the indicator is provided in the methods document.
5/1	P19, L16-L18	**Comment:** 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?
		Response: Because the indicator includes data for the years1999-2010, which have data for 3 year olds, using the age grouping of 3-17 is inclusive of all data.
5/1	P191, L22-L25	**Comment:** 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.
		Response: These sentences summarize all the data available from NHANES, including the data available for adults. Therefore, the sentences apply to both indicator B4 and indicator B5.
5/1	P20, Data Summary Tables	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: A sentence was added to address the shift in detection limits in recent years as follows: "…improvements in laboratory methods made it possible to detect cotinine levels at lower concentrations starting with the 2001-2002 survey cycle." Additional details on the laboratory methodology are outside the scope of this report.
5/1	P20, Table B5	**Comment:** 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.
		Response: Because the indicator covers data from 1999-2010, which includes data on 3 year olds, using the age grouping of 3-17 is inclusive of all data. We have added a footnote to indicate which years included data on 3 year olds. It reads "For NHANES III, in 1988-1994, serum cotinine data were not measured on children age 3 years, so these data are for children ages 4 to 17 years."
5/1	P30-P34	**Comment:** 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.
		Response: The tables in the methods section were provided in order to transparently explain the detailed methodologies used for calculating the indicator. Because the report is geared toward a broad audience, rather than only a technical audience, the highlights and key findings from the indicator were outlined in bullets underneath the indicator graph. The methods section will not be included in the printed copies of the report, but will be available online to provide additional details for those who are interested.
5/1	N/A Overall statistical approach	**Comment:** 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)
		Response: No response necessary.
5/2	P14, References	**Comment:** Yes, the documentation appears to be complete and transparent.
		Response: No response necessary.
5/3	P31, Table 2	**Comment:** 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.

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		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.
		Response: We have clarified the tables by modifying the column headings and footnotes to be more descriptive. Because the methods section is unlikely to be relevant to a broad audience, it will not be included in the printed report, but will be available online for those who are interested.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Biomonitoring

Topic: Perfluorochemicals (PFCs)

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	N/A Overall topic text	**Comment:** 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.
		Response: Responses to each of the specific examples are given below.
1/1	N/A Overall topic text	**Comment:** 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.
		Response: While we do rely heavily on epidemiological data, we provide a summary of the toxicological research when epidemiological data were not available. We addressed the specific concerns below. We have added a discussion about the advantages and limitations of both epidemiological and animal toxicological studies to the report introduction.
1/1	N/A Overall topic text	**Comment:** 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).
		Response: A sentence was added to explain data available on the various PFCs to read "Although some studies have addressed PFHxS and PFNA specifically, the majority of scientific research has focused on PFOS and PFOA."
1/1	P1, L10	**Comment:** 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.

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		Response: We have identified additional studies that support the statement that PFCs have long half-lives in humans. The sentences now read, "Due in part to their chemical properties, some PFCs can remain in the environment and bioconcentrate in animals. Data from human studies suggest that some PFCs can take years to be cleared from the body."
1/1	P1, L10	**Comment:** 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.
		Response: We changed the language about environmental persistence and added a number of references. The sentence now reads "However, the fact that some of these chemicals may be persistent in the environment and have a long half-life in humans means that they may continue to persist in the environment and in people for many years, despite reductions in emissions."
1/1	P1, L31-L32	**Comment:** 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.
		Response: We edited the introduction sentence to try to make clear the many potential pathways of exposure to PFCs to read as follows "The major sources of human exposure to PFCs are poorly understood, but may include food, water, indoor and outdoor air, breast milk, and dust." However, we do try to make clear the uncertainties by saying that the sources of human exposure to PFCs are poorly understood and we are careful to point out the fact that only 2 studies found food consumption was the primary pathway of exposure. Furthermore, we explain the potential for exposure through breast milk and dust.
1/1	P1, L38	**Comment:** Pg 1, line 38: The following references can be added: Llorca M, FarréM, PicóY, 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The references were added as suggested.
1/1	P1, L39	**Comment:** 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?
		Response: EPA has not established quantitative risk assessment values for PFCs, in either daily intake or biomonitoring units. EFSA risk assessments are not always consistent with EPA values. We also note that the EFSA TDIs are based on animal data, while there are several epidemiological studies finding associations with relatively low serum PFCs.
1/1	P1, L41	**Comment:** Pg 1, line 41: Why would children be more exposed to "certain" PFCs in dust? Which ones? Why not all?
		Response: The sentence was rephrased to make it clear that infants and children may be more highly exposed to the PFCs that are present in house dust, rather than certain PFCs found in house dust. It now reads, "Infants and small children may be more highly exposed to the PFCs present in house dust than adults are, due to their frequent and extensive contact with floors, carpets, and other surfaces where dust gathers, as well as their frequent hand-to-mouth activity."
1/1	P2, L3	**Comment:** 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.
		Response: This reference was added as suggested.
1/1	P2, L9-L10	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We rephrased the section to address variability between studies and uncertainty in the results. The section now reads "Some PFCs have been widely detected in pregnant women and in umbilical cord blood, suggesting that the developing fetus can be exposed to PFCs while in the womb. However, findings between studies vary. For example, PFOS and PFOA were detected in 99–100% of blood samples collected from both pregnant and non-pregnant women in 2003–2004. Additionally, PFOS and PFOA were detected in 99% and 100% of umbilical cord blood samples, respectively, collected from newborns in Baltimore. In another study conducted in Japan, the level of PFOS circulating in a pregnant woman's blood was highly correlated with the level in cord blood. However, PFOA was detected in maternal samples but was not detected in umbilical cord samples in the Japanese study. Even though studies suggest that the correlation between maternal and fetal exposure may vary, the ubiquitous presence of PFOS, PFOA, and other PFCs in blood of women of child-bearing age and in umbilical cord blood may indicate that fetal exposure to these chemicals is widespread."
1/1	P2, L12-L13	**Comment:** 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.
		Response: We revised the text to better reflect the variable findings between studies. However, given the format of the report and its aim to provide a summary of the science that supports the inclusion of the topic in the report, we don't believe a data summary table will fit into the section. The section now reads "Some human health studies have found associations between prenatal exposure to PFOS or PFOA and a range of adverse birth outcomes, such as low birth weight, decreased head circumference, reduced birth length, and smaller abdominal circumference. However, there are inconsistencies in the results of these studies, and two other

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		studies did not find an association between prenatal PFC exposure and birth weight. The participants in all of these studies had PFC blood serum levels comparable to levels in the general population."
1/1	P2, L26-L29	**Comment:** 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)"
		Response: The paragraph has been rephrased to "Findings from a limited number of studies suggest that exposure to PFOS or PFOA may have negative impacts on human thyroid function. However, there are inconsistencies in the findings between these studies. Some studies have found that PFC exposures are associated with alterations in thyroid hormone levels, as well as an increased risk of thyroid disease in the general public and in workers with occupational exposures. However, a recent study of pregnant women with exposures comparable to those in the general population found that increasing levels of PFOS, PFOA, and PFHxS were not associated with differences in thyroid hormone levels. The results from animal studies have been more consistent. Multiple animal studies have found that thyroid hormone levels are altered in animals exposed to PFOS. One of these studies also found that PFOA-treated rats have altered thyroid hormone levels. The health risks associated with maternal thyroid hormone disruption during pregnancy may make this a cause for concern. Moderate deficits in maternal thyroid hormone levels during early pregnancy have been linked to reduced childhood IQ scores and other neurodevelopmental effects, as well as unsuccessful or complicated pregnancies."
1/1	N/A Overall topic text	**Comment:** 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.
		Response: Please see the above response.
1/1	P2, L40	**Comment:** 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"?

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The sentence has been rephrased to make the meaning more clear: "This could be a potential concern for children, because the mother's body provides a source of cholesterol and triglycerides to the developing fetus. Cholesterol and fatty acids support cellular growth, differentiation, and adipose accumulation during fetal development."
1/1	P2, L42	**Comment:** 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?
		Response: Human studies have not been conducted (although one in vitro study was recently published). The sentence was rephrased to reflect this. "Finally, although human studies have not looked at the associations between PFC exposure and the immune system, animal studies have found an association between PFOS and PFNA exposure (in utero and in adulthood) and immune suppression, including alterations in function and production of immune cells and decreased lymphoid organ weights."
1/1	N/A Overall topic text	**Comment:** 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.
		Response: We have prepared a discussion of these broader issues in the report introduction. A basic purpose of environmental indicators is to look at how a particular indicator changes over time; this may include a lack of change. It is also important to evaluate differences by demographic group (especially those defined by race/ethnicity and income) to identify possible concerns relevant to environmental justice and health disparities. We have revised the text, as discussed above. EPA has not reached any general conclusions regarding weight of evidence for effects of these compounds. EPA has not established quantitative risk assessment values for PFCs (e.g. a reference dose) in either daily intake or biomonitoring units. The purpose of the text is to summarize findings relevant to children's health, and demonstrate why PFCs are considered relevant to children's environmental health. We believe the structure of the presentation is appropriate and provides a standard approach that is effective for conveying an important public health message when

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		applied across all 23 ACE3 topics. The topic text discusses the significance of the issue for children's environmental health, followed by presentation of the data and bullet points to highlight key findings from the data. Integrating the two types of information to derive a single, succinct message goes beyond the scope of this report. The introductions to the report and the Biomonitoring section are intended to orient the readers and help guide them through the report. We did not include a summary table to be consistent with the rest of the report.
1/2	N/A Overall topic text	**Comment:** 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 (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) offers insight into distribution in environments subject to local-source contamination.
		Response: We tried to focus our description of PFC chemical properties around those that are most relevant to routes of exposure and to explain why the compounds are used in industry. Given that this report will be read by both scientific and non-scientific audiences, we feel it is not necessary to add additional information about PFC chemical properties. We added the Shin et al., reference to our description of industrial exposure.
1/2	N/A Overall topic text	**Comment:** 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 ClinEndocrinolMetab. 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.
		Response: We include findings from the C8 science panel when they have been published in final form (e.g. as journal articles); but not status reports or preliminary findings

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		provided on their website. While the connection between exposure and menopause is interesting, we did not include a reference to the study because the focus of this report is on children's health.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: A discussion about risks from cumulative exposure has been added to the Biomonitoring section introduction.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: The statement inserted to address issue 1 also addresses this issue.
1/3	P2, L12	**Comment:** 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.
		Response: We agree that it is important to explain to the reader why low birth weight is important for children's health. Because of that, we have an entire topic area in our "Health" section devoted to addressing adverse birth outcomes. We will refer all readers interested in better understanding the implications of low birth weight for children's health to the adverse birth outcomes section.
1/3	P14, References	**Comment:** 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.

<table>
<tr><th>Charge Question/ Reviewer #</th><th>Page/Line</th><th>Peer Review Comments and EPA Response</th></tr>
<tr><td></td><td></td><td><u>Response:</u>
The references have been corrected.</td></tr>
<tr><td>1/3</td><td>P14, References</td><td><u>Comment:</u>
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</td></tr>
<tr><td></td><td></td><td><u>Response:</u>
These were used as references for the text that was added on health outcomes from cumulative exposures in the Biomonitoring section introduction. Woodruff et al. was added to the section on PFC levels in women of child-bearing age.</td></tr>
<tr><td>1/3</td><td>N/A Overall organization</td><td><u>Comment:</u>
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:

<table><tr><th>Page</th><th>Line</th><th>Text for a subheading</th></tr><tr><td>1</td><td>2</td><td>How are PFCs used?</td></tr><tr><td>1</td><td>17</td><td>What action has been taken on PFCs?</td></tr><tr><td>1</td><td>30</td><td>How are people exposed?</td></tr><tr><td>2</td><td>11</td><td>What are the possible health effects?</td></tr></table></td></tr>
<tr><td></td><td></td><td><u>Response:</u>
While we appreciate the suggestion and agree that subheadings might help readers navigate the information, our format needs to be consistent across topics and including subheadings would make achieving that consistency, while addressing issues unique to each topic, difficult.</td></tr>
<tr><td>1/3</td><td>P1, L3</td><td><u>Comment:</u>
Page 1, Line 3 - Strike “manmade”, and insert “synthetic”</td></tr>
<tr><td></td><td></td><td><u>Response:</u>
The change was made.</td></tr>
<tr><td>1/3</td><td>P1, L9</td><td><u>Comment:</u>
Page 1, Line 9 - Insert italicized word: “…PFCs are highly persistent…”</td></tr>
<tr><td></td><td></td><td><u>Response:</u>
This phrase was changed due to other peer-review comments, so this comment is no longer applicable.</td></tr>
</table>

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/3	P1, L12	**Comment:** Page 1, Line 12 - What is the production volume? (For the relevant TSCA inventory reporting year)
		Response: Production volumes are not generally available - protected as confidential business information.
1/3	P1, L31	**Comment:** Page 1, Line 31 - Need a clearer overall statement of exposure routes at the opening of this section.
		Response: Text has been added.
1/3	P1, 37	**Comment:** Page 1, Line 37 - Insert italicized text: "…have been found *at high levels* in drinking water…"
		Response: These words were added.
1/3	P2, L9	**Comment:** Page 2, Line 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.
		Response: The word "ubiquitous" was added as well as the reference.
1/3	P2, L29	**Comment:** Page 2, Line 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).
		Response: As the reference we already included also focuses on neurodevelopmental effects as the most important outcome to children born to exposed mothers, we will focus on these outcomes in the text.
1/3	P2, L35	**Comment:** Page 2, Line 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…"*
		Response: The change was made as suggested and reference added. The sentence now reads "Both animal and human studies show a relationship between PFCs exposure and cholesterol and/or triglyceride levels, although physiological differences between humans and experimental animals may cause lipid levels to vary in opposite directions."

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2/1	P4, Overview box	**Comment:** 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.
		Response: The sentence was changed to emphasize that the current literature points to an association between in utero exposure and an increased risk of children's health outcomes. It now reads "The focus on women of child-bearing age is based on concern for potential adverse effects in children born to women who have been exposed to PFCs."
2/1	P4, L17-L19	**Comment:** 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.
		Response: Including data for adolescents for all four PFCs would greatly lengthen the section. In addition, the information gained would be limited since it is for a narrow age group. At this time, we do not feel that the additional resources required to add the data for 12-19 year olds will match the amount of insight it is likely to give about children's environmental health.
2/1	P4, L30	**Comment:** Pg 4, line 30: This statement on persistence again argues for inclusion of NHANES data on 12-19 year olds.
		Response: Please see the above response.
2/1	P5, L40 P6, L1 P6, L2-L4	**Comment:** 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

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		– the health significance of these numbers is unclear.
		Response: Explanation of statistical significance (which has been revised) and the limits of biomonitoring data are now covered in the introduction to the Biomonitoring section.
2/1	P7, Graphs and Tables	**Comment:** Pg 7: The text leading up to this point does not prepare the reader for seeing data on the four individual PFCs.
		Response: The indicator text discusses, in detail, the four individual PFCs that are presented in the indicator (see description under heading "Perfluorinated Compounds" on page 4).
2/1	N/A Overall indicator text	**Comment:** I have already commented on this above. I do think that the Indicators section will be impossible for most non-researchers to read.
		Response: We have revised the text and believe the current version will be more accessible. However, to be complete in describing data and research it is often difficult to avoid some technical language; information provided will still be useful to non-researchers. The report introduction and the expanded Biomonitoring section introduction should help orient non-researchers to the report content.
2/2	N/A Overall indicator text	**Comment:** 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.
		Response: Information about why NHANES data was used and the criteria used to make decisions about topics and data sources are now discussed in an introduction to the entire Biomonitoring section. NHANES is the only source of biomonitoring data in the U.S. that is nationally representative and that collects comparable data on a continuing basis over time.
2/2	N/A Overall indicator text	**Comment:** 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

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		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.)
		Response: We have revised the text and believe the current version will be more accessible. However, to be complete in describing data and research it is often difficult to avoid some technical language; information provided will still be useful to non-researchers. The report introduction and the expanded Biomonitoring section introduction should help orient non-researchers to the report content. We have also addressed the issue of explaining basic topics by defining them once in the Biomonitoring introduction instead of repeating them for each topic. We believe the report to be at a consistent level.
2/2	P4, L19	**Comment:** 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.
		Response: We have noted that many scientific reports use the word "womb" and believe it is unnecessary to make this change.
2/2	P4, L27	**Comment:** Under Perfluorinated Compounds. The word "respectively" should be inserted after "women" in Page 4, Line 27.
		Response: The text was edited to reflect data for women of childbearing age for 2007-2008 and reads "The four selected PFCs were detected in 99% to 100% of the individuals sampled in NHANES 2007–2008."
2/3	P4, L3	**Comment:** Page 4, Line 3 - See comment below (question 3) on utility of addressing only the *change* in blood PFC concentration over time.
		Response: Please see response to question 3.
2/3	P4, L12	**Comment:** Page 4, Line 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".
		Response: The language used by the CDC is "environmental chemicals". Since we are referring specifically to the measurements done by the National Center for Environmental Health, we think it is important to use their language.
2/3	P5, L13	**Comment:** Page 5, Line 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

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		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.
		Response: We have included the percentage of women with detectable levels of PFCs in the introduction and in a paragraph above (see "Perfluorinated Compounds"). We decided to include a time series because it can be easily interpreted by both researchers and non-researchers and gives an idea about whether or not levels are going up or down over time.
2/3	P5-6	**Comment:** Page 5, Line 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."* Page 5, Line 40-41 -"…to detect [strike 'a'] *that* difference when *a large number of* samples have been *tested* in those groups…" Page 6, Line 1 -"…within each group, then [strike 'a'] *the* difference…" Page 6, Line 4-5 -"…does not [strike 'necessarily suggest any interpretation regarding the'] *address any potential* health implications."
		Response: We have revised the discussion of statistical significance and moved it to the Biomonitoring introduction.
3/1	P5, L4-L11	**Comment:** 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.
		Response: Birth-rate adjustment makes an important difference for some of the chemicals included in the ACE3 Biomonitoring section, and we apply a consistent approach to how the data are analyzed for each chemical reported. Given the context of children's health and in utero exposure, we believe most readers will understand that women >40 years should not be weighted the same as younger women. For this edition of ACE, we have substantially expanded the number of biomonitoring topics and the amount of data reported for each topic, but it is not feasible to include all values of interest. With four separate PFCs included, adding a second population group would substantially increase the amount of analysis conducted and presented for this topic. Note that also the number of samples in children is relatively small: PFCs are measured in a 1/3 subsample; children younger than 12 are excluded; and sampling of adolescents in NHANES has been reduced, beginning with the 2007-2008 survey.

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3/1	P5, L4-L11 and the Overall indicator text	**Comment:** 1. Leave out the birth-adjusted years data and present the biomonitoring data on its own.
		Response: Please see the above response.
3/1	P5, L4-L11 and the Overall indicator text	**Comment:** 2. Include 12-19 year olds.
		Response: Including data for adolescents for all four PFCs would greatly lengthen the section. In addition, the information gained would be limited since it is for a narrow age group. At this time, we do not feel that the additional resources required to add the data for 12-19 year olds will match the amount of insight it is likely to give about children's environmental health.
3/1	Overall indicator text	**Comment:** 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.
		Response: We believe that these tables include comparisons that are useful and address important questions about how exposure might be different between different race/ethnicity and income groups. We use this format throughout the report, and while some comparisons for other chemicals might present more significant findings, we are aiming to be transparent and consistent in our approach to all topics.
3/1	P21, Footnote	**Comment:** 4. Mention prior to a footnote on pg 21 that data from 2001-2002 were not included.
		Response: This information is provided in the indicator text under the "Perfluorinated Compounds" heading.
3/1	P23	**Comment:** 5. In the table on pg 23, define in a footnote what is meant by "missing data."
		Response: A footnote was added to define "missing data" to read "Non-missing values include those below the analytical LOD, which are reported as LOD/√2. Missing values are the number of sampled women ages 16 to 49 years in the Mobile Examination Center (MEC) sub-sample that have no value reported for the particular variable used in calculating the indicator."
3/1	Overall indicator text	**Comment:** 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

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		questionnaire that might be explanatory. Just because an assessment *can* be done, it doesn't mean it *should* be done!
		Response: We believe that these comparisons are useful and address important questions about how exposure might be different between different income groups. We use this format throughout the report, and while some comparisons for other chemicals might present more significant findings, we are aiming to be transparent and consistent in our approach to all topics. Reasons for reporting these data are discussed in the introduction to the report.
3/1	P31, L19	**Comment:** 7. Pg 31, line 19. The issue of multiple comparisons is contentious (see, for example, NeurotoxicolTeratol. 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.
		Response: We have added notes and explanations that there is no adjustment for multiple comparisons. There is precedent for this approach in CDC/NCHS documents, e.g. the annual Health Summary Statistics for U.S. Children reports presenting data from the National Health Interview Survey. Multiple comparisons can be implemented in various ways (e.g., alternate definitions of the extent of a comparison group). Since we provide the p-values, interested readers will be able to apply their own adjustments, e.g., by using a simple Bonferroni probability approach. Although we report large numbers of p-values in some cases, we did not use all these p-values to make our reporting decisions; instead we used the p-values to determine whether some of the patterns that we had already found were expected to have occurred "by chance." We have also streamlined the p-value table to reduce the number of comparisons by race/ethnicity and income. We have made the decision not to adjust for multiple comparisons as we feel it is important to identify all potentially important differences, and adjustment for multiple comparisons will increase the challenge in conveying findings of statistical testing to non-technical audiences. We clearly explain in the text that this may increase the probability that some of these differences may actually have occurred randomly. Bonferroni adjusted p-values are relatively easy to compute but tend to be overly conservative since they do not account for possible dependence between different tests. An important consideration for multiple comparison adjustments is that the "experiment" for which the experiment-wise error rate is calculated is not well defined for ACE biomonitoring indicators since there are multiple chemicals and multiple percentiles.
3/2	N/A Overall presentation of data	**Comment:** 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.

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		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.
		Response: We agree that different elements of the presentation (figures, bullet points, data tables) may meet the needs of different readers, and that is a strong reason for our inclusion of all three. We believe that the introductions to the report and the Biomonitoring section will help orient the different types of readers to allow them to find the most relevant information to them.
3/3	N/A Overall presentation of data	**Comment:** **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?
		Response: Further study, beyond the scope of this report, is necessary to answer such questions. We believe it is useful to provide the time series while acknowledging the limitations of our knowledge regarding PFCs exposure and effects.
3/3	N/A Overall presentation of data	**Comment:** 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: (EXAMPLES ARE LISTED BELOW AS SEPARATE COMMENTS)

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		Response: Responses to each of the specific examples are given below.
3/3	N/A Overall presentation of data	**Comment:** 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.*
		Response: We agree with the importance of communicating the percentage of exposed women. We have included the percentage of women with detectable levels of PFCs in the introduction and in a paragraph above (see "Perfluorinated Compounds"). We decided to include a time series because it can be easily interpreted by both researchers and non-researchers and gives an idea about whether or not levels are going up or down over time.
3/3	N/A Overall presentation of data—additional reference	**Comment:** 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.
		Response: We have added a sentence into the topic text summarizing findings from the Woodruff et al. (2011) reference. It reads "PFOS and PFOA were detected in 99–100% of blood samples collected from both pregnant and non-pregnant women in 2003-2004."
3/3	N/A Overall presentation of data	**Comment:** 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.
		Response: As the reviewer notes, there is no established RfD for any of the perfluorochemicals. Relating the observed perfluorochemical values to particular health outcomes is beyond the scope and purpose of an indicators report. EPA also has not defined any thresholds for potentially harmful perfluorochemical exposures in biomonitoring units. The literature is rapidly developing, and a fuller assessment (well beyond the scope of ACE) would be necessary to determine if thresholds for potentially harmful perfluorochemical exposures can be defined.
3/3	Overall data presentation, e.g. P8, L5. L15	**Comment:** 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).

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We think the current presentation of these findings is appropriate and highlights the key issues.
3/3	N/A Overall data presentation	**Comment:** 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.
		Response: The relevance of the weighting is largely a function of any relationship between biomonitoring levels and age. Persistence is one important factor that may result in associations of biomonitoring levels with age, but there are other factors.
4/1	N/A	**Comment:** This is addressed in my previous comments.
		Response: No response necessary.
4/1	N/A data gaps	**Comment:** By highlighting the data gaps, policy makers should understand the need to provide funding for research on these chemicals.
		Response: No response necessary.
4/1	N/A additional information	**Comment:** 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-

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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.
		Response: The reference has been added. Note also that EPA has not established quantitative risk assessment values for PFCs, in either daily intake or biomonitoring units. EFSA risk assessments are not always consistent with EPA values. We also note that the EFSA TDIs are based on animal data, while there are several epidemiological studies finding associations with relatively low serum PFCs.
4/2	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.
4/3	N/A Overall indicator text	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		continued attention—that exposures early in development can have significant and unpredicted effects later in childhood or adulthood.
		Response: No response necessary.
4/3	N/A Overall indicator text	**Comment:** 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.
		Response: As the reviewer notes, there is no established RfD for any of the perfluorochemicals. Relating the observed perfluorochemical values to particular health outcomes is beyond the scope and purpose of an indicators report. EPA also has not defined any thresholds for potentially harmful perfluorochemical exposures in biomonitoring units. The literature is rapidly developing, and a fuller assessment (well beyond the scope of ACE) would be necessary to determine if thresholds for potentially harmful perfluorochemical exposures can be defined.
4/3	N/A Overall indicator text	**Comment:** 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?
		Response: The information that is available regarding changes in PFCs usage over time is provided in the Topic text; however, to specifically connect trends in blood PFC levels to causal factors or levels in environmental media (which are not well characterized) is a significant undertaking beyond the scope of ACE. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3. The ACE presentation can, however, highlight the various types of information needed to better understand, explain and interpret the findings from the biomonitoring data.
5/1	P14, References	**Comment:** Additional references are provided in these comments. Using birth-rate adjusted data makes the indicator less transparent.
		Response: Please see the above responses.
5/2	P14, References	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: No response necessary.
5/3	P14, References	**Comment:** 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.
		Response: At this time, including systematic reviews of the literature for all the topics presented is beyond the scope of this document. However, we acknowledge the importance of establishing methods for systematic review and are working towards incorporating these methods into future reports.
G/1		**Comment:** 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."
		Response: We believe the structure of the presentation is appropriate and provides a standard approach that is effective for conveying an important public health message when applied across all 23 ACE3 topics. The topic text discusses the significance of the issue for children's environmental health, followed by presentation of the data and bullet points to highlight key findings from the data. Please see the responses above regarding birth rate adjustment.
G/3	N/A Overall text	**Comment:** 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.
		Response: No response necessary.

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Section: Biomonitoring

Topic: Polychlorinated Biphenyls (PCBs)

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P1	**Comment:** 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.
		Response: Text has been added in regards to these two different categories.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: EPA has not defined any thresholds for potentially harmful PCB exposures in biomonitoring units; further, the RfD (in intake units) was last revised in 1994. The literature is rapidly developing, and a fuller assessment (well beyond the scope of ACE) would be necessary to determine whether a threshold for potentially harmful PCB exposure can be identified.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: This issue is addressed in the introduction to the report.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: We discuss dietary intake as an important route of exposure along with the other routes. We have also added this reference: Schecter et al. Perfluorinated compounds, polychlorinated biphenyls, and organochlorine pesticide contamination in composite food samples from Dallas, Texas, USA. Environ Health Perspect. 2010 Jun;118(6):796-802. We chose not to include Type 2 diabetes in the summary of the PCBs literature because the findings are in adults. We do discuss these findings in the ACE3

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		obesity text.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: This is more detail than intended for this text. We have added general text to the introduction about potential interactions between the different environmental contaminants that are discussed individually in ACE3.
1/2	N/A Overall text	**Comment:** 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.
		Response: Issues related to cumulative exposure are now addressed in the introduction to the Biomonitoring section.
1/3	N/A Overall topic text	**Comment:** The initial pages are reasonably done but could use improvement as illustrated below.
		Response: No response necessary.
1/3	P1, L14-L17	**Comment:** P 1, lines 14-17: The literature also describes respiratory secretions and altered functions, eye pathology, skin effects, and cancer.
		Response: We have added a line about skin effects in children. These lines refer to children born to mothers exposed to high levels of PCBS in Japan and Taiwan, for whom the most significant health effects experienced are neurodevelopmental in nature. The health effects listed in this comment have more limited findings and are more typical of a Japanese or Taiwanese patient who was directly exposed to high levels of PCBs, but are not particularly related to children.
1/3	P2, L16-L18	**Comment:** 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.
		Response: We have added text discussing remediation in heavily contaminated environments such as the Hudson River.
1/3	N/A Overall topic text	**Comment:** Biomonitoring has also shown elevation in children's blood levels, as Schecter and Wolff showed in children playing with PCB contaminated materials.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We have added a reference: Windham, G.C., et al., Body burdens of brominated flame retardants and other persistent organo- halogenated compounds and their descriptors in US girls. Environ. Res. (2010). Other studies were either not current or not based on data from children in the US.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: We did not add this exposure scenario to the text since it is likely not occurring currently.
1/3	N/A Overall topic text	**Comment:** This document ignores the male sex without any comment. The reasons are not stated. Is this scientifically sound?
		Response: This report focuses on children's health. Data on women of childbearing age are included due to PCBs' ability to prenatally transfer from mother to fetus and exposure through breast milk.
1/3	P1, L3-L4	**Comment:** Page 1, lines, 3 and 4: produced "commercially and used"
		Response: The text has been revised.
1/3	P1, L19	**Comment:** P1, l9: Also distributed in humans, not only found in the environment.
		Response: The text is clear regarding widespread exposure to humans.
1/3	P1, L19	**Comment:** Page 1: l9 Superfund is not defined.
		Response: The term will be familiar to most readers.
2/1	N/A Overall indicator text	**Comment:** 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?

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We chose not to focus on the distinction in describing the indicator, because most of the epidemiological studies of PCBs and neurodevelopment do not make a distinction between dioxin-like and non-dioxin-like PCBs.
2/1	N/A Overall indicator text	**Comment:** Why Mexican-American were chosen over other Hispanics is not clear.
		Response: This decision is based on the design of NHANES and is now addressed in the introduction to the Biomonitoring section.
2/1	N/A Overall indicator text	**Comment:** It would also be useful to define the poverty level.
		Response: This level is defined in the introduction.
2/2	N/A Overall indicator text	**Comment:** The text provides sufficient information about the data set and the indicator calculation to enable understanding. This is very clear.
		Response: No response necessary.
2/3	N/A Overall text	**Comment:** 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.
		Response: Selection of NHANES is discussed in the introduction. NHANES is exclusively used for the biomonitoring indicator data as it is the best available nationally representative data and is conducted on a continuing basis, which will enable evaluation of changes over time.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: Text has been added regarding trends in PCB levels since the 1970s and1980s. Additional references have been incorporated: Schecter et al. Polybrominated diphenyl ether flame retardants in the U.S. population: current levels, temporal trends, and comparison with dioxins, dibenzofurans, and polychlorinated biphenyls. J Occup Environ Med. 2005 Mar;47(3):199-211 Sjödin A, et al. Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States. Environ Health Perspect. 2004 May;112(6):654-8.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.
2/3	N/A Overall text	**Comment:** The document should read to be understood by the educators, government officials and concerned parents mentioned as part of the intended audience.
		Response: No response necessary.
2/3	P4, L14	**Comment:** P4, L 14: "Body burden" not defined or explained.
		Response: This term has been removed.
2/3	P5, L7	**Comment:** P5, l 7: "Statistically significant" not defined nor contrasted with clinically or biologically significant.
		Response: Text regarding statistical significance has been expanded to further explain the interpretation and is now provided in the introduction to the Biomonitoring section.
2/3	P5, L10	**Comment:** P5, L10: Perhaps "by chance" might be easier to understand than "randomly".
		Response: We have made this change.
3/1	N/A Overall Data presentation	**Comment:** 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.
		Response: No response necessary.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/2	N/A Overall indicator text	**Comment:** 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.
		Response: Nationally representative data are not available for umbilical cord serum samples.
3/3	P6, graph	**Comment:** Page 6: Complicated graph. Why so many comparisons in the graph.
		Response: We have added discussion to the report introduction regarding the importance of evaluating potential differences by race/ethnicity and income. We apply a consistent approach to report these values across the NHANES indicators, regardless of the nature of similarities/differences found in the indicator values.
3/3	N/A Overall indicator text	**Comment:** Why is no other data than NHANES also included so women under 16 years or over 49 years are included?
		Response: Data on women 16-49 years are included to represent women of child-bearing age. This selection is discussed in the Biomonitoring introduction. We rely on NHANES for the biomonitoring indicator data as it is the best available nationally representative data and is conducted on a continuing basis, which will enable evaluation of changes over time.
3/3	N/A Overall indicator text	**Comment:** Is "race" meaningful and how does NHANES determine it? The above is subject to intense debate which should not be ignored in this important document.
		Response: Each participant in NHANES is asked questions regarding race and ethnicity; participant responses are used in this analysis. The selection of race/ethnicity is addressed in the introduction to the report and the Biomonitoring introduction. It is a priority for EPA to identify and address disparities in environmental conditions by race/ethnicity.
3/3	N/A Overall indicator text	**Comment:** Is "ethnic group" meaningful and how does NHANES determine it. The above is subject to intense debate which should not be ignored in this important document.
		Response: See response above.
3/3	N/A data presentation	**Comment:** 5^{th}, 10^{th}, 25^{th}, 75^{th}, 90^{th} and 95 percentiles would be of interest here and useful to the readers I recommend adding them.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: 95th percentiles are included in the data tables and are noted in a bullet point following the indicator figure. The 50th and 95th percentiles provide a sense of the variability; it is beyond the scope and resources of ACE to provide more detailed statistical characterization.
3/3	N/A Overall data presentation	**Comment:** Explanations are not offered for the results: Is one possible explanation of lower levels in Mexican women
		Response: Explanations of the cause of these levels would require substantial analysis beyond the scope of this report. We are unaware of any publications that have addressed this point.
3/3	P9, L15	**Comment:** 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.
		Response: Birth-rate adjustment makes an important difference for some of the chemicals included in the ACE3 Biomonitoring section (PCBs in particular, due to their association with age), and we apply a consistent approach to how the data are analyzed for each chemical reported. Given the context of children's health and in utero exposure, we believe most readers will understand that the reasoning for why women >40 years are not be weighted the same as younger women. The method has recently been published: Axelrad, D.A., and J. Cohen. 2011. Calculating summary statistics for population chemical biomonitoring in women of childbearing age with adjustment for age-specific natality. *Environmental Research* 111 (1):149-155.
3/3	P8, L25-L26	**Comment:** Page 8, Lines 25, 26: "Standard error" and "relative standard error" are not defined nor explained.
		Response: These are described in the methods section which will be available on line.
4/1	P8, Data Tables section	**Comment:** 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.
		Response: The columns for 100-200% and >200% of poverty level have been deleted. Explanations for these disparities are beyond the scope of this report. We are unaware of any publications addressing this point, and would not want to speculate. We have added text to the report introduction and edited the phrasing of the principal objectives to clarify the scope and intent of ACE3.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/2	N/A Overall indicator text	**Comment:** The indicator is quantifiable and relevant to the environment and children in the USA.
		Response: No response necessary.
4/2	N/A Overall indicator text	**Comment:** The indicator can be used to inform discussions among policy makers and the public about to improve data.
		Response: No response necessary.
4/2	N/A Overall indicator text	**Comment:** 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.
		Response: We generally agree with these observations, though the review we cite by Boucher et al. (2009) provides some interesting insights regarding fairly consistent signals in the literature.
4/2	N/A Overall explanation of data	**Comment:** 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.
		Response: No response necessary.
4/2	N/A Overall explanation of data	**Comment:** Another would be to use data in addition to NHANES if from peer reviewed scientific documents or other government reports.
		Response: We are unaware of any other suitable data sources. An important criterion for our indicators is that the data source provides data that are comparable over time, so that trends can be assessed.
4/2	N/A Overall explanation of data	**Comment:** Other comments have been listed prior to this section.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: No response necessary.
5/1	P16, Methods	**Comment:** 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.
		Response: We agree; these details are not intended for the generic reader and will be provided online only, so that they are available for interested technical experts.
5/2	P10, References	**Comment:** The documentation is complete and transparent.
		Response: No response necessary.
5/3	P10, References	**Comment:** A glaring omission is that of omitting the WHO 2005 dioxin TEF documentation. The DL PCBs are mentioned in the text without a reference.
		Response: The Van den Berg et al. 2006 reference has been added.
5/3	P10, References	**Comment:** No toxicology data and no wildlife data which could help interpret meaning of PCB potential health effects is cited.
		Response: We have added brief information about neurodevelopmental deficits observed in rats and monkeys exposed to PCBs.
5/3	P10, References	**Comment:** 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
		Response: This citation has been added: Masuda. Toxic effects of PCB/PCDF to human observed in Yusho and other poisonings. Fukuoka Igaku Zasshi. 2009 May;100(5):141-55.
5/3	P16, Methods	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The indicator text is intended to provide sufficient technical information to orient lay readers. The detailed methods are provided for interested technical experts, and are not intended for lay readers.
5/3	P10, L49-L51	**Comment:** Ref 14 has an incomplete citation and needs to be corrected.
		Response: The reference has been corrected.
5/3	P14, Metadata	**Comment:** "Metadata" is not defined nor explained
		Response: The explanation is provided in the complete report.

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Section: Biomonitoring

Topic: Polybrominated Diphenyl Ethers (PBDEs)

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
General/1	N/A Overall text	**Comment:** 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.
		Response: No response necessary.
1/1	P11, References	**Comment:** 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.

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		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.
		Response: Because there are so many toxicology studies, we chose to cite only selected examples, along with the review article by Costa et al. (reference 27). Most of the toxicology studies suggested here are included in the Costa review. We have incorporated citations to the Chevrier and Rose studies.
	N/A Overall indicator text	**Comment:** 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.

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		Response: We believe the current level of detail regarding congeners and commercial mixtures is appropriate for this text.
	P2, L14-L16	**Comment:** Second, the sentence describing reference 14 is not that clear.
		Response: The sentence has been revised.
	P3, L6	**Comment:** 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.
		Response: We have revised the end of the sentence on line 6 of page 3 to read: "However, children of all ages (as well as adults) are likely to be exposed to dust contaminants through hand-to-mouth activity and other ingestion pathways, such as the settling of dust onto food and food preparation surfaces in the kitchen, as well as inhalation and absorption of PBDEs through the skin." [added citation for EPA exposure report]
1/2	P2, L8	**Comment:** P2, L8: References 4-10 are cited. The following 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.
		Response: Stasinska is only a conference abstract, not a journal article, and therefore has not been added. Wei has been added.
1/2	P2, L30-L35	**Comment:** 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.
		Response: Mention of placental tissues has been added, with reference to the Dassanayake paper.
1/2		**Comment:** P1, L9: Delete "anywhere" because fractional numbers are invalid here.

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		Response: This change was made.
1/2		**Comment:** P1, L10: Change "from 1-10" to "from 1 to 10".
		Response: We use en dashes (–) in the main text of ACE3 to indicate ranges for numerical values other than ages.
1/2		**Comment:** P1, L13: A period "." is missing at the end of the paragraph.
		Response: We have made the correction.
1/2		**Comment:** P1, L15: Change "mixtures PBDEs" to "PBDE mixtures".
		Response: We have made the revision.
1/2		**Comment:** 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.
		Response: According to EPA's Exposure Assessment for PBDEs, production began "in the 1960s and 1970s." We have added this information to the paragraph.
1/2		**Comment:** P2, L44: Change "based on measured levels" to "from measured concentrations".
		Response: We changed "levels" to "concentrations" but left the rest of the sentence as is.
1/3	N/A Overall topic text	**Comment:** 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.

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		Response: We agree with this assessment of NHANES data, and believe these have been addressed in our text. We have added text to the Biomonitoring introduction summarizing NHANES strengths and limitations, including the omission of young children for most chemicals.
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: We have added information on the number of people in NHANES with PBDEs measurements.
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: We believe the paragraph starting at the bottom of page 4 is sufficient on this point.
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: We have added this sentence: "Data are insufficient at this time to assess and quantify differences in toxicity of the measured PBDE congeners or to inform approaches other than an unweighted summation of the ten congeners."
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: Please see response above.
2/1	P6, L5	**Comment:** In the statistical testing section, changes over time are discussed, yet no comparisons are made in the text.
		Response: The text has been revised.
2/2	N/A	**Comment:**

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	Throughout text	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.
		Response: The NHANES paragraph on p. 4, line 7 states that PBDEs were measured in participants ages 12 and older; the overview paragraph states why the indicator focus is on women ages 16 to 49 years.
2/2	N/A Overall indicator text	**Comment:** 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.
		Response: NHANES does not provide PBDEs measurements in newborns. The evidence for children's effects from PBDE exposures during pregnancy (as reflected by measurements of PBDEs in adult women) is greater than the evidence for children's effects from PBDE exposures at ages 12-17 years. We believe this is adequately described.
2/2	N/A Overall indicator text	**Comment:** 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.
		Response: We believe these details are not necessary for this report. PBDEs are commonly measured in serum; and since NHANES measures them only in serum we have no alternative options for the indicator.
2/2	N/A Overall indicator text	**Comment:** 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

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		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.
		Response: Our text states that BDE-209 was not measured in NHANES in 2003-2004. There are some published reports of BDE-209 human measurements in the published literature, but they are few in number (particularly in U.S. samples) and typically with small numbers of people sampled. Therefore, we did not feel that we could adequately quantify the effect. Note, however, that in Lunder et al. (2010) serum levels of BDE-209 do not account for a large proportion of sum (serum PBDEs) measured in mothers and young children.
2/2	N/A Overall indicator text	**Comment:** 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)
		Response: We do not believe the issue of inconsistency in lipid measurement applies to the NHANES samples which were all measured in the same lab using the same techniques.
2/3	N/A Overall indicator text	**Comment:** "Body burdens" and "nanograms" not defined or explained.
		Response: Definition of nanograms is not necessary. We changed "Body burdens of PBDEs are measured and expressed on a lipid-adjusted basis" to "Concentrations of PBDEs in serum are measured and expressed on a lipid-adjusted basis."
2/3	N/A Overall indicator text	**Comment:** **"**Demographic groups" are not defined nor illustrated.

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		Response: We have addressed this in the report introduction and Biomonitoring section introduction.
2/3	N/A Overall indicator text	**Comment:** "Randomly" not defined
		Response: "Randomly" was replaced with "by chance."
2/3	N/A Overall indicator text	**Comment:** "Relative standard error" not defined, explained.
		Response: This was discussed in the "Introduction to Biomonitoring Topics" document provided to reviewers, and has been incorporated in the introduction to the Biomonitoring section in the final report.
3/1	P6, L5	**Comment:** 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.
		Response: We have replaced the bullet with other information. Upon further examination, we determined that estimates stratifying by both race/ethnicity and income were not statistically reliable.
3/1	P9, Table PBDE1	**Comment:** 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.
		Response: We have added information to the data tables on number of people sampled for PBDEs in NHANES for each race/ethnicity and income group.
3/1	P10, Table PBDE1a, and overall text	**Comment:** 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.
		Response: Key findings from the data table regarding children are summarized in the final bullet point beneath the indicator graph, and the table is referenced in the indicator text.
3/2	N/A Overall indicator text	**Comment:** C1. Poverty lines need specifications of the time and location. Poverty guideline figures given by U.S. DHH are time and location dependent. In

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		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.
		Response: A definition of poverty level is provided in the introduction to the Biomonitoring section and the report introduction. U.S. government definitions of the income considered poverty level do not vary by location. We use the poverty level variable that is incorporated into the NHANES data files, which use dollar-value poverty levels corresponding to the year in which data were collected. CDC does not reveal the locations in which NHANES is conducted, so information is not available on whether residents of Hawaii or Alaska were sampled.
3/2	P7, graph	**Comment:** 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", "> poverty 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?
		Response: "> poverty level" means income greater than poverty level, i.e. not living in poverty. We believe this is clear, but have also provided an explanation in the report introduction.
3/2	P7, Graph	**Comment:** 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.
		Response: This is a good suggestion; however, we have replaced the bullet with other information. Upon further examination, we determined that estimates stratified by both race/ethnicity and income were not statistically reliable, since PBDEs data are available for only a single two-year NHANES cycle.
3/2	P9, L14-L18 and P5, L27	**Comment:** P9. The explanation in the 2nd Note on should also be given on page 5, line 27, in the Indicator Text section.

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		Response: The birthrate adjustment is now described in detail in the introduction to the Biomonitoring section. This will introduce the readers to the concept before the indicator data are given.
3/3	N/A All figures	**Comment:** Figures are complicated. Why needed? Could more simple displays convey all intended? Or a few sentences?
		Response: We believe the figure efficiently displays the relevant information. We use a standard graph design for all NHANES comparisons by race/ethnicity and income, which we believe will be clearer to readers than an approach that provides a different focus for each chemical presented. The bullet points convey the key information for the particular chemical in a few sentences. However, upon further examination, we determined that estimates stratified by both race/ethnicity and income were not statistically reliable for PBDEs. This applies only to PBDEs, for which data are available only for one survey cycle (two years).
3/3	N/A Overall text	**Comment:** "Median" not defined. No ranges provided. No important congeners described as such. For example, BDE 47.
		Response: Median is now defined in the Biomonitoring introduction. We have also added a footnote explaining why 95th percentiles are not currently provided; we should be able to do so whenever CDC releases data for 2005-2006. We believe that it is more useful to focus on the sum of congeners rather than singling any out, particularly since we currently have data only for one 2-year NHANES cycle. It may be interesting and informative to look at individual congeners when enough NHANES data are available to provide a time series.
3/3	P8	**Comment:** No statement about statistical significance of last sentence on page 8.
		Response: We have added a statement that the difference is not statistically significant.
3/3	P9	**Comment:** Page 9: Statistical significance seems missing.
		Response: Statistically significant differences may be identified from the tables of p-values provided at the end of the document.
3/3	P9, table PBDE1	**Comment:** 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.
		Response: Bullet points under the indicator figure summarize the key points. The data table is provided for individuals interested in the particular values depicted in the figure, and also provides some additional detail not captured in the figure. For all Biomonitoring topics, we have streamlined the race/ethnicity and income data

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		tables, removing the following columns: unknown incomes, 100-200% of poverty, and >200% of poverty. For PBDEs, we have further simplified the table because (with data from only one NHANES cycle available at this time) many of the estimates considering both race/ethnicity and income group lack statistical reliability.
3/3	P9, L23-L25	**Comment:** Page 9, lines 23-25 will not be understood by most readers. Explain and maybe use different more simple words.
		Response: Further explanation is provided in the introduction to the Biomonitoring section.
3/3	P9, Table PBDE1	**Comment:** Page 9: Does the table represent all US women or only those in an NHANES report?
		Response: As stated in the indicator text, NHANES data are nationally representative.
3/3	P9, Data Tables section	**Comment:** 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.
		Response: We have added this sentence to the indicator introduction on page 6: "Data are insufficient at this time to assess and quantify differences in toxicity of the measured PBDE congeners or to inform approaches other than an unweighted summation of the 10 congeners."
3/3	P15-P16	**Comment:** Pages 15-16 focus exclusively on NHANES. Why is this needed? NHANES is not the only source of the data.
		Response: NHANES is the only source of data for the PBDEs indicator. No other data source provides PBDEs measurements for a representative sample of the population, and no other source will provide a consistent time series.
3/3	P17-P19	**Comment:** Pages 17-19 more detailed than needed. Why such detail. Wasting space when major points could be made.
		Response: The detailed documentation will be provided online for interested readers, but will not be included in the published report.

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3/3	P20-P28	**Comment:** 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.
		Response: The detailed documentation will be provided online for interested readers, but will not be included in the published report.
4/1	N/A Overall text	**Comment:** 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.
		Response: We have added this sentence to the indicator introduction on page 6: "Data are insufficient at this time to assess and quantify differences in toxicity of the measured PBDE congeners or to inform approaches other than an unweighted summation of the 10 congeners."
4/1	N/A Overall text	**Comment:** 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.
		Response: We agree. When sufficient data are available to provide a time series, we will be able to see if there are any trends.
4/1	N/A Overall indicator text	**Comment:** 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.
		Response: We believe our presentation makes clear the data that are and are not available for PBDEs, and readers may draw upon that information to make judgments about improvements in the data. We have also edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
4/1	N/A Overall indicator text	**Comment:** c) I think the indicator will provide an adequate way of assessing temporal trends.
		Response: No response necessary.
4/2	P15, Row 7	**Comment:** Only minor comments are given for this section: P15 Row 7, right: Please specify what "NCHS" stands for.
		Response: We have made this edit in the metadata table.

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4/2	P16, Row 3	**Comment:** P16 Row 3: Please specify what "QA" stands for.
		Response: We have made this edit in the metadata table (and all other metadata tables for ACE3).
4/3	N/A Overall text	**Comment:** 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.
		Response: We have added a new sentence on page 2 describing this trend: "Studies comparing archived and current samples of blood and pooled serum from various locations in the United States have shown marked increases in PBDE levels since the late 1970s," citing the two papers indicated.
4/3	N/A Overall text	**Comment:** 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.
		Response: We focus on NHANES because it is the source of data that is nationally representative and will be collected on a continuing basis. We have cited a number of other sources (most from academic researchers) in the topic text that provide important information not captured by NHANES – e.g. exposure pathways, serum levels in younger children. In some cases we rely on review studies and government reports that incorporate numerous individual studies, rather than citing each article. The intent of this text is to inform readers of important issues concerning PBDEs and children's health; not to provide a comprehensive discussion of all relevant research. We have added several citations specifically suggested by this reviewer and others to further support key points in the draft text or to address important issues that had been omitted, and we appreciate those suggestions.
4/3	N/A Overall Indicator text	**Comment:** c. Congener specific measurement of PBDEs, including BDE 209, will provide data on levels. Determining toxicity of each congener will help characterize health risks.
		Response: Please see responses above.

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5/1	N/A Overall text on documentation	**Comment:** 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.
		Response: We have added a footnote to the table with this explanation. The missing values represent the women in the subsample with no values reported for all 10 PBDE congeners. Missing lipid values were not an issue for this indicator.
5/1	P26, Table 1	**Comment:** 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.
		Response: We apologize for the errors. They have been corrected.
5/1	N/A, Overall data presentation	**Comment:** There should be some sort of N values associated with the groups.
		Response: We have added the n into the data table column and row headings where appropriate.
5/1	N/A Overall text	**Comment:** 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.
		Response: Unknown income represents sampled individuals for whom income data are missing. We have decided to remove the unknown income data from the tables; those sampled individuals will still be included in the "all incomes" values.
5/2	P26-P28, Tables 1-6	**Comment:** 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.
		Response: The reviewer is correct that we do not provide the median data values used for these calculations, which are medians by age group, sex, race/ ethnicity, and income (in combination). Nor do we provide the regression model coefficients which would tell us, for example, whether medians tend to be higher for boys than girls (based on our statistical model). While we could provide this information, it is more detail than necessary, and creating user-friendly tables of these data for all indicators would require substantial resources. We disagree that the adjusted p-

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		values are not useful by themselves, since they tell us whether the differences can be attributed to real population differences in PBDEs after accounting for demographic differences in the two populations being compared.
5/2	N/A Overall dataset text	**Comment:** 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.
		Response: Most elements of the dataset for children 12-17 are identical to those for women 16-49 years – NHANES samples are handled the same and analyzed in the same way for all individuals. We place greater emphasis on the data for women 16-49 years because the evidence for children's effects from PBDE exposures during pregnancy (as reflected by measurements of PBDEs in adult women) is greater than the evidence for children's effects from PBDE exposures at ages 12-17 years.
5/2	N/A Overall indicator data	**Comment:** 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.
		Response: We will consider reporting the unadjusted values on the ACE website.
5/2	N/A Overall indicator data	**Comment:** 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?
		Response: We apologize for the errors. They have been corrected.
5/2	P17, Row6	**Comment:** 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.
		Response: We have added a footnote to explain this term.
5/2	P21, L4	**Comment:** P21 L4: What is "indicator B2"?
		Response: We apologize for the error; it should have read "Indicator PBDE1." In the final report, this is now "Indicator B8."

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5/3	P11, References	**Comment:** 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.
		Response: The intent of this text is to inform readers of important issues concerning PBDEs and children's health; not to provide a comprehensive discussion of all relevant research. We chose to use more current references for PBDEs in breast milk and food (including Schecter et al. 2009 – reference 15 in the review draft). We have added reference to Schecter et al. 2010 (Chemosphere) for PBDEs in breast milk. We have added Schecter et al. 2005 concerning the increase in U.S. human levels of PBDEs. We chose not to include the Schecter et al. reference regarding cooked food because we do not present data on individual foods, or estimates of intake based on measurements in uncooked food.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Biomonitoring

Topic: Phthalates

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1/1		**Comment:** 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.
		Response: We have added the suggested references and sentences to address this issue as follows "A handful of studies have reported associations between prenatal exposure to some phthalates and preterm birth, shorter gestational length, and low birth weight; however, one study reported phthalate exposure to be associated with longer gestational length and increased risk of delivery by Cesarean section."
1/1	N/A Overall content	**Comment:** • 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.
		Response: These findings are very interesting; however, the introduction is meant to give a broad overview of why the topic is important to children's health, and we feel that including this level of detail is outside the scope of the report.
1/1	P1, Topic section	**Comment:** • 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.
		Response: We agree that it is important to state the limitations of observational research for making causal inferences; we have included discussion of this matter in the report

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		introduction.
1/1	P1, L18	**Comment:** 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?
		Response: We do not believe that these statistics are available.
1/1	P2, L4	**Comment:** 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.
		Response: We agree that these types of exposures are most likely rare—however, we feel it is important to note these exposures as they involve a very vulnerable subpopulation.
1/1	P2, L32	**Comment:** 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?
		Response: The exposure levels used in animal studies can vary a great deal and interpreting what the results might mean for the human population can be challenging. In order to address this more fully, we have included a discussion in the report introduction explaining the advantages and limitations of both animal studies and observational human studies.
1/2	N/A Overall topic text	**Comment:** I think the topic text does appropriately describe the topic.
		Response: No response necessary.
1/2	N/A Overall topic text	**Comment:** 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?
		Response: We have revised the text and believe the current version will be more accessible. However, to be complete in describing data and research it is often difficult to avoid some technical language; information provided will still be useful to non-researchers. The report introduction and the expanded Biomonitoring section introduction should help orient non-researchers to the report content.

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1/2	P1, L27, L28 (and references)	**Comment:** 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?)
		Response: We have changed the citation of references as suggested and have added additional references.
1/2	P1, L44	**Comment:** Again on line 44 the reference '9' listed after lotions refers to a paper describing personal care product use in men (cologne, aftershave,etc) but not nailpolish. The reference for the nailpolish 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.
		Response: The suggested reference has been added to sentences that refer to nail polish.
1/2	P2, L18	**Comment:** 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??)
		Response: We have added the suggested reference.
1/2	P1, L15 and P1, L33	**Comment:** 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.
		Response: We have added citations for this statement and now include the ATSDR profiles for the phthalates, the recent National Academies of Sciences publication on phthalates, and the suggested reference (Nassberger, et al.).
1/2	P1, L15 and P1, L33	**Comment:** Otherwise if referring to secondary sources I would stick with the ATSDR documents.

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		Response: We have added citations for this statement and now include the ATSDR profiles for the phthalates, the recent National Academies of Sciences publication on phthalates, and the suggested reference (Nassberger, et al.).
1/2	P1, L15 and P1, L33	**Comment:** 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.
		Response: The statement is made in the introduction of the review, and then is discussed in detail in later sections where numerous studies are cited that have found a variety of phthalates present in dust in homes, schools, and other indoor environments. One of the cited studies appears in Table 4 of the review and found associations between phthalate levels in dust and allergies/asthma in children. We have added an additional reference that supports our statement that dust can be ingested by children.
1/2	P1—References	**Comment:** 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.
		Response: We have tried to limit citation of secondary literature to situations where the statement we are making is based on well-established concepts and citation of the primary literature would be difficult due to the many studies that could be cited to support the statement.
1/2	P1, L39 (with ref. 10) And P2, L20 (with ref. 21, 22)	**Comment:** 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
		Response: The potential routes of phthalate exposure for humans have been studied by a number of groups; therefore, we prefer to cite secondary literature in this case. We have added citations to line 39 that are used by CDC in their exposure reports as references for a similar statement. The statement regarding phthalates as potential endocrine disruptors is also supported by many primary studies; therefore, we have chosen to cite secondary literature. However, we have removed the current citations and added references to more appropriate review articles and an EU report for this statement.

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1/2	P4, L7	**Comment:** 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.
		Response: We have removed reference #61.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: We have added sentences that discuss alternatives to phthalates to read "As use of phthalates is reduced, they are being replaced by other chemicals, such as di-isononylcyclohexane-1,2-dicarboxylate (DINCH) and di(2-ethylhexyl) terephthalate (DEHT), that increase the flexibility of plastics. EPA is planning to conduct an assessment of alternatives for several phthalates."
1/3	N/A Overall topic text	**Comment:** 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
		Response: We have added text to address the concept of cumulative risk for phthalates to read "It is important to note that while the following indicators present data on individual phthalate metabolites, evidence suggests that exposures to multiple phthalates may contribute to common adverse outcomes. The National Research Council has concluded that multiple phthalates may act cumulatively to adversely impact male reproductive development." We have also added a discussion about cumulative exposures to the Biomonitoring section introduction.
1/3	N/A Overall topic text	**Comment:** 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.

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		Response: We agree that making correlations based on observational epidemiological studies has limitations. This is why we try to explain the uncertainty surrounding many associations between exposure and health outcome. In cases where epidemiological studies are lacking, animal studies are described, which can strengthen the evidence as they do not have the same limitations regarding co-exposures. We have included a discussion in the report introduction that describes the limitations and advantages of both observational epidemiological and animal studies.
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: In the absence of strong information identifying differences in phthalate exposure or metabolism in pregnant women, we believe it is preferable to be more inclusive.
2/1	P6, L22-42	**Comment:** 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.
		Response: We noted similar comments from other reviewers and decided to remove the creatinine adjustment.
2/1	P6, L22-42	**Comment:** 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.
		Response: Please see response to the above comment.
2/1	P7, L29-P8, L 5	**Comment:** 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

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		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.
		Response: We feel that the concept of a median will be easier for non-researchers to understand. Our approach of providing both the median and 95th percentile is meant to give an idea about variability in the population. We are also providing standard errors online for interested readers.
2/1	P7, L37	**Comment:** 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.
		Response: We have added notes and explanations that there is no adjustment for multiple comparisons. There is precedent for this approach in CDC/NCHS documents, e.g. the annual Health Summary Statistics for U.S. Children reports presenting data from the National Health Interview Survey. Multiple comparisons can be implemented in various ways (e.g., alternate definitions of the extent of a comparison group). Since we provide the p-values, interested readers will be able to apply their own adjustments, e.g., by using a simple Bonferroni probability approach. Although we report large numbers of p-values in some cases, we did not use all these p-values to make our reporting decisions; instead we used the p-values to determine whether some of the patterns that we had already found were expected to have occurred "by chance." We have also streamlined the p-value table to reduce the number of comparisons by race/ethnicity and income. We have made the decision not to adjust for multiple comparisons as we feel it is important to identify all potentially important differences, and adjustment for multiple comparisons will increase the challenge in conveying findings of statistical testing to non-technical audiences. We clearly explain in the text that this may increase the probability that some of these differences may actually have occurred randomly. Bonferroni adjusted p-values are relatively easy to compute but tend to be overly conservative since they do not account for possible dependence between different tests. An important consideration for multiple comparison adjustments is that the "experiment" for which the experiment-wise error rate is calculated is not well defined for ACE biomonitoring indicators since there are multiple chemicals and multiple percentiles.
2/1	P8, L3	**Comment:** 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

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		NHANES…to measure associations with statistical certainty given the sample size and weighting to make it representative of the U.S. population.
		Response: We have modified the discussion of statistical testing for biomonitoring indicators, clarifying the interpretation of what it means to be statistically significant and noting that differences that do not reach statistical significance may still be important. We have moved this discussion to the Biomonitoring section introduction. We mention differences that are not statistically significant because even NHANES can lack statistical power, especially within strata; and since the tables and graphs in the ACE reports show the unadjusted trends, we expect that readers of the report will want to know if the patterns they can see show significant trends (i.e., the unadjusted trend analyses) as well as knowing if these apparent trends are attributable to demographic changes (i.e., the adjusted trend analyses). A similar perspective applies to demographic comparisons. Our approach is to note changes/differences that appear to be large, then discuss whether or not they are significant.
2/2	P5, Overview box	**Comment:** 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.
		Response: The titles for the indicators are directly above the overview box and specifically say which indicator is for women vs. children.
2/2	P7, L35 & L39	**Comment:** I did find the discussion about birthrate adjustment straightforward here but in the methods section I got confused again.
		Response: We have added calculations for the adjusted survey weights to further clarify the birth rate adjustment in the methods section.
2/2	P7, L35 & L39	**Comment:** 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'.
		Response: We made both of these changes and have moved this discussion to the Biomonitoring section introduction.
2/2	P8, L3-L5	**Comment:** 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.'

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		Response: We have changed this paragraph to incorporate suggestions from various reviewers and have moved this discussion to the Biomonitoring section introduction.
2/2	P6, L11 (ref. 10)	**Comment:** 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.
		Response: Additional references were added, including ATSDR profiles for phthalates.
2/2	P6, L12 (ref 10, 66), P6, L14 (ref 67), P6, L18 (ref 62)	**Comment:** 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
		Response: The statements made on line 12 and 14 are generally well-accepted statements in the field. We feel that citing secondary sources is sufficient for these types of statements. In addition, we have added citations for ATSDR profiles for phthalates. The data presented on Line 18 is from the ACE report and has been expanded upon in a separate paragraph.
2/2	P7, L4	**Comment:** Page 7, line 4: change "distribution of children's prenatal" to "distribution of prenatal"
		Response: We rephrased this sentence to read "Indicator B9 uses measurements of phthalate metabolites in urine of women ages 16 to 49 years to represent the distribution of phthalate exposures to women who are pregnant or may become pregnant."
2/3	N/A Overall indicator text	**Comment:** The focus on urinary metabolites is appropriate and also on women of child bearing age and children
		Response: No response necessary.
2/3	N/A Overall indicator text	**Comment:** For both indicators the text provides adequate information about the data set and the calculation to enable a basic understanding of the indicator.
		Response: No response necessary.

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2/3	P 39, L19	**Comment:** 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.
		Response: We feel that a description of how adjustments are made for multiple comparisons is too technical for some members of the report's audience and beyond the scope of the report. We provide the relevant information in the Biomonitoring section introduction, where it says "the large number of comparisons involved increases the probability that some differences identified as statistically significant may actually have occurred randomly."
3/1	P9 & P11, Bar Charts	**Comment:** 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, 25^{th} and 27^{th} 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.
		Response: We have graphed the data both ways and determined that the bar chart presents comparisons more clearly—the reader is led to compare how metabolites of a particular phthalates have changed over time, which is what we are trying to convey. A line graph presents the data in such a way that the concentration differences between the metabolites receive greater emphasis. This comparison is not as relevant, as the metabolites have different activity, etc. Also, we have chosen to display the median and 95^{th} percentile because we believe that this concept will give readers an idea about variability and is easier to understand for those individuals outside the field.
3/1	P13, Data tables	**Comment:** 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?
		Response: We show the median and 95^{th} percentile values as a way to convey variability. We define the relative standard error in a footnote for each table. Calculation of the RSE is a standard diagnostic tool used by CDC statisticians to assess relative uncertainty of survey estimates. We will also provide the standard errors online for interested readers.

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3/1	P14, table PHTL1a	**Comment:** 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.
		Response: In Table PHTL1a, a footnote provided an explanation for why the 2005-2006 DEHP value was not reported, i.e. a high RSE. After updating the indicator and switching to values without creatinine adjustment, the value now has a lower RSE and is now included in Table B9a (updated version of PHTL1a).
3/1	N/A Overall presentation of data	**Comment:** 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.
		Response: We have referenced the CDC Fourth National Report on Human Exposures to Environmental Chemicals. This document provides detail about how the measurements were obtained and additional references. It is outside the scope of ACE to include these details.
3/1	N/A All tables and figures	**Comment:** It is important to show sample sizes somewhere in the Figures or in the Tables.
		Response: We have added this information to the text and Tables.
3/1	P9 & P11, Bar Charts	**Comment:** What do the white lines on the bar graphs represent?
		Response: The white lines are gridlines used to indicate the y axis values so that the bar values are easier to read.
3/1	P9 & P11, Bar Charts	**Comment:** The y axis should be labeled “median concentrations,” or else just rely on the title and don’t label the y axis.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We believe that the labeling of the chart is clear.
3/1	P10, L1	**Comment:** 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?
		Response: Comparing the median and 95th percentile values is intended to give readers an idea about the variability in concentration levels within the population.
3/1	P10, L7	**Comment:** 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.
		Response: This information is provided in the methods section.
3/1	P10, L16 and P11, L9	**Comment:** 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.
		Response: We control for demographic variables for all metabolites—this information is provided in the methods section. When both the unadjusted and adjusted p-values are significant, we simply say the finding is significant. When only the adjusted or unadjusted is significant, we try to explain that to the reader in the bullets.
3/1	P12, L3	**Comment:** 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.
		Response: We use the bullets to try to explain what is seen in the figure and what cannot be seen in the figure. Sometimes a trend may look significant and we try to indicate whether or not that is the case in the bullets. Similarly, sometimes a trend does not look significant, but is, in which case we note that in the bullets. Also, as discussed elsewhere, differences that are not statistically significant may still be meaningful.
3/1	P15, Table PHTL1b	**Comment:** 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.
		Response: In the interest of space, we have made the decision to only include time series figures for Biomonitoring topics in those cases where sufficient data are available. We agree that the demographic comparisons provide important information, which

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		is why we have included data tables for these comparisons. We will revisit our approach in future editions of ACE. We feel that providing the median and 95th percentile is the best way to convey concepts of common exposure levels and variability to our audience.
3/1	P17, L10	**Comment:** 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.
		Response: We are now including sample sizes. Additionally, we are including text that will better describe issues of between-person and within-person variability from urine spot testing.
3/2	P9 & P11, Bar Charts	**Comment:** 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.
		Response: We have graphed the data both ways and determined that the bar chart presents comparisons more clearly—the reader is led to compare how metabolites of a particular phthalate have changed over time, which is what we are trying to convey. The line graph presents the data in such a way that the concentration differences between the metabolites receive greater emphasis. This comparison is not as relevant, as the metabolites have different activity, etc.
3/2	P9 & P11, Bar Charts	**Comment:** 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.
		Response: Please see above response.
3/2	P9 & P11, Bar Charts	**Comment:** Also a footnote to determine if these are crude or adjusted models would be helpful in both graphs.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The reported values are for the median. There has been no modeling of the data or statistical adjustment.
3/2	P9, L12 and P11, L6	**Comment:** 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?
		Response: Yes, we performed a time trend analysis. We have rephrased the bullets to better emphasize that the findings are based on time trend analysis.
3/2	P10, L3	**Comment:** 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?
		Response: We included this information to give an idea about the range of values across cycles and metabolites. This comparison is based on each of the various time points—the ratio was calculated for each cycle. We will consider adding analysis of trend in the differences between the median and 95th percentile levels to future editions of ACE.
3/2	P10, L16-L20	**Comment:** 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.
		Response: We have removed the word "only".
3/2	P13, Table PHTL1	**Comment:** **PHTL1 page 13:** Titles, headings and subheadings are clear and easy to understand
		Response: No response necessary.
3/2	N/A All tables and figures	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: Sample sizes have been added.
3/2	P13, Table PHTL1	**Comment:** **PHTL1 page 13:** The footnote ii for this table: should you add the bolded words 'combined **sum of** urinary levels of MnBP and MiBP…?
		Response: We cannot use the word "sum" as the metabolites were summed for the 2001-2008 survey cycles, but measured together for the 1999-2000 cycle. We believe that using the word "combined" adequately describes what is presented in the tables, overall.
3/2	P14, Table PHTL1a	**Comment:** **PHTL1a page 14** Same comments as above plus: Line 20-23: couldn't it just as easily underestimate high end exposures?
		Response: The exposure distribution of interest is of the long-term average urinary phthalate concentration for an individual in a given demographic group. Thus the high-end exposure of interest is the 95th percentile of individual's averages for different individuals rather than the 95th percentile of phthalate concentrations for the same or different individuals at different times of the day. Because phthalates do not accumulate in bodily tissues, as well as variation in urine volume, the urinary concentrations for a given individual will vary significantly over a given day, so that the distribution of the spot urine phthalate concentrations will tend to have longer tails and thus higher 95th percentiles than the distribution of individual's average phthalate concentrations.
3/2	P15, Table PHTL1b	**Comment:** **Table PHTL1b page 15** Not sure why data is restricted to 2003-2006. Nowhere in the text prior or in these bullets does it describe why (same comment for table PHTL2b and c)
		Response: We focus on the most recent data for making demographic comparisons – using the two most current NHANES cycles. We have added language to better clarify why we are presenting this data to the Biomonitoring section introduction.
3/2	P15, Table PHTL1b	**Comment:** **Table PHTL1b page 15** Again I would like to see the sample size listed for each of the groups in the column headers
		Response: This has been added—please see above response.
3/2	P15, Table PHTL1b	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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.
		Response: The fact that the values are the same is a coincidence. Data for all years 2003-2006 were combined into a single distribution—the reported values and statistics are based on that distribution.
3/2	P15, Table PHTL1b	**Comment:** In this table I would like the sample sizes in row and column headers
		Response: This has been added—please see above response.
3/2	P16, Table PHTL2 and PHTL2a	**Comment:** **Table PHTL2 and 2a** Just add sample size to column headers
		Response: This has been added—please see above response.
3/2	P16, Table PHTL2 and PHTL2a	**Comment:** **Table PHTL2 and 2a** Also the note on page 17, line 12: the reference #72 doesn't seem to reflect the title of the article??
		Response: This reference was included because it discusses that collecting one-time urine samples may overestimate high-end exposures. Although the reference is based on perchlorate, the sampling issue is similar for phthalates. We have also included an additional reference regarding spot urine testing and determining phthalate exposure variability.
3/2	P16, Table PHTL2 and PHTL2a	**Comment:** **Table PHTL2 and 2a** That article is on perchlorate?
		Response: Please see above response.
3/2	P17, Table PHTL2b	**Comment:** **Table PHTL2b** Again why only 2003-2006?
		Response: We focus on the most recent data for making demographic comparisons – using the two most current NHANES cycles. We have added language to better clarify why we are presenting this data to the Biomonitoring section introduction.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/2	P17, Table PHTL2b	**Comment:** **Table PHTL2b** Sample sizes in column and row headers
		Response: This has been added—please see above response.
3/2	P18, Table PHTL2c	**Comment:** **Table PHTL2c** Why 2003-2006 (and not 1999)?
		Response: We focus on the most recent data for making demographic comparisons – using the two most current NHANES cycles. We have added language to better clarify why we are presenting this data to the Biomonitoring section introduction.
3/2	P18, Table PHTL2c	**Comment:** **Table PHTL2c** Sample sizes in column and row headers
		Response: This has been added—please see above response.
3/2	N/A Overall data tables	**Comment:** **Comparison groups;** I agree with race/ethnicity, income and survey year.
		Response: No response necessary.
3/2	N/A Overall data presentation	**Comment:** 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 so I don't know what those groups should be? Perhaps elementary school, middle school and high school ages???)
		Response: This information is presented in the updated Table B10c.
3/2	N/A Overall data presentation	**Comment:** 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?
		Response: NHANES provides a number of possibilities for further stratifying the data, but for the scope of ACE3 we consider only the demographic variables – race/ethnicity, income, and age.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/2	P13, Table PHTL1	**Comment:** Abbreviations missing from notes section
		Response: Notes to the tables have been added defining the abbreviations.
3/2	P17, Table PHTL2b	**Comment:** **Table PHTL2b** BBzP row header format is fouled up
		Response: This has been corrected.
3/3	N/A Overall data presentation	**Comment:** The presentation of each indicator is fine and needs no further description, at least in my opinion
		Response: No response necessary.
4/1	N/A Overall data presentation	**Comment:** PHTL1 and PHTL2 (responses are the same for both indicators) 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.
		Response: We have prepared a discussion of these broader issues in the report introduction. A basic purpose of environmental indicators is to look at how a particular indicator changes over time; this may include a lack of change. It is also important to identify differences by demographic group (especially those defined by race/ethnicity and income). Relating the observed phthalate metabolite values to particular health outcomes is beyond the scope and purpose of an indicators report and we have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3. EPA has not defined any thresholds for potentially harmful phthalate exposures in biomonitoring units. The literature is rapidly developing, and a fuller assessment (well beyond the scope of ACE) would be necessary to determine if thresholds for potentially harmful phthalate exposures can be defined.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/1	N/A Overall data presentation	**Comment:** b) 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.
		Response: The phthalates topic is just one of many included in the ACE report. The ACE report is meant to provide an overview of many different topics that might be important to children's environmental health. This report is not intended to be an in-depth phthalate exposure assessment or risk assessment.
4/1	N/A Overall data presentation	**Comment:** c) 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.
		Response: This indicator is meant to present a characterization of phthalate levels in women of childbearing age and children and how those levels have changed over time. The ACE report is meant to inform discussion among 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 report is not intended to be a risk assessment.
4/1	N/A Overall	**Comment:** 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.
		Response: There are three principal objectives of ACE: a) to present concrete, quantifiable indicators for key factors relevant to the environment and children's health in the United States; b) to inform discussions among policymakers and the public about how to improve data on children's health and the environment; and c) to provide indicators that can be used by policymakers and the public to track trends in children's environmental health, ultimately, to help identify and evaluate ways to minimize environmental impacts on children. We include discussion about these objectives in the report introduction.
4/2	N/A Overall indicator text	**Comment:** a) yes it meets this objective
		Response: No response necessary.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/2	N/A Overall indicator text	**Comment:** b) 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.
		Response: No response necessary.
4/2	N/A Overall indicator text	**Comment:** c) the time trends will be particularly helpful as legislation and public opinion sway manufacturers to remove phthalates from commercial products.
		Response: No response necessary.
4/3	N/A Overall indicator text	**Comment:** 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
		Response: We are including text that will better explain the limitations of urine spot testing and how it might affect variability.
4/3	N/A Overall indicator text	**Comment:** As already mentioned, DINCH and DEHT should be mentioned as future compounds important to monitor.
		Response: We have added sentences that discuss alternatives to phthalates to read "As use of phthalates is reduced, they are being replaced by other chemicals, such as di-isononylcyclohexane-1,2-dicarboxylate (DINCH) and di(2-ethylhexyl) terephthalate (DEHT), that increase the flexibility of plastics. EPA is planning to conduct an assessment of alternative for several phthalates."
4/3	N/A Overall indicator text	**Comment:** 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.
		Response: We have prepared a discussion of these broader issues in the report introduction. A basic purpose of environmental indicators is to look at how a particular indicator changes over time; this may include a lack of change. It is also important to identify differences by demographic group (especially those defined by race/ethnicity and income). Relating the observed phthalate metabolite values to

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		particular health outcomes is beyond the scope and purpose of an indicators report and we have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3. EPA has not defined any thresholds for potentially harmful phthalate exposures in biomonitoring units. The literature is rapidly developing, and a fuller assessment (well beyond the scope of ACE) would be necessary to determine if thresholds for potentially harmful phthalate exposures can be defined.
5/1	N/A Overall documentation	**Comment:** The documentation is quite extensive and could be shortened. For example, the birthrate adjustment is explained numerous times.
		Response: We appreciate your comment, but feel that it is important to thoroughly explain the adjustments made to the data used in the indicators in the interest of transparency and for clarity. Additionally, the methods section will not appear in the published document; rather it will be available online for those who are interested in obtaining more detail.
5/1	N/A Overall data tables	**Comment:** 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.
		Response: The methods section will not be included in the published document; rather it will be made available online for those who are interested in obtaining more detail about how the indicator was calculated. We believe that the interested parties can cross-reference the tables.
5/1	N/A Overall data tables	**Comment:** 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?
		Response: We have renamed this group "All Other Races/Ethnicities" and added a discussion about the category, including the race/ethnicity groups that are included in the category, to the Biomonitoring section introduction. All race/ethnicity classification relies on responses by the survey participants. Although the "All Other Races/Ethnicities" category is less clearly defined than the race/ethnicities targeted in the NHANES design (i.e. non-Hispanic White, non-Hispanic Black, Mexican-American), we believe it is important to report the values for this group as opposed to leaving them out, since for some chemicals the "All Other Races/Ethnicities" race/ethnicity has relatively high biomonitoring values.
5/1	P43, table 3 P46, Table 6	**Comment:** Table 3,6. It is not clear what the comparison is in this table. Could it be stated more simply?
		Response: We have expanded the explanatory notes under the tables of p-values to clarify the comparisons.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
5/1	N/A Overall data tables	**Comment:** 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.
		Response: We have added notes and explanations that there is no adjustment for multiple comparisons. There is precedent for this approach in CDC/NCHS documents, e.g. the annual Health Summary Statistics for U.S. Children reports presenting data from the National Health Interview Survey. Multiple comparisons can be implemented in various ways (e.g., alternate definitions of the extent of a comparison group). Since we provide the p-values, interested readers will be able to apply their own adjustments, e.g., by using a simple Bonferroni probability approach. Although we report large numbers of p-values in some cases, we did not use all these p-values to make our reporting decisions; instead we used the p-values to determine whether some of the patterns that we had already found were expected to have occurred "by chance." We have also streamlined the p-value table to reduce the number of comparisons by race/ethnicity and income. We have made the decision not to adjust for multiple comparisons as we feel it is important to identify all potentially important differences, and adjustment for multiple comparisons will increase the challenge in conveying findings of statistical testing to non-technical audiences. We clearly explain in the text that this may increase the probability that some of these differences may actually have occurred randomly. Bonferroni adjusted p-values are relatively easy to compute but tend to be overly conservative since they do not account for possible dependence between different tests. An important consideration for multiple comparison adjustments is that the "experiment" for which the experiment-wise error rate is calculated is not well defined for ACE biomonitoring indicators since there are multiple chemicals and multiple percentiles.
5/1	N/A Overall text	**Comment:** pre-natal should be changed to prenatal
		Response: We have edited our drafts to use prenatal in all instances.
5/2	P27, Methods	**Comment:** 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.
		Response: We will revisit the text and make revisions to clarify where necessary.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
5/2	P28-P29, Data Summary	**Comment:** **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
		Response: We have verified all values.
5/2	P28, Data Summary	**Comment:** What was going on with MBP in 2001-2002
		Response: These values have been checked for accuracy.
5/2	P32, L25-P33, L4	**Comment:** 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?
		Response: In response to several reviewer comments, we decided against creatinine adjustment and now present unadjusted values for the indicator. The text referred to in this comment is no longer included.
5/2	P33, L13	**Comment:** Page 33, line 13. Do you mean you readjust the phthalate metabolite levels BEFORE any analysis is conducted??
		Response: Yes, an adjusted distribution of metabolite levels was computed, and the median and 95th percentile were taken from that distribution.
5/2	P33, L22	**Comment:** 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.
		Response: We have added the equation as suggested.
5/2	P33, L31	**Comment:** Page 33 line 31: should 'family units' be 'poverty level'?? Not sure what you are saying.
		Response: We have revised the text. The family unit defines the number of individuals in the family and the associated family income, as well as the appropriate value to use for poverty level.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
5/2	P35, L17-L21	**Comment:** Page 35 lines 17-21. Sorry, lost me.
		Response: We will revisit the text and make revisions to clarify where necessary.
5/2	P36	**Comment:** 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.
		Response: We will revisit the text and make revisions to clarify where necessary.
5/2	P40, Table 1	**Comment:** Page 40 Table 1. Again why 2003-2006 instead of starting in 1999?
		Response: We focus on the most recent data for making demographic comparisons – using the two most current NHANES cycles. We have added language to better clarify why we are presenting this data to the Biomonitoring section introduction.
5/2	P40-P46, tables	**Comment:** 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
		Response: We have added sample sizes to the data tables and made some changes to the format/content of the p-value tables. We are selective in use of these comparisons in the bullet point text, but provide the full set of p-values for readers with interest in more details.
5/2	P28, Data Summary	**Comment:** Also the format of the row heading for MBzP is off.
		Response: This has been corrected.
5/3	N/A Overall documentation	**Comment:** The documentation appears transparent and complete. There are no problems here
		Response: No response necessary.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Biomonitoring

Topic: Bisphenol A

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P1, Front Matter	**Comment:** The front matter is transparent but many terms are incorrectly or non-factually defined.
		Response: Comments regarding front matter are not relevant to ACE3; this content is from the 2003 report and website.
1/1	N/A Overall topic text	**Comment:** The topic information adequately links the topic to exposure but does a less successful job in relating it to health.
		Response: Causal links between BPA exposure and adverse health outcomes are not available. Links between BPA and adverse health outcomes in human populations are described on page 2 of the topic text, and characterize positive as well as negative associations.
1/1	N/A Overall topic text	**Comment:** The language seems too simplistic even for lay persons.
		Response: ACE3 is written for multiple audiences. Other reviewers have commented that it is too complex. More general issues, like definition of the median, have been moved to the Biomonitoring section introduction so that they are not repeated for each topic.
1/1	Glossary	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The Biomonitoring introduction notes that NHANES is not designed to characterize highly-exposed populations and further describes challenges in interpretation.
1/1	Glossary	**Comment:** 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.
		Response: This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/1	Glossary	**Comment:** Deciliter. Should also add 100 milliliters.
		Response: This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/1	Glossary	**Comment:** 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.
		Response: The term has been changed from "body burden" in ACE2 to "biomonitoring" in ACE3. This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/1	Glossary	**Comment:** 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.
		Response: This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/1	Glossary	**Comment:** 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.

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		Response: The term has been changed from "body burden" in ACE2 to "biomonitoring" in ACE3. This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/2	N/A Overall topic text	**Comment:** The topic text does 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.
		Response: Additional recent references have been included to try and capture the rapid developments in BPA research.
1/2	P1, L3 through P2	**Comment:** 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.
		Response: Some of the suggested citations have been added (see below), and the introductory text has been expanded to address BPA's association with other adverse effects.
1/2	P15 L1 (Reference section)	**Comment:** 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. ReprodToxicol. 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 DevReprodToxicol. 89(6):441-66. Review. Erratum in: Birth Defects Res B DevReprodToxicol. 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.

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		Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM, Lanphear BP. Prenatal bisphenolA 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.
		Response: While we strive to cover as much of the published literature regarding BPA as we can, it is not possible to summarize all studies to date. The Canelas et al. and Lubick citations did not appear to be peer reviewed journal articles/reviews and were not included. The primary contributions of the Cantonwine et al. and Casas et al. citations are measurements in non-US populations, which do not significantly add to the material presented here. The Meeker citation does not provide any significant additional information to the text. The Braun et al. citation was already in the document. The Clayton et al., Miao et al., and Golub et al. publications were added.
1/2	P1, L3 through P2	**Comment:** The text is clear and accessible for individuals with varying levels of scientific and medical expertise.
		Response: No response necessary.
1/3	P1, L3 through P2	**Comment:** 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;[2] altered metabolism of sugars and fats;[3] and neurodevelopmental and behavioral

[2]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

[3] 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.

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		impacts, including impaired learning, increased aggressiveness and hyperactivity.[4] In this context, it should be made 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.
		Response: The introductory text was expanded to clarify some of the other adverse effects associated with BPA exposure. However, more detailed discussion of MOA and epigenetics is beyond the scope of this indicator introduction. References for cancer (Soto et al. and Ho et al.) were added to the text. We did not include the suggested Alonso-Magdalena et al. 2005 study, but have cited a related 2006 study by the same lead author. The Braun et al. reference was already discussed in the text. The Ishido et al., Kawai et al., and Miyagawa et al. references were added.
1/3	P1, L3 through P2	**Comment:** Sources of exposures should be broadened beyond dietary sources to include, in particular, house dust.[5] 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.
		Response: Other routes of BPA exposure have now been identified in the text.
1/3	P1, L8	**Comment:** 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.
		Response: The tense was corrected to indicate ongoing use and the acronym added.

[4] See, for example, Braun JM et al (2009) Prenatal BisphenolA 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.

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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/3	P1, L13-19	**Comment:** Second para 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.
		Response: The intent of this paragraph is to provide a brief description of exposures and prevalence in the US population. Information about children and their potential susceptibility due to metabolic differences is discussed in greater detail near the end of the introductory text.
1/3	P1, L13	**Comment:** Line 13 should also mention *in utero* exposures and highlight the fact that BPA can cross the placental barrier,[6] with BPA measured in amniotic fluid at levels up to five times higher than in maternal blood.[7]
		Response: This information, and a citation for the Balakrishnan et al. reference, has been added to the indicator text. However, the Ikezuki et al. reference, while interesting, was not added since it relies on a non-standard measurement method for calculating BPA levels.
1/3	P1, L16	**Comment:** Suggest replacing "prevalent" with "widespread" or other more commonly understood term.
		Response: Prevalent (and prevalence) are used throughout the ACE document. We feel the term is appropriate for the intended readership.
1/3	P1, L26-27	**Comment:** 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.
		Response: Explanations of dose-response relationships, while important, are beyond the scope of the text. The factual statement regarding the comparatively low affinity of BPA with the estrogen receptor does not undermine the evidence summary of low-dose effects described in the following

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

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

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

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		paragraph.
1/3	P2, L1-4	**Comment:** 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 acknowledge that BPA is one among many EDCs and that potential synergies/interactions among multiple exposures to multiple contaminants is not well understood, particularly for the developing fetus and child.
		Response: These issues are discussed (and the Endocrine Society statement cited) already.
1/3	P2, L30	**Comment:** 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.
		Response: The last paragraph has been modified to describe the concerns associated with BPA in a broad manner based on the exposures described previously in the topic text. General statements characterizing the rationale for the indicators are included for each indicator in ACE3.
1/3	P2, L32	**Comment:** Line 32: could state explicitly that data are not available for younger children.
		Response: The indicator text states what age ranges have data available and this issue is further discussed in the Biomonitoring section introduction.
1/3	P1, L3 through P2	**Comment:** 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.
		Response: We have revised the text and believe the current version will be more accessible. However, to be complete in describing data and research it is often difficult to avoid some technical language; information provided will still be useful to non-researchers. The report introduction and the expanded biomonitoring section introduction should help orient non-researchers to the report content. The detailed documentation will be provided online for interested readers, but will not be included in the published report.

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1/3	P1, L33 & P1, L39	**Comment:** 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.
		Response: An additional sentence was added to clarify differences between high and low dose studies.
2/1	P4, L6	**Comment:** Clarify that biomonitoring levels do not equal exposure levels
		Response: This is addressed in the Biomonitoring section introduction.
2/1	P1, L24 and P4, L6 et seq.	**Comment:** How do animal concentrations associated with health outcomes compare to human biomonitoring levels?
		Response: Comparing animal concentrations to biomonitoring levels is beyond the scope of this text. A general qualitative characterization of exposure levels in health effects studies is included in the text, and a discussion of this issue is included in the Biomonitoring section introduction.
2/1	P4, L14-19	**Comment:** 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%.
		Response: Discussion of BPA and its metabolites is included in the indicator text.
2/1	P4, L30-P5, L2	**Comment:** Should include reference to Rees Clayton 2011 paper on immune parameters derived from NH data. EHP 119:390-396.
		Response: This reference has been added.
2/1	P3, L20 (section on Creatinine adjustment)	**Comment:** 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).

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		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment. The accompanying text has been extensively revised.
2/1	P4, L6-L11	**Comment:** Page 4, second paragraph. "Urinary creatinine concentrations "can" vary…" They DO vary SIGNIFICANTLY with the variables listed.
		Response: The indicator has been revised to present BPA concentrations without creatinine adjustment. The accompanying text has been extensively revised.
2/1	P4, L6-L11	**Comment:** Creatinine correction does NOT improve the comparability of urinary chemical measurements across populations when the populations differ in age, sex, race/ethnicity.
		Response: The indicator has been revised to present BPA concentrations without creatinine adjustment. The accompanying text has been extensively revised.
2/1	P4, L30-P5, L2	**Comment:** 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.
		Response: BPA data for the 2007-2008 and 2009-2010 cycles have now been released and have been incorporated into the data analysis. Therefore time series data are now presented.
2/1	P5, L4-25	**Comment:** What was the minimum cell number requirement for statistical evaluation?
		Response: There was no minimum cell number requirement. Number of persons sampled, by race/ethnicity and by income group, has been added to the data table. Consideration of the degrees of freedom has been added to the determination of whether the uncertainty is acceptable for each estimate. Estimates with between 7 and 11 degrees of freedom have a notation stating that they should be interpreted with caution. Estimates with fewer than 7 degrees of freedom were considered unreliable and are not reported.
2/1	P6-P9	**Comment:** Was there a poverty-creatinine interaction term?
		Response: No.

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2/1	P9, L14-20	**Comment:** I firmly believe that the child findings are not real but an artifact of creatinine correction.
		Response: The indicator has been revised to present results from unadjusted analyses.
2/1	Starting on P10 (Data tables)	**Comment:** 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.
		Response: We believe there is substantial information presented that goes beyond CDC's report. There is no clear way to provide environmental data and biomonitoring data together since there are rarely one-to-one relationships (e.g., drinking water contaminants include several chemicals presented in biomonitoring indicators).
2/1	P23, L33-P24, L2	**Comment:** I liked the use of adjustment of age-specific natality. Great concept.
		Response: No response necessary.
2/1	P1, L25	**Comment:** Page 1, line 25. Change to "early and adolescent development"
		Response: The text has been revised.
2/1	P1, L29	**Comment:** Line 29. Restructure sentence to avoid "There has been"
		Response: The text has been revised.
2/2	P3, L1 et seq: Overall indicator text	**Comment:** 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.
		Response: No response necessary.

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2/2	P4, L14-18	**Comment:** 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.
		Response: The sentence has been clarified to refer to BPA metabolites as non-estrogenic. BPA metabolites are commonly referred to as inactive, based on findings showing little/no estrogenic activity. Studies in animal and human cell lines (summarized in Vandenberg et al. 2009, Matthews et al. 2001, and Shimizu et al. 2002) state that glucuronidation as well as sulfation both dramatically reduce or abolish estrogenic activity of BPA.
2/3	P4, L30-P5, L25	**Comment:** In general, the description of the data source and indicator calculation is adequate, if a bit high literacy.
		Response: No response necessary.
2/3		**Comment:** Title of the indicator should state "women of childbearing age" or other similar reference to the concern about *in utero* exposure.
		Response: For consistency across indicators, data are presented identifying the age groups of subjects. However, the last paragraph of the topic text has been modified to make the link between women 16-49 and the term, "women of childbearing age."
2/3	P1, L9-11	**Comment:** Overview para, 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.
		Response: The intent of the overview paragraph is to identify the indicator, the data source, and provide a broad statement on the rationale for the indicator. The reader can get specific information on concerns associated with BPA exposures from the topic text.

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2/3	P4, L18	**Comment:** Line 18: Point about conversion of metabolites to active form when crossing the placenta should also be made in the introductory section (page 1).
		Response: This content is included on page 2.
2/3	P4, L43	**Comment:** 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.
		Response: An explanation of how poverty levels are defined is provided in the report introduction.
3/1	P6 & P8 – graphs	**Comment:** Should note statistical significance on graphs.
		Response: For simplicity and readability, statistical significance is not shown on figures. It would be difficult to provide clear indication of which comparisons were being noted as significantly different; this could make the graphs significantly more difficult to read for less technical audiences. P-values for all comparisons are provided in the documentation. In addition, with the release of BPA data for additional NHANES cycles, these figures now present time series data rather than demographic comparisons.
3/1	P10 –P14, all Data Tables	**Comment:** Tables. Should define NA.
		Response: We have made this change.
3/1	N/A, Overall document	**Comment:** Color scheme was not particularly appealing.
		Response: The color scheme was chosen for uniformity, to highlight differences in the data while not detracting from the information presented, and to meet requirements for both professional printing and website presentation.
3/2	P10 –P14, Data Tables section	**Comment:** The indicator graph, bullet points, and data tables provide an appropriate and understandable summary of the underlying data.
		Response: No response necessary.

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3/2	P6 & P8 – graphs	**Comment:** 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".
		Response: We believe the notation will be readily understood, and provide an explanation in the introduction.
3/2	P10 –P14, Data Tables section	**Comment:** 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.
		Response: No response necessary.
3/3	P6, graph	**Comment:** 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.
		Response: This term is used in the topic text as well as in the overview paragraph.
3/3	P6, graph	**Comment:** Re: Indicator BPA1 Graph: 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?
		Response: With the release of additional NHANES data, the BPA indicator graphs have been revised to present BPA concentration time series from 2003-2010, rather than demographic comparisons.
3/3	P6, graph	**Comment:** Re: Indicator BPA1 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."
		Response: The bullets have been revised to focus on presentation of time series in the graph and tabled data on race/ethnic groups. However, the bullet this comment refers to has been revised to clarify the statistical comparisons being made.
3/3	P6, graph	**Comment:** Re: Indicator BPA1 Graph: Bullet 1: it might be helpful as context to state the median concentration in the general US population.

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		Response: General population concentrations are now included in the indicator text.
3/3	P6, graph	**Comment:** Re: Indicator BPA1 Graph: 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.
		Response: The bullets have been revised and present new data and accompanying statistical analysis.
3/3	P6, graph	**Comment:** Re: Indicator BPA1 Graph: 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.)
		Response: It is not clear why different income groups may experience different exposures to BPA. The bullets have been revised to reflect updated differences between income groups.
3/3	P6, graph	**Comment:** Re: Indicator BPA1 Graph: 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.
		Response: This information is provided in the topic text. The bullet text specifically addresses the content in the accompanying figures and tables.
3/3	P8, graph	**Comment:** 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.
		Response: The bullet text specifically addresses the content in the accompanying figures and tables. The analysis presented does not provide information that would support describing reasons why children in different income brackets may have different levels of exposure to BPA. Substantial analysis would be necessary to examine this question that is beyond the scope of ACE; we are unaware of any published studies we could

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		reference on this point.
3/3	P8, graph	**Comment:** Re: Indicator BPA2 Graph: 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.
		Response: The bullet text has been revised to reflect updated analyses, and to clarify the presentation of data. Our judgment is that, in many cases, use of the statistical note format will improve readability for audiences with varied technical backgrounds. Introduction text regarding statistical testing has been expanded.
3/3	P8, graph	**Comment:** Re: Indicator BPA2 Graph: Bullet 3: Same comment as above: the main bullet and technical bullet should be merged and expressed in plain language.
		Response: The bullet text has been revised to reflect updated analyses, and to clarify the presentation of data.
3/3	P8, graph	**Comment:** Re: Indicator BPA2 Graph: 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.
		Response: Information on general population exposures to BPA are now included in the indicator text.
3/3	P8, graph	**Comment:** Re: Indicator BPA2 Graph: 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.

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		Response: The bullet has been revised to reflect updated data, as well as revised to indicate that younger children have higher BPA concentrations.
3/3	P8, graph	**Comment:** 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.
		Response: It is not feasible to present all data of interest in figures in ACE3. Median and 95th percentile trends are now presented as the main figures, and the table was determined to be the best way to present similar data on different age groups. Results have changed due to removal of the creatinine adjustment (see above comments and responses). The revised values do not suggest much difference by age in median BPA concentrations, whereas levels do decrease with age at the 95th percentile. This result is statistically significant after adjustment for other demographic variables, and is described in a revised bullet point.
3/3	P11, Table BPA1a	**Comment:** Comments on data tables and related text: Table BPA1a: Explanation is needed for the 24.5 level for all races – unknown income.
		Response: Data tables have been updated. We have chosen to remove all estimates for "unknown income," although surveyed individuals lacking income information are still included in the "all incomes" calculations.
3/3	P13, Table BPA2a	**Comment:** Comments on data tables and related text: Table BPA2a: Explanation is needed for the 61.3 level for all races – unknown income and for white non-hispanic – unknown income.
		Response: Data tables have been updated. We have chosen to remove all estimates for "unknown income," although surveyed individuals lacking income information are still included in the "all incomes" calculations.
4/1	P4, L7	**Comment:** The limitations of this report are not worded strongly enough.
		Response: Specific limitations identified by the reviewer are addressed above.
4/1	P21, L12-P22, L2	**Comment:** It is not clear how this report differs too much from CDC's existing report on biomonitoring data.

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		Response: We believe there is substantial information presented that goes beyond CDC's report. There is no clear way to provide environmental data and biomonitoring data together since there are rarely one-to-one relationships (e.g., drinking water contaminants include several chemicals presented in biomonitoring indicators). The ACE report presents data on multiple topics relevant to children's environmental health, not just biomonitoring data on chemicals of interest. Also, the presentation of different age groupings and demographic groups represent information not provided in the CDC report.
4/1	N/A Overall text	**Comment:** It would be more valuable to integrate environmental information in with the biomonitoring data.
		Response: Please see above.
4/2	N/A Overall text	**Comment:** 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.
		Response: Human epidemiological data does not support a specific mechanism by which BPA may exert adverse effects. Generally our understanding of how biochemical signaling pathways interact to produce adverse health impacts is limited. In that regard, BPA's estrogenic activity may contribute to adverse health effects. The focus on BPA's estrogenicity is appropriate given the current state of our understanding of BPA's activity. Other non-estrogenic activity of BPA, including aryl hydrocarbon receptor activation, anti-androgenic activity, ERR-gamma, or thyroid hormone receptor affinity, is less well understood, and beyond the scope of this text. However, text has been added to address the potential non-estrogenic modes of action postulated by current research.
4/2	N/A Overall text	**Comment:** a. The document presents concrete, quantifiable indicators of key factors relevant to BpA in the environment and children in the United States.
		Response: No response necessary.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/2	N/A Overall text	**Comment:** 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.
		Response: See response to previous comment regarding the effects discussed in this indicator.
4/2	N/A Indicator text	**Comment:** 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.
		Response: No response necessary.
4/3	P6, L3-P7, L10	**Comment:** Indicator BPA 1 (BPA levels in women of childbearing age): 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.
		Response: Information provided in the bullets is intended to aid in understanding the data presented, not to address the implications of that data.
4/3	P6, L3-P7, L10	**Comment:** Indicator BPA 1 (BPA levels in women of childbearing age): Objective (a): Yes, this objective is met. Trend information will be valuable, once available.
		Response: Trend information was added in revision.
4/3	P6, L3-P7, L10	**Comment:** Indicator BPA 1 (BPA levels in women of childbearing age): Objective (b): Somewhat. The text could make it clearer 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 amino levels 5x greater than maternal blood levels). It would be ideal to have more insight/information on sources of exposure and their relative importance.
		Response: The Ikezuki et al. reference, while interesting, uses a non-standard method to calculate BPA levels, thus the reference was not included. The rationale for the indicators is clearly described at the end of the topic text. We have

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		included information on sources of exposure and their relative importance as supported by the current literature.
4/3	P8, L3-P9, L20	**Comment:** Indicator BPA 1 (BPA levels in women of childbearing age): 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.
		Response: Trend information was added in revision. Additional context to go along with the bulleted text was not added. See previous response describing the focus of bullet text.
4/3	P8, L3-P9, L20	**Comment:** 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.
		Response: Information provided in the bullets is intended to aid in understanding the data presented, not to address the implications of that data. Health and developmental implications of exposure are addressed in the indicator text.
4/3	P8, L3-P9, L20	**Comment:** Indicator BPA 2 (BPA levels for children): Objective (a): Yes, this objective is met. Trend information will be valuable, once available.
		Response: Trend information was added in revision.
4/3	P8, L3-P9, L20	**Comment:** Indicator BPA 2 (BPA levels for children): 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.
		Response: Information on age groups and data available is provided in the introduction to the Biomonitoring section. Text providing general information on exposure is provided in the introductory text.
4/3	P8, L3-P9, L20	**Comment:** Indicator BPA 2 (BPA levels for children): 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		in the suggested additions above.
		Response: Trend information was added in revision. Additional context to go along with the bulleted text was not added. See previous response describing the focus of bullet text.
5/1	N/A Overall text	**Comment:** Yes, the transparency is to be applauded EXCEPT with the creatinine correction issue. I still feel like this is a faulty finding.
		Response: The analyses for the relevant biomonitoring indicators have been revised to present unadjusted values.
5/2	P15, Reference section	**Comment:** 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.
		Response: Additional and updated references have been included during the review process.
5/3	P15, Reference section	**Comment:** Yes, the documentation appears to be complete and transparent.
		Response: No response necessary.
5/3	P24, L4-P25, L5	**Comment:** 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…)
		Response: Poverty levels are further defined in the report introduction, with an example.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Biomonitoring

Topic: Perchlorate

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
G/2	N/A Overall text	**Comment:** 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.
		Response: No response necessary.
1/1	N/A Overall text	**Comment:** 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.
		Response: We have added text to the Biomonitoring introduction noting that NHANES is not designed to identify highly exposed groups or areas. We also highlight other data limitations.
1/1	N/A Overall text	**Comment:** 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.
		Response: This title of this section has been changed to "Biomonitoring" for ACE3. The term "body burden" was not used in the perchlorate document being reviewed; it appears that the reviewer is referring to information from the 2003 edition of ACE

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		that is not included in the current review packet.
1/1	N/A Introduction	**Comment:** The front matter is transparent but many terms are incorrectly or non-factually defined.
		Response: No response necessary.
1/1	N/A Overall topic text	**Comment:** The topic information adequately links the topic to exposure but does a less successful job in relating it to health.
		Response: The topic text describes the biological and physiological harms of exposure to perchlorate for women of child-bearing age, fetuses, and infants, including the chronic health effects of such exposures.
1/1	N/A Overall topic text	**Comment:** The language seems to simplistic even for lay persons.
		Response: ACE3 is written for multiple audiences. Other reviewers have commented that it is too complex. More general issues, like definition of the median, have been moved to the Biomonitoring section introduction so that they are not repeated for each topic.
1/1	Glossary	**Comment:** 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.
		Response: The term has been changed from "body burden" in ACE2 to "biomonitoring" in ACE3. This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/1	Glossary	**Comment:** 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.
		Response: This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/1	Glossary	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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.
		Response: This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/1	Glossary	**Comment:** Deciliter. Should also add 100 milliliters.
		Response: This comment refers to content from the 2003 edition of ACE, rather than the materials under review for ACE3.
1/2	N/A Overall topic text	**Comment:** 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).
		Response: The previous references were studies performed in the southwest United States. However the Murray et al., 2008 study suggested by the reviewer was a national study. Therefore text on line 8, page 1 has been changed to "Perchlorate has been detected in surface water; dairy products; and in some food crops, including lettuce, spinach, grapes, carrots, tomatoes, and other fruits and vegetables, produced in the United States and internationally. Perchlorate has been detected in some fertilizers produced in Chile; however, fertilizers appear to be a negligible source of perchlorate in the United States. The numerous sources of perchlorate located across the United States result in widespread exposures of perchlorate to the U.S. population."
1/2	P1, L12-L13, and L18	**Comment:** 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.
		Response: The text has been changed to "Perchlorate has been detected in human breast milk, urine, blood, amniotic fluid and saliva."

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	P13, References	**Comment:** 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.
		Response: The references have been added.
1/2	P1, L35	**Comment:** Page 1, line 35: A reference is needed for the statement that deficits in maternal thyroid hormone can reduce childhood IQ.
		Response: Morreale de Escobar et al., 2000 was added as a reference.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: We have added information on exposure of newborns to perchlorate. The Blount et al. reference does not appear to provide measurements of perchlorate in newborns; the exposure metrics reported are all related to fetal exposure.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: As discussed in the text, the primary health concern is related to the effects on the developing fetus of reduced maternal thyroid hormone during pregnancy. The available epidemiological studies of both women and infants (neonates) have been summarized.
1/3	Overall topic text	**Comment:** 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).

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment. After that change, we observed no significant difference in urinary perchlorate between age groups 6-10 years and 11-17 years. Therefore, the data results for children are now provided for a single combined age group, children ages 6-17 years.
2/1	P3, L17	**Comment:** 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."
		Response: This text has been changed to "Perchlorate passes quickly through the body unchanged and is excreted in urine, with an elimination half-life on the order of hours."
2/1	P3, L22	**Comment:** 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.
		Response: Given the short half-life of perchlorate, we can infer that in order to see detects in all samples, exposure is continuous.
2/1	P3, L24-L30	**Comment:** 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).
		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment.
2/1	P4, L8-L13	**Comment:** Page 4, second paragraph. "Urinary creatinine concentrations "can" vary…" The DO vary SIGNIFICANTLY with the variables listed.
		Response: The text has been revised, and creatinine adjustment removed.
2/1	P4, L8-L13	**Comment:** Creatinine correction does NOT improve the comparability of urinary chemical measurements across populations when the populations differ in age, sex, and race/ethnicity.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The text has been revised, and creatinine adjustment removed.
2/1	P5, Statistical Testing	**Comment:** 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.
		Response: Recently 2005-2006 and 2007-2008 cycles have been released and have been incorporated into the data analysis. Therefore the figure has been revised to present a time series rather than demographic comparisons.
2/1	P5, Statistical Testing	**Comment:** What was the minimum cell number requirement for statistical evaluation?
		Response: There was no minimum cell number requirement. Number of persons sampled, by race/ethnicity and by income group, has been added to the data table. Consideration of the degrees of freedom has been added to the determination of whether the uncertainty is acceptable for each estimate. Estimates with between 7 and 11 degrees of freedom have a notation stating that they should be interpreted with caution. Estimates with fewer than 7 degrees of freedom were considered unreliable and are not reported.
2/1	N/A Throughout document	**Comment:** Should note statistical significance on graphs.
		Response: It would be difficult to provide clear indication of which comparisons were being noted as significantly different; this could make the graphs significantly more difficult to read for less technical audiences.
2/1	N/A Overall indicator text	**Comment:** Was there a poverty-creatinine interaction term?
		Response: No.
2/1	N/A Overall indicator text	**Comment:** Non-Hispanic blacks have higher creatinine concentrations than other race/ethnicities. Did this add to their lower creatinine-adjusted perchlorate levels (artifactually)?
		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment.
2/1	N/A Overall indicator text	**Comment:** I firmly believe that the final finding is not real but an artifact of creatinine correction.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment.
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: We believe there is substantial information presented that goes beyond CDC's report. There is no clear way to provide environmental data and biomonitoring data together since there are rarely one-to-one relationships (e.g., drinking water contaminants include several chemicals presented in biomonitoring indicators).
2/1	P20, L20-L27	**Comment:** I liked the use of adjustment of age-specific natality. Great concept.
		Response: No response necessary.
2/1	N/A Overall text	**Comment:** 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.
		Response: ACE3 is geared toward multiple audiences; the text and data are presented for a variety of backgrounds. Other people have also commented that the text is too complex and the text has been revised taking all comments into account. The report introduction and the expanded Biomonitoring section introduction will help orient the different types of readers to allow them to find the most relevant information to them. The detailed documentation and standard errors will be provided online for interested readers, but will not be included in the published report.
2/1	P21, Calculation of Indicator	**Comment:** 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?
		Response: CDC's methods for data collection and measurement are thoroughly reviewed; further considering limitations to their methods are beyond the scope of this report.
2/1	P4, L42	**Comment:** Page 4, last paragraph. One does not "capture exposure" but "assesses exposure" using biomonitoring data.
		Response: The text has been changed to "assess exposure".

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/1	P5, L23	**Comment:** Page 5, last paragraph, line 23. Urinary concentrations or levels are NOT "exposure levels." This should be changed.
		Response: The text has been changed to clarify use of urinary concentrations and how they imply exposure.
2/1	N/A Overall data tables	**Comment:** Tables. Should define NA.
		Response: Definition of NA has been added to the table notes.
2/2	N/A Overall discussion of dataset	**Comment:** 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.
		Response: The number of persons sampled by population group was added to the data tables.
2/2	P4, L24-L27	**Comment:** Page 4, lines 24-27: median is described here. It is also important to mention about the 95^{th} percentile, because values for 95^{th} percentile are discussed and described in tables and text. For non-experts, 95^{th} percentile is hard to understand and may even be interpreted as 95 percent of samples had that level described as 95^{th} percentile.
		Response: We now provide explanation of both the median and 95^{th} percentile in the introduction to the Biomonitoring section, and include reference to that information in the Perchlorate indicator text.
2/2	P4, L34	**Comment:** 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.
		Response: Information on how poverty level is defined is now provided in the introduction to the Biomonitoring section and the report introduction.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/2	P4, L41	**Comment:** Page 4, line 41: "NHANES survey" should be NHANES program. The word 'survey' is embedded in NHANES and 'NHANES survey' is verbiage.
		Response: The text has been revised.
2/3	P3, Overview box	**Comment:** 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.
		Response: This information is adequately discussed in the topic text. The overview text box is meant to provide a brief description of the data presented.
2/3	N/A Overall indicator text	**Comment:** Also, the studies in both animals and humans that show some possible adverse effects need to be better incorporated.
		Response: Findings from both human and animal-based studies have been incorporated into the topic text.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment.
3/1	N/A Overall graphs	**Comment:** Should note statistical significance on graphs.
		Response: It would be difficult to provide clear indication of which comparisons were being noted as significantly different; this could make the graphs significantly more difficult to read for less technical audiences.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/1	N/A Overall data tables	**Comment:** Tables. Should define NA.
		Response: Definition of NA has been added to the table notes.
3/1	N/A Overall data presentation	**Comment:** Color scheme was not particularly appealing.
		Response: The color scheme was chosen for uniformity, to highlight differences in the data while not detracting from the information presented, and to meet requirements for both professional printing and website presentation.
3/2	N/A Overall graphs and tables	**Comment:** 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).
		Response: Though not presented in the figures and tables, detection of perchlorate and median and 95th percentile urinary perchlorate levels for all NHANES participants is now reported in the indicator text.
3/2	N/A Overall indicator text	**Comment:** Benchmarks are not available and public may be in quandary.
		Response: The introduction and topic text will help orient readers to the nature of the presentation and the uncertainties regarding the health effects data. With release of NHANES perchlorate data for 2005-2006 and 2007-2008, indicator presentation has been re-oriented to focus on the time series.
3/2	N/A overall data	**Comment:** I would add the information on the number of samples for each categories in tables or figures (i.e., n=???).
		Response: Sample sizes have been be added to the data tables as well as the indicator text.
3/3	P8, Data Tables	**Comment:** 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.
		Response: For ACE3, it is not feasible to provide all statistics of interest in the data tables; mean values and standard errors will not be added to the published report, but standard errors will be available online for interested readers. To help give a sense of variability in the population, 95th percentile values are provided.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/3	N/A Overall indicator text	**Comment:** 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 than women under the poverty level, which is very interesting, since with more environmental pollutant indicators are higher in poor people than 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, creatinine.
		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment.
4/1	P4, L8-L13	**Comment:** The limitations of this report are not worded strongly enough.
		Response: We have addressed the reviewer's specific points regarding limitations. Limitations are provided in several sections including the Biomonitoring introduction, Perchlorate indicator text, and appendix for the Perchlorate indicator.
4/1	N/A Overall text	**Comment:** It is not clear how this report differs too much from CDC's existing report on biomonitoring data.
		Response: Our analysis and presentation of the data differs from CDC's in a number of ways (grouping women 16-49 years; applying birth rate adjustment; providing stratification by race/ethnicity and income specifically for women 16-49). Our background text provides more explanation for readers with less technical background, and provides information not included in CDC's report.
4/1	N/A Overall text	**Comment:** It would be more valuable to integrate environmental information in with the biomonitoring data.
		Response: It is beyond the scope of ACE3 to integrate indicator data across topics. We have edited the phrasing of the principal objectives and added additional text to the report introduction to clarify the scope and intent of this report.
4/2	N/A Overall text	**Comment:** 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.
		Response: We have added information from a study measuring urinary perchlorate in U.S. infants. We have also incorporated information from the suggested study by Zhang et al.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/3	N/A Overall text	**Comment:** 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 perchlorate as an indicator needs to be better explained. The relevant literature is in the EPA Health Advisory draft
		Response: Biomonitoring indicators for several other environmental pollutants are included in ACE3; their selection is discussed in the Biomonitoring introduction. Explanation for the focus on women of child-bearing age is provided in the text.
4/3	N/A Overall text	**Comment:** 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.
		Response: The current text provides the rationale for focusing on perchlorate in women of child-bearing age.
5/1	N/A Overall text	**Comment:** 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.
		Response: Based on this comment and other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment.
5/2	P16, Metadata	**Comment:** 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.
		Response: Discussion of measurement techniques is beyond the scope of ACE3; thorough documentation can easily be accessed by those with technical knowledge and interest.
5/2	N/A Overall text	**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.
		Response: Detection of perchlorate and the median and 95th percentile urinary perchlorate levels for all NHANES participants is now reported in the indicator text. Further

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		interpretation of the results is beyond the scope of this report and text has been added to the report introduction to clarify the scope and intent of ACE3.
5/2	P19, Table, Row 5	**Comment:** 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.
		Response: Measurement of perchlorate is in ug/L; though with application of creatinine adjustment, ug/L is changed to ug/g. Based on other peer review comments, we have decided to present indicators derived from measurements in urine without creatinine adjustment. Therefore, all perchlorate results are now in ug/L.
5/3	N/A	**Comment:** [No Comment Provided by the Reviewer]
		Response: NA

Health

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Health

Topic: Respiratory Disease

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P1-4 (Topic Text)	**Comment:** Yes, the topic text clearly describes the topic and its importance for children's environmental health.
		Response: No response necessary.
1/1	P1-4 (Topic Text)	**Comment:** 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.
		Response: We have added a paragraph about HAPs that addresses the lack of data on many of them and identifies several that may be of concern.
1/1	P1-4 (Topic Text)	**Comment:** 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.
		Response: We have added a sentence along with the suggested references.
1/1	P1-4 (Topic Text)	**Comment:** 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.
		Response: We have added a paragraph on HAPs to accomplish this and have reworded the description of criteria pollutants.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
	P1-4 (Topic Text)	**Comment:** The term "ambient" may also not be intuitive to all audiences.
		Response: We have rephrased the text to remove this term, except where it is used as part of the phrase "National Ambient Air Quality Standards."
1/1	P1, L17	**Comment:** Consider the following detailed edits. On page 1, line 17, consider using the term "criteria" over "common."
		Response: We removed "common." The term "criteria pollutants" is introduced in the next sentence.
1/1	P4, L13	**Comment:** Consider the following detailed edits. On page 4, line 13, consider using "respiratory disease" for "respiratory effects."
		Response: The text was changed accordingly.
1/1	P4, L32-33	**Comment:** Consider the following detailed edits. On page 4, lines 32-33, consider deleting "with asthma" after children since it is already implied and this would improve readability.
		Response: "With asthma" is needed here because the asthma death rate was compared only between black and white children with asthma to account for differences in asthma prevalence between the two groups.
1/2	P1-4 (Topic Text)	**Comment:** 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–
		Response: No response necessary.
1/2	P1-4 (Topic Text)	**Comment:** 1. importance of upper respiratory tract outcomes – particularly allergic rhinitis and
		Response: Please see the response below.
1/2	P1-4 (Topic Text)	**Comment:** 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.
		Response: Please see the response below.
1/2	P1-4 (Topic Text)	**Comment:** Finally, consider a mention to emerging exposures of concern for which the evidence base is preliminary (phthalates, bisphenol A, pesticides) yet are the

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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.
		Response: We added a paragraph but left out BPA as all evidence is for immune effects but not specifically respiratory effects.
1/2	P1-4 (Topic Text)	**Comment:** 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.
		Response: The suggested changes have been made.
1/2	P1, L13-15	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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
		Response: Chronic conditions comment- We believe this is not needed since we are only listing asthma and not upper airway allergies. Upper airway allergies comment- The evidence for environmental contaminants and the development of allergies is not as strong as for the onset of asthma. We left this sentence as is, but added allergy exacerbation to the previous sentence and mentioned the possible initiation of new allergies in the section on traffic pollutants. We added citation 32 and used Parker et al. as a citation for allergy exacerbation (it does not necessarily support the claim that air pollution causes the onset of new allergies). We now cite the following review article in the paragraph on traffic pollutants (it includes Morgenstern et al. as well as other studies): Bråbäck L, Forsberg B. Does traffic exhaust contribute to the development of asthma and allergic sensitization in children: findings from recent cohort studies. Environ Health. 2009 Apr 16;8:17.
1/2	P1, L25	**Comment:** 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.
		Response: Development of asthma was already included in the section on traffic-related pollutants and we have added reference 32 there. We added upper airway allergic disease to the paragraph on traffic-related pollutants.
1/2	P1, L42	**Comment:** Line 42, page 1 – can include reference 32 alongside ref 15 in support of link between NO2 and incident asthma.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The sources mainly implicate traffic pollution, and NO2 is likely to be a marker for other traffic-related pollutants. We have removed mention of NO2 and incident asthma, but it is still mentioned in the traffic paragraph.
1/2	P1, L42	**Comment:** For the ozone paragraph starting on line 27, page 1, in first sentence include reference to association with development of new disease, reference 11.
		Response: Changes have been made to the text.
1/2	P1, L10-15	**Comment:** 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).
		Response: We added a sentence to address infant mortality in the Particulate Matter (PM) paragraph.
1/2	P23-27 (References section)	**Comment:** 3. Impact on infant mortality due to respiratory causes 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.)
		Response: We added both references.
1/2	P1, L32	**Comment:** 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.
		Response: This change has been made.
1/2	P1, L43	**Comment:** Line 43, page 1 – reference 16 supports the sentence components regarding susceptibility to respiratory infections but ref 16 did not assess bronchial reactivity per se. Was another reference intended for this component of the sentence?
		Response: This sentence has been deleted.
1/2	P2, L35	**Comment:** Line 35, page 2, "Combustion byproducts" is a term that may not be understandable to more general, lay audiences such as parents, educators (consider

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		a parenthetical with examples, such as constituents of smoke from woodburning stoves, etc.).
		Response: We have reworked the paragraph so that "combustion byproducts" should be more understandable.
1/2	P2, L36	**Comment:** 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)
		Response: The change has been made and the citation has been added.
1/2	P3, L5	**Comment:** Line 5 page 3, reference 32 also provides evidence on this issue of exposure during pregnancy and development of asthma.
		Response: Reference 32 is cited in the next sentence.
1/2	P1-4 (Topic Text)	**Comment:** 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. Exposures: 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) Outcomes: 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
		Response: Unfortunately this does not fit in the format of the report.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	P3, L13-17	**Comment:** 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***.
		Response: This change was made with the exception that we left out poor oxygenation because it doesn't seem to fit with the others as a recognizable health outcome.
1/2	P3 (Asthma section)	**Comment:** 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).
		Response: We added this to list of symptoms at the end of the first paragraph (deaths from other respiratory diseases such as pneumonia are also important). Asthma deaths are also discussed in the text on ER Visits and Hospitalizations for Respiratory Diseases in the context of the disparity between White children and Black children.
1/2	P3, L26	**Comment:** 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.***
		Response: This was added to the text.
1/2	P2, L24	**Comment:** Line 24, page 2, the word decreased is misspelled.
		Response: The text was changed accordingly.
1/2	P2, L32	**Comment:** 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).

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: In reworking the paragraph, this sentence has been deleted.
1/2	P3, L23-26	**Comment:** 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.
		Response: The text was changed accordingly.
1/2	P4, L12	**Comment:** Line 12, page 4 – change the parenthetical to (such as asthma, upper ***and lower respiratory infections such as bronchiolitis and pneumonia)***
		Response: The text was changed accordingly.
1/2	P4, L14	**Comment:** 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.)
		Response: The text was changed accordingly.
1/3	P1, L17	**Comment:** 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: 1) 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.
		Response: We changed "most" to "five." Lead has not been linked to respiratory diseases, but EPA's Integrated Science Assessment for CO identifies a number of positive associations between short-term exposure to CO and respiratory symptoms in individuals with asthma.
1/3	P1. L21	**Comment:** 2) Page 1, line 21: delete "and lead".
		Response: We did not delete "lead" but reworked the sentence to make it clear that lead has not been linked to respiratory diseases.
1/3	P1, L30	**Comment:** 3) Page 1, line 30: cite McDonnell et al. (2002 – Your Ref. # 11) for O_3 causing incident asthma.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The suggested change was made to the text.
1/3	P1, L32	**Comment:** 4) 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)].
		Response: We restructured the sentence to cite the EPA ozone document which cites Thurston et al. 1997.
1/3	P1-2, L41-	**Comment:** 5) 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.
		Response: We removed these sentences and added the references to the traffic section.
1/3	P2, L2	**Comment:** 6) 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).
		Response: This is mentioned in the traffic section. Ref 19 does not specifically implicate NO2 but rather proximity to major roads. We changed the language in the traffic section to match the wording suggested here.
1/3	P1-4 (Topic Text)	**Comment:** 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.
		Response: While we agree that a discussion of preventive measures is an important part of the dialogue regarding how to protect children's health, it is beyond the scope of the information presented in ACE3.
1/3	P1-4 (Topic Text)	**Comment:** The literature cited was appropriately summarized only in part. Some additional literature that should have been cited is mentioned above.
		Response: Please see responses above.
1/3	P1-4 (Topic Text)	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: Links to references will be provided on the ACE3 website.
2/1	P5-10 (Indicator D1 and Indicator D2) P6, L14-19	**Comment:** 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.
		Response: We added a sentence noting this table.
2/1	P12, L4-5	**Comment:** 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.
		Response: The intent of the Overview is to very briefly describe the nature of the information provided in the indicator, but not the results – which are amply highlighted by the figure and the bullet points. We do not discuss trends in any of the "Overview" boxes throughout ACE3; these are intended to remain unchanged even as newer data permit the indicators and bullet points to be updated.
2/2	P5-22 (Indicator D1, Indicator D2, and Indicator D3)	**Comment:** 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.
		Response: This has been added to the text.
2/2	P6, L21	**Comment:** 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).
		Response: The suggested change has been made to the text.
2/2	P5, L6	**Comment:** (*regarding indicator text*) Overview paragraph after line 6, page 5, insert "**each year**" at the end of the second sentence.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The text was changed accordingly.
2/3	P5-22 (Indicator D1, Indicator D2, and Indicator D3)	**Comment:** For reasons that are not explicitly described, the presentation is divided into three specific indicators and for different periods of years, i.e.: 4) D1 - % of children ages 0 to 17 years with asthma, 1997-2008; 5) D2 - % of children ages 0 to 17 years reported to have current asthma, by race/ethnicity and family income, 2005-2008; 6) 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?
		Response: D1: We state that NHIS was redesigned in 1997 and current asthma prevalence was added in 2001. D2: We state that 2005-2008 are combined in order to increase statistical reliability. D3: We added an explanation of why we start with 1996. We are not aware of findings that directly explain the observed trends, and it would be inappropriate to speculate. To give some context to the observed differences in temporal trends, We have added text to emphasize the difference between current asthma prevalence and outcomes for children with asthma (asthma attack prevalence, ER visits and hospital visits).
2/3	P5-22 (Indicator D1, Indicator D2, and Indicator D3)	**Comment:** 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.
		Response: Please see responses above.
3/1	P8 (Figure)	**Comment:** For Indicator D1: The y-axis should list all years. It is awkward and confusing to have 1997 as the only odd year. It would be better to present the sub-bullet without the heading "statistical note."

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We believe the current style is effective; there is not enough room to provide every year with horizontal labels.
3/1	P8 (Figure)	**Comment:** Indicator D1: 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.
		Response: No, none were significant. We would include results for subgroups in this circumstance only if some subgroups were significant.
3/1	P8 (Figure)	**Comment:** Indicator D1: It would be better to present the sub-bullet without the heading "statistical note."
		Response: We no longer include a sub-bullet under this particular indicator. For other sub-bullets throughout the report, e.g. under indicators H2 and H3, we have removed the phrase "statistical note" as suggested.
3/1	P8 (Figure)	**Comment:** Indicator D1: 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.
		Response: The NHIS public data files do not contain locational information.
3/1	P10 (Figure)	**Comment:** For Indicator D2: The gridlines and poverty labels are extremely hard to read.
		Response: We have revised the formatting of this figure and believe the revisions address this concern.
3/1	P10 (Figure)	**Comment:** For Indicator D2: The wording of the second bullet point on page 11 is very awkward.
		Response: The wording has been revised.
3/1	P10 (Figure)	**Comment:** For Indicator D2: Should the Table referred to in the 3rd and 4th bullet points on page 11 be D2a and not D2b.
		Response: Yes, we have corrected the table number (now H2a).

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/1	P10 (Figure)	**Comment:** For Indicator D2: I'm not clear what we learn from the 4th bullet point. Wouldn't older children be more likely to be diagnosed with asthma?
		Response: It is interesting to compare age groups, because the question is asked "Does your child STILL have asthma?" Just because a child has asthma when they are younger does not mean they will always have it.
3/1	P10 (Figure)	**Comment:** For Indicator D2: 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.
		Response: The NHIS public data files do not contain locational information.
3/1	P14 (Figure)	**Comment:** For Indicator D3: The line and label for asthma is difficult to see.
		Response: We reviewed the figure and believe the asthma line and label are readable on-screen and printed out in both color and black-and-white.
3/1	P14 (Figure)	**Comment:** For Indicator D3: Under bullet point#2, did the rate of emergency room visits for all respiratory causes other than asthma change over time? Was it significant?
		Response: There was no significant change over time in these values.
3/1	P14 (Figure)	**Comment:** For Indicator D3: 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.
		Response: Tables were re-ordered as suggested.
3/1	P8, P10, P14 (Graphs)	**Comment:** The current template for the indicator graphs is hard to read when printed out in black and white.
		Response: We have chosen to design the graphs in color as we believe they will be viewed this way the vast majority of the time. Formatting of all figures as been refined, and the layout of Indicator H2 (formerly D2) has been revised.
3/2	P8, L11	**Comment:** 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…

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The suggested edit is incorrect. The percentage is of all children.
3/2	P8, L11	**Comment:** 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.
		Response: We have considered it and decided not to do this in order to preserve readability for non-technical audiences. We will provide standard errors online for interested readers.
3/3	P5-22 (Indicator D1, Indicator D2, and Indicator D3)	**Comment:** 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.
		Response: No response necessary.
3/3	N/A data presentation	**Comment:** 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.
		Response: We have added some text to help explain the selection of the indicators. Regarding interpretation of values, this is addressed briefly in the introduction but in general is beyond the scope of this report.
3/3	P5-22 (Indicator D1, Indicator D2, and Indicator D3)	**Comment:** 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.
		Response: We are unaware of studies explaining these trends. We conferred with the National Center for Health Statistics; which provides the data; they could not supply explanations. Identification of the underlying causes for the trends would be a significant research effort that is beyond the scope of this report.
3/3	P5-22 (Indicator D1, Indicator	**Comment:** 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

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	D2, and Indicator D3)	mean to the temporal changes in the underlying morbidity.
		Response: These data are collected in a manner that is comparable over time; definitions of the indicators are constant.
4/1	P5-22 (Indicator D1, Indicator D2, and Indicator D3)	**Comment:** 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.
		Response: The NHIS public data files do not contain locational information.
4/2	N/A (Overall Text) P4, L17-22	**Comment:** 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.
		Response: No response necessary.
4/2	P5-22 (Indicator D1, Indicator D2, and Indicator D3)	**Comment:** 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

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		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.)
		Response: Brief text was added, with citation to the two suggested references.
4/2	P12-22 (Indicator D3)	**Comment:** 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.
		Response: It is not practical to include figures in ACE3 for all data of interest. We chose to give primary focus to time series where available, then to supplement this with snapshot demographic comparisons that are backed up by data tables.
4/3	P8-9 (Indicator D1)	**Comment:** 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.
		Response: No response necessary.

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4/3	P10-11 (Indicator D2)	**Comment:** 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.
		Response: No response necessary.
4/3	P14-15 (Indicator D3)	**Comment:** 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.
		Response: We agree that further investigation into these declines is warranted.
5/1	N/A (Overall Text)	**Comment:** The documentation is very thorough and transparent. It would be possible for someone to replicate all calculations.
		Response: No response necessary.
5/2	P16, L13-15 (Table D1a)	**Comment:** 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.)
		Response: The text was changed accordingly.
5/3	N/A (Overall Text)	**Comment:** Yes.
		Response: No response necessary.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Health

Topic: Childhood Cancer

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1/1	N/A Overall topic text	**Comment:** 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.
		Response: No response necessary.
1/1	N/A Overall topic text	**Comment:** 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.
		Response: We have added a sentence to address this issue: "Radon is a naturally occurring radioactive element that has been associated with lung cancer; some studies have also found an association between childhood leukemia and radon while other studies have not." We also added sentences discussing cell phone use: "Many studies have examined whether there is an association between cellular phone use and brain cancer. Some of these studies have found an association between cellular phone use and some types of brain cancer, while other studies have found no association. Because the use of cellular phones by children has only recently become more common, no long-term epidemiological studies of cancer related to cellular phone use by children are available." Sentences were added discussing living near power lines: "Associations between proximity to extremely low frequency electromagnetic radiation, such as radiation from electrical power lines, and childhood leukemia have been investigated for many years. Some studies suggest an effect on cancer risk, while others do not. At this time, a variety of national and international organizations have concluded that the link between exposure to extremely low frequency electromagnetic fields and cancer is controversial or weak."
1/1	N/A Overall topic text	**Comment:** Yes

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		Response: No response necessary.
1/1	N/A Overall topic text	**Comment:** 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.
		Response: We have added a sentence to address this issue: "Radon is a naturally occurring radioactive element that has been associated with lung cancer; some studies have also found an association between childhood leukemia and radon while other studies have not."
1/1	P2, L38-P3, L4	**Comment:** In general the text is understandable for readers with a diverse background of knowledge. However, the description of carcinogens from page 2, line 38 through page 3, line 4 seems to deviate away from the focus of the topic and may be removed.
		Response: We have removed the description of carcinogens and have added sentences to better explain mechanisms of cancer initiation.
1/2	N/A Overall topic text	**Comment:** 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?
		Response: We believe the text provides an appropriate summary of the literature with the proper amount of detail for this report.
1/2	N/A Overall topic text	**Comment:** There are a couple of things of current importance that I would emphasize/add. The first is the foetal 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 leukaemia, with the strongest risk for exposure during pregnancy. Outdoor exposure and exposure of children (after pregnancy) were not significantly associated with childhood leukaemia, for example.

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		Response: We have added sentences to address prenatal exposures related to childhood cancers to read, "Different types of cancer affect children at different ages. This pattern may reflect the different types of exposures and windows of vulnerability experienced by children as they grow older, and the time between the initiation of cancer and its clinical presentation. Children can be affected by exposures that occur during different developmental stages, such as during infancy and early childhood. Scientific evidence suggests that early childhood cancers may be related to exposure in the womb, or even to parents' exposures prior to conception. Furthermore, recent studies suggest that susceptibility to some cancers that arise later in adulthood also may be determined while in the womb."
1/2	N/A Overall topic text	**Comment:** 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 leukaemias, 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
		Response: Please see above response regarding additional text added to address prenatal exposures. The topic text is meant to be an introduction to the topic and an explanation about why the topic is important for children's environmental health. We feel that including a list of all environmental risk factors is beyond the scope of this report.
1/2	N/A Overall topic text	**Comment:** 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 hypothesise 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.
		Response: We have added text to address epigenetic mechanisms to read, "The development of cancer, or carcinogenesis, is a multistep process leading to the uncontrolled growth and division of cells. This process can begin with an inherited genetic mutation or DNA damage initiated by an exogenous agent, such as exposure to a carcinogenic chemical or radiation. Additionally, many external influences, such as environmental exposures or nutrition, can alter gene expression without changing the DNA sequence. These alterations, referred to as epigenetic changes, can promote alterations in the expression of genes important for controlling cell growth and division. Because the initiation of carcinogenesis is a multistep process, multiple factors are thought to contribute to the development of cancer. Newer research suggests that childhood cancer may be caused by a combination of genetic

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		predisposition and environmental exposure."
1/2	N/A Overall topic text	**Comment:** 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 germline 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 germline 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 germline mutation. The application of new technologies will greatly enhance our understanding of mutation in humans exposed to environmental mutagens.
		Response: We appreciate the comment. However, discussion of these issues is beyond the scope of this report.
1/2	P2, L1-L12	**Comment:** Page 2 first paragraph: Be careful not to fall into the trap of "evidence inconclusive=no evidence" We live in a complex world where multicausality 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 leukaemia 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
		Response: We have added a paragraph that better explains the mechanisms that might cause cancer, including a discussion of multicausality and gene-environment interaction. The section reads, "The development of cancer, or carcinogenesis, is a multistep process leading to the uncontrolled growth and division of cells. This process can begin with an inherited genetic mutation or DNA damage initiated by an exogenous agent, such as exposure to a carcinogenic chemical or radiation. Additionally, many external influences, such as environmental exposures or nutrition, can alter gene expression without changing the DNA sequence. These alterations, referred to as epigenetic changes, can promote alterations in the expression of genes important for controlling cell growth and division. Because the initiation of carcinogenesis is a multistep process, multiple factors are thought to contribute to the development of cancer. Newer research suggests that childhood cancer may be caused by a combination of genetic predisposition and environmental exposure."

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	N/A Overall topic text	**Comment:** Action points for policy makers etc are missing :
		Response: This report is meant to provide scientific information and indicators of children's environmental health and is not meant to be a policy document.
	N/A Overall topic text	**Comment:** What about tobacco? Is banning smoking in public places helpful? Has it been? Is there any evidence
		Response: At this time, the evidence regarding childhood cancer outcomes associated with smoke-free legislation is limited.
	N/A Overall topic text	**Comment:** 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 aetiology of childhood leukemia is poorly understood.
		Response: This report is meant to provide scientific information and indicators of children's environmental health and is not meant to be a policy document. In regards to the issue of confounding, bias, and chance, we have added a section to the introduction that discusses the advantages and limitations of epidemiological data and issues of interpretation.
1/2	P28, Statistical comparisons	**Comment:** 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%.
		Response: We agree that a finding that does not reach statistical significance may be biologically relevant. We have revised our text regarding statistical testing to better explain the meaning of statistical significance. This discussion has been moved to the Health section introduction. However, a discussion of the merits or

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		shortcomings of setting a cut point for statistical testing is beyond the scope of this document.
1/2	P10, L13-18	**Comment:** 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?
		Response: We have added text to introduce why cancer rates may vary by child's age to read "Different types of cancer affect children at different ages. This pattern may reflect the different types of exposures and windows of vulnerability experienced by children as they grow older, and the time between the initiation of cancer and its clinical presentation. Children can be affected by exposures that occur during different developmental stages, such as during infancy and early childhood. Scientific evidence suggests that early childhood cancers may be related to exposure in the womb, or even to parents' exposures prior to conception. Furthermore, recent studies suggest that susceptibility to some cancers that arise later in adulthood also may be determined while in the womb."
1/3	N/A Overall topic text	**Comment:** 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 in 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.
		Response: The topic text is meant to give a background on childhood cancers and explain how the outcome is related to children's environmental health. Our standard format is to first introduce the health outcome, which is particularly important to lay audiences, and then explain how the environment may be related.
1/3	N/A Additional references	**Comment:** 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? [1] Also- there is one line about combination of genetic predisposition and environmental exposures but I think this warrants additional discussion/emphasis. [2] ---------- 1. Smith, M.T. Advances in understanding benzene health effects and susceptibility. Annu Rev Public Health 31, 133-148 132 p following 148 (2010).

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		2. 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).
		Response: We have added text to better explain children's susceptibility to cancer, including the importance of windows of vulnerability and latency to read, "Different types of cancer affect children at different ages. This pattern may reflect the different types of exposures and windows of vulnerability experienced by children as they grow older, and the time between the initiation of cancer and its clinical presentation. Children can be affected by exposures that occur during different developmental stages, such as during infancy and early childhood. Scientific evidence suggests that early childhood cancers may be related to exposure in the womb, or even to parents' exposures prior to conception. Furthermore, recent studies suggest that susceptibility to some cancers that arise later in adulthood also may be determined while in the womb." We could not find a discussion about childhood mobility and exposure assessment in the Smith et al. publication suggested; challenges in conducting epidemiological research are beyond the scope of this text, but we have added a general discussion of epidemiology to the report introduction. We have added the Holland et al. reference to our discussion of genetic predisposition and environmental exposures.
1/3	N/A General text	**Comment:** 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
		Response: We have added information about childhood melanoma to read, "Although childhood melanoma is rare, the incidence of melanoma is increasing in children, especially in adolescents. Environmental factors associated with melanoma include sunburns, especially in childhood, and increased exposure to ultraviolet (UV) radiation. Depletion of the ozone layer causes more ultraviolet radiation to reach the earth's surface. Even though the use of ozone depleting compounds has been largely phased out and the ozone layer will eventually be restored, higher levels of ultraviolet radiation reaching the earth's surface will persist for many years to come. Finally, the increased rates of melanoma in adolescent girls and young women may reflect increased UV exposure from sunbathing or from the widespread practice of indoor tanning."
1/3	N/A Additional references	**Comment:** 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.

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		Response: We have added new review references for pesticide exposure and childhood leukemia. Also, we think it is important to include references that summarize the data, where available, which is why we have included the U.S. Surgeon General's report for all cancers that are associated with ETS exposure. However, we have changed the wording of the sentences regarding ETS to avoid seeming too redundant.
1/3	N/A Additional references	**Comment:** References to Consider:[3,4] ---------- 3. 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). 4. 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).
		Response: We have added the suggested references.
1/3	P2, L29-L37	**Comment:** Paragraph 7- pg 2 – the first and last sentences are inconsistent – is there or is there not evidence that Wilm's Tumors and Ewing Sarcoma's are environmental – e.g. there is limited evidence to suggest that both ionizing radition and pesticides may contribute to the incidence of Wilm's and Ewing Sarcoma but the only known causes are birth defects and genetic conditions.
		Response: We have edited for clarification to read, "While the only known causal factors for Wilms' tumor and Ewing's sarcoma are certain birth defects and genetic conditions, there is limited research indicating that exposure to pesticides may also be a causal factor in the development of Wilms' tumor and Ewing's sarcoma in children."
1/3	P2, L29-L37	**Comment:** I think it would help to move paragraph 8 up in the text, maybe even as the first paragraph.
		Response: We have revised paragraph 8 and moved it up in the text, to paragraph 4.
1/3	P14, L9-L11	**Comment:** 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.
		Response: We have added a newer reference for this sentence.

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1/3	P1, L15, L16	**Comment:** 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. ----
		Response: This change has been made as suggested. It now reads, "However, the President's Cancer Panel recently concluded that the causes of the increased incidence of childhood cancers are not fully understood, and cannot be explained solely by the introduction of better diagnostic techniques. The Panel also concluded that genetics cannot account for this rapid change. The proportion of this increase caused by environmental factors has not yet been determined."
1/3	P2, L35-L37	**Comment:** Pg. 2 lines 35-37 are not consistent with the rest of the paragraph –
		Response: We have revised the sentence for clarity to read, "While the only known causal factors for Wilms' tumor and Ewing's sarcoma are certain birth defects and genetic conditions, there is limited research indicating that exposure to pesticides may also be a causal factor in the development of Wilms' tumor and Ewing's sarcoma in children."
1/3	P2, L38-P3, L4	**Comment:** Pg. 2 – paragraph starting at line 38 – this paragraph has a lot of good information that could be moved up to frame the issue prior to going into each separate cancer.
		Response: We have made some revisions to the paragraph and moved it up in the text to become paragraph 4.
1/3	P3, L11 & L12	**Comment:** Pg. 3 – line 11 and 12 severity should really read magnitude – the death and survival really measure the severity.
		Response: The incidence may measure the magnitude but in the sentence we are discussing both the mortality and incidence, so severity is also represented. The sentence was edited to read, "However, showing childhood cancer mortality rates in conjunction with childhood cancer incidence rates highlights the magnitude and severity of childhood cancer and indicates the proportion of children that survive."
2/1	N/A Overall indicator text	**Comment:** Yes
		Response: No response necessary.
2/1	P4, L12-L14	**Comment:** 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

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		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.
		Response: We feel it is important to mention limitations of the data set we use to calculate the indicator. We did not identify any SEER publications that address this point. Also, we believe the interpretation of the statement is fairly straightforward.
2/2	N/A Overall indicator text	**Comment:** The information presented is very clear. Shortcomings are already presented.
		Response: No response necessary.
2/3	P4, starting L7	**Comment:** 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.
		Response: We have added a sentence about the quality of SEER as a national database. As we do not use state based registries we feel that adding this information may confuse the reader. Additional information is provided in the methods section. However, we feel it is important to briefly describe the data source in the indicator text, particularly since the methods section will only be available online, rather than in the printed report.
2/3	P17, Metadata	**Comment:** Information from the metadata re: spatial representation of the database would be helpful to include in the descriptive text for the indicators.
		Response: This information has been added to the indicator text to read, "The registries include the Alaska Native, Atlanta, Connecticut, Detroit, Hawaii, Iowa, Los Angeles, New Mexico, Rural Georgia, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound, and Utah tumor registries."
2/3	P5, L8-L16	**Comment:** 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.
		Response: We feel that an introduction to the data source is necessary before discussing how the data is used in the indicator. We moved the "statistical testing" section to the Health section introduction, which shortens the indicator description section and better highlights the information on Pg.5 L8-16.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/3	P5, Statistical Testing	**Comment:** 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.
		Response: We have revised this text and include the description of statistical testing in the introduction to the Health section. We have decided not to include an example for the sake of brevity.
3/1	P7, and P9, Indicator graphs	**Comment:** Overall the indicator graphs provide an understandable summary of the SEER data.
		Response: No response necessary.
3/1	P7, and P9, Indicator graphs	**Comment:** 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.
		Response: We have added "age-adjusted" to the indicator graph labels and tables, as suggested. Additional text was not added as this would make the labels too lengthy and is more detail than needed. Details about the how the age-adjustment was made to the U.S population are included in the Methods section.
3/1	P7, L3	**Comment:** The term, "a statistically significant increase", in the first sentence on page 7, line 3, should be "a statistically significant trend of increase"
		Response: The phrasing has been revised.
3/1	P7, L8	**Comment:** 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.
		Response: This change was made as suggested.
3/1	P7, L13-P8, L3	**Comment:** 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.
		Response: We use the bullets to highlight key findings from the tables and think this is important, especially for those readers who may not study the tables in detail. The Health introduction section has been edited to mention the statistical issues with multiple comparisons.

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3/1	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.
3/2	P7, and P9, Indicator graphs	**Comment:** 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.
		Response: The ACE introductory text includes discussion of both individual studies and published meta-analyses, if available. Additionally, we have added a section to the report introduction that explains the limitations of epidemiological studies. This document is not intended to serve as a policy document, but rather a scientific document that can be used to better understand trends in childhood cancer.
3/2	P7, and P9, Indicator graphs	**Comment:** …offer suggestions to policy makers/public to help in interpretation of results….. For example: 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.
		Response: We have added a section to the report introduction that explains the limitations of epidemiological studies. We have also expanded our discussion of statistical significance and moved it to the Health section introduction.
3/2	P7, and P9, Indicator graphs	**Comment:** …offer suggestions to policy makers/public to help in interpretation of results….. For example:

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		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.
		Response: We have added a section to the report introduction that explains the limitations of animal toxicological studies.
3/3	P7, graph	**Comment:** Indicator D5 – 1) suggest adding a footnote about the spatial representation of these data – e.g. a subset of US population sample.
		Response: We have added a description of where the SEER registries are located to the indicator text and feel that it would be redundant to list the locations again in the graph.
3/3	P7, L8-L11	**Comment:** 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.
		Response: We have added a bullet as suggested to read: "In 2007-2009, the difference in cancer incidence between boys and girls was not consistent for all races/ethnicities. No statistically significant difference in cancer incidence by sex was seen among Black non-Hispanic children or Asian or Pacific Islander non-Hispanic children. Among American Indian and Alaska Native non-Hispanic children, cancer incidence was greater for girls than for boys, although this difference was not statistically significant. Cancer incidence was greater for boys than for girls and statistically significant among White non-Hispanic children (after adjustment for age) and Hispanic children. (See Table H4a.)"
3/3	P8	**Comment:** Pg. 8 – how "representative" are the racial and ethnic minority groups of the nation as a whole in the SEER population?
		Response: We believe our statement in the first paragraph of the indicator text sufficiently addresses this issue.
3/3	P8, L11-L16	**Comment:** 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.
		Response: We have added a discussion regarding windows of vulnerability, etc. to the topic text to read, "Different types of cancer affect children at different ages. This

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		pattern may reflect the different types of exposures and windows of vulnerability experienced by children as they grow older, and the time between the initiation of cancer and its clinical presentation. Children can be affected by exposures that occur during different developmental stages, such as during infancy and early childhood. Scientific evidence suggests that early childhood cancers may be related to exposure in the womb, or even to parents' exposures prior to conception. Furthermore, recent studies suggest that susceptibility to some cancers that arise later in adulthood also may be determined while in the womb."
3/3	P10, L13	**Comment:** 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.
		Response: We have added a discussion to the topic text to read, "Different types of cancer affect children at different ages. This pattern may reflect the different types of exposures and windows of vulnerability experienced by children as they grow older, and the time between the initiation of cancer and its clinical presentation. Children can be affected by exposures that occur during different developmental stages, such as during infancy and early childhood. Scientific evidence suggests that early childhood cancers may be related to exposure in the womb, or even to parents' exposures prior to conception. Furthermore, recent studies suggest that susceptibility to some cancers that arise later in adulthood also may be determined while in the womb." We feel it is important to keep the bullet as well, since it presents data from the indicator; however, we have revised the bullet to clarify that the data being presented is from the indicator.
4/1	N/A Overall indicator text for D5 and D6	**Comment:** 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.
		Response: No response necessary.
4/1	Overall indicator D5	**Comment:** 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.
		Response: No response necessary.

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4/1	N/A Overall indicator text for D5 and D6	**Comment:** 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.
		Response: No response necessary.
4/1	N/A Overall indicator text for D5 and D6	**Comment:** 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.
		Response: No response necessary.
4/2	N/A Overall indicator text	**Comment:** 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
		Response: ACE is intended to provide information on a range of children's environmental health topics. It is not intended (by itself) to fully satisfy each of these objectives, but to serve as a starting point to stimulate further interest and investigation. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the intent and scope of ACE3.
4/2	Overall text	**Comment:** As mentioned previously, there is no single cause for childhood leukaemia 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 leukaemia or a tumour in the brain or central nervous system. The study identified 1397 British children registered with leukaemia 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 that 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.
		Response: We have added a discussion on the advantages and limitations of epidemiological studies to the report introduction. The topic text is meant to provide a brief background on the topic and why it is important for children's environmental

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		health. Discussing the details of each study cited is beyond the scope of this report.
4/2	Overall text	**Comment:** 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 centiles of modeled power density; for childhood leukaemia (which has a higher incidence) the figure is over 99%.
		Response: Please see above response.
4/2	Overall text	**Comment:** 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.
		Response: Please see above response.
4/2	Overall text	**Comment:** 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.
		Response: Please see above response.
4/2	Overall text	**Comment:** 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.
		Response: More detail regarding preventative measures is beyond the scope of this report.
4/2	Overall text	**Comment:** 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

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		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.
		Response: The main goal of ACE3 (as a whole) is to provide indicators relevant to children's environmental health. The text for each topic is meant to summarize the current state of the literature regarding the vulnerability of children to environmental contaminants and conditions. The important research initiatives mentioned have led to the publication of manuscripts cited in ACE3. ACE3 is not intended to serve as a policy document to discuss current initiatives, research objectives, or funding priorities. These topics are beyond the scope of ACE3.
4/3	N/A Overall indicator text	**Comment:** **a)** these indicators show important temporal trends in childhood cancers over time
		Response: No response necessary.
4/3	N/A Overall data presentation	**Comment:** b) if these are the only reliable childhood cancer data, a section on limitations of data availability for studying childhood cancer nationally is needed.
		Response: ACE3 is not intended to serve as a policy document to discuss current initiatives, research objectives, or funding priorities. These topics are beyond the scope of ACE3.
4/3	N/A Overall data presentation	**Comment:** **c)** 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?
		Response: In most cases, the reasons for why a trend is increasing or decreasing are largely unknown. Information about the advantages and limitations of epidemiological studies is addressed in the report introduction. ACE3 is meant to serve as an informative scientific document, rather than a policy document or risk assessment. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the intent and scope of ACE3.

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4/3	N/A Overall data presentation	**Comment:** d) I think having a discussion on regional variations in cancer incidence would be useful, having only temporal trends by gender, age, race/ethnicity 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.
		Response: In the report introduction, we explain that one of the criteria for a dataset to be included in ACE3 is that it is nationally representative. We also added a sentence to the indicator text explaining why SEER was used. We feel that SEER provides the best nationally representative data on childhood cancer over time. While regional variations are important, we have had to make decisions about what can reasonably be covered in this version of ACE.
5/1	N/A Overall text	**Comment:** Yes
		Response: No response necessary.
5/2	N/A Overall text	**Comment:** The document is transparent but as already outlined above, it feels a little incomplete to me.
		Response: We have addressed the above comments.
5/2	N/A Overall text	**Comment:** 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?
		Response: This limitation applies only to data from Washington, DC and North Dakota. We have revised the metadata, and added a note to the data table explaining that these jurisdictions are excluded from the calculation of mortality by race/ethnicity.
	P23, Table	**Comment:** 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.
		Response: We concluded the text explanation was sufficient in this case.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Health

Topic: Neurodevelopmental Disorders

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1/1	N/A Overall topic text	**Comment:** 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 thimerosal, 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.
		Response: Text has been added discussing findings regarding neurodevelopmental disorders and maternal alcohol and tobacco consumption. We chose not to add food colors/additives due to the varied interpretations of this information and resulting difficulty in providing a clear, brief characterization . We believe the current text regarding thimerosal is clear and complete for the purposes of ACE. The study by Wakefield that was withdrawn addressed MMR vaccine, not thimerosal.
1/2	N/A Overall topic text	**Comment:** No, the text was very poorly written and does [not] 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.
		Response: The text has been extensively rewritten. We have included clarification about why lead, mercury, and PCBs have been discussed to the greatest extent. In addition, we have included relevant information about other toxicants. One of the purposes of ACE is to concisely describe the potential health effects associated with environmental exposures. Given the many neurodevelopmental disorders and potentially relevant environmental exposures, we believe the text written and presented as edited, while brief in some areas, meets this criterion and is appropriately written for our target audience. Toxicants are also described in greater detail in the Biomonitoring topics.
1/2	N/A Overall topic text	**Comment:** On the other hand, the relevant literature is adequately cited. One additional behavioral problem associated with childhood lead exposure and prenatal tobacco

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		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.
		Response: We included information regarding the link between lead exposure and antisocial behaviors in the review draft on p. 1, line 40. We subsequently revised the text to report the findings of the NTP monograph on lead and problem behaviors, including antisocial behavior.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: We have included relevant information regarding the prevalence of neurodevelopmental conditions on p. 1, paragraph 2.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: Discussions of regulatory and/or advisory efforts to reduce exposures to environmental toxicants have been included in relevant sections of the report (see Biomonitoring sections for lead, mercury, PCBs, PBDEs, and phthalates). NHANES data regarding trends in blood lead and cotinine levels have been included in their respective sections as well.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: We have added text on risk factors for neurodevelopmental outcomes, including adverse birth outcomes and other factors during pregnancy. Detailed discussions regarding prematurity and related issues are included in the Adverse Birth Outcomes section of the report. Sensory impairments and cerebral palsy are mentioned briefly in the revised text.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/3	N/A Overall topic text	**Comment:** 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 (see 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.
		Response: We recognize that socioeconomic factors are important determinants of health and have included information in this section (p. 1, paragraph 3, p. 4 paragraph 2) in addition to relevant discussions in other sections of the report. For instance, issues regarding lead exposure and the association with older/lower income housing and/or poverty are included in the Lead section. We also discuss issues related to living on or near contaminated lands and attending schools/childcare facilities with pesticide contamination in the "Contaminated Lands" and "Contaminants in Schools and Child Care Facilities" sections, accordingly. Where available, data for contaminants and/or health outcomes are stratified by race/ethnicity and income, allowing readers to draw conclusions about the socioeconomic determinants of health. Data presented in this section are presented this way as well (see Tables ND2b, ND3b, and ND4b). We also discuss health disparities in the introduction to the report. These issues are discussed in detail throughout the entirety of the ACE report.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: The treatment of environmental exposures and remediation is beyond the scope of ACE. The data here is presented to inform discussions among policy makers and

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		researchers who can take the next step.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: Scientific findings on these points tend to be limited and mixed.
1/3	N/A Overall topic text	**Comment:** 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 many 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.
		Response: Epigenetics may have an influence on many of the topics discussed in this report; in most cases investigation into these mechanisms are at an early stage. Discussion of how environmental chemicals may cause adverse outcomes is generally beyond the scope of ACE, particularly when they are not well-established.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: The multi-faceted nature of disease and differing effects for different children are illustrated in the introduction of the report since these themes apply to many topics. Describing the mechanisms of the exposure disease relationship is beyond the scope of ACE.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: Presenting new strategies is beyond the scope of ACE but the presentation of this data is done to inform discussions among policy makers and researchers who can take the next step.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/1	P8, L5	**Comment:** 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.
		Response: We have modified the statement to say that NHIS could underestimate (rather than "likely underestimate"). We have added the latest data on children with one or more disorders (15%), and emphasized that (for example) many children with ADHD also have learning disabilities or other disorders. We have also expanded the text on limitations of the NHIS estimates.
2/2	P7-P8	**Comment:** 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.
		Response: The detailed documentation will be provided online for interested readers, but will not be included in the published report. Report layout and introductory text will aid readers in finding the information of most interest.
2/2	P7-P8	**Comment:** The text to describe the data set and the indicator should be no longer than one page.
		Response: We believe we have included only the necessary information. The "Overview" box is intended to give the basic information for those readers who do not wish to read through the details.
2/3	N/A Overall indicator text	**Comment:** The indicator text is good.
		Response: No response necessary.
3/1	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.

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3/1	N/A Overall indicator text	**Comment:** 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?
		Response: We have confirmed that the ADHD values shown in the figure are correct; year-to-year variability most likely represents limitation of the survey sampling design. Nevertheless, an overall pattern is apparent when looking over a number of years. For graph ND4, our determination was that the year-to-year variability in prevalence by sex is so great (more so than for ADHD, likely due to the lower prevalence) that including it in the figure would not be informative.
3/2	P18, Data Tables	**Comment:** 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).
		Response: The trend data are already shown in graphics; in these cases, the tables provide the actual values shown in the graphics for those readers who are interested. It is most practical to apply a standard table template with cells for each value of interest, rather than customizing the table design for each indicator, and revisiting this with each update. In addition, the complete table format is transparent; a more abbreviated table would prompt questions as to why data for certain stratifications are not shown. This also indicates limitations of the data sources and may inform consideration of where further data collection is necessary.
3/3	P18, Data Tables	**Comment:** The presentations are good and quite straight forward and easy to follow and think about.
		Response: No response necessary.
4/1	P20, Table ND2b and P24, Table	**Comment:** 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).
		Response: Key interpretations and comments for the indicators are presented below the graphs (in this case, Figure ND2), and are reported in a consistent manner across indicators. We would not want to speculate on reasons for differences by race/ethnicity, which are known in few cases. Regarding Table ND4b, the decision to not report survey-based estimates with relative standard error (RSE) greater than 40% is consistent across ACE3.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/2	N/A Overall indicator text	**Comment:** 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.
		Response: We have rewritten this section. Text has been added on the potential role of tobacco smoke in ADHD. Information on lead has been reorganized into a single paragraph and expanded. We chose not to include the population attributable risk.
4/2	N/A Overall indicator text	**Comment:** 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.
		Response: As noted in the comment, limitations of the research tend to be similar across many topics. Rather than discuss these separately (and redundantly) in each topic, we have presented these issues in the expanded introduction to ACE3. While it is true that parental psychopathology is not considered in most of the ADHD studies, it is not clear that this is likely to confound the relationships. This is an issue for studies of ADHD and parental smoking, because both parental smoking and child ADHD may be associated with parental psychopathology. It is less clear that parent or child environmental contaminant exposures may be associated with parental psychopathology.
4/2	N/A Overall indicator text	**Comment:** 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.
		Response: Discussions of exposure sources and regulatory and/or advisory efforts to reduce exposures to environmental toxicants have been included in relevant sections of the report (see Biomonitoring sections for lead, mercury, PCBs, PBDEs, and phthalates).
4/2	N/A Overall indicator text	**Comment:** In addition to describing the neurobehavioral endpoints, this document should also describe the status of exposure and regulations for the putative risk factors.
		Response: Discussions of regulatory and/or advisory efforts to reduce exposures to environmental toxicants have been included in relevant sections of the report (see Biomonitoring sections for lead, mercury, PCBs, PBDEs, and phthalates).

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/2	N/A Overall indicator text	**Comment:** 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.
		Response: We have added some additional information about exposure sources potentially leading to adverse neurodevelopmental outcomes. Detailed discussions of potential exposure sources are included in each toxicant's respective section (see Biomonitoring sections for lead, mercury, PCBs, PBDEs, and phthalates, etc.).
4/3	N/A Overall indicator text	**Comment:** They definitely present the trends. They do indeed inform discussions. They are significant enough to use for policy planning.
		Response: No response necessary.
5/1	P41, Methods	**Comment:** The methodology is exhaustively presented, and would be useful to the specialist, less to the generic reader.
		Response: The detailed documentation will be provided online for interested readers, but will not be included in the published report.
5/2	N/A Documentation	**Comment:** See comments above and attached PDF.
		Response: We have made the relevant changes.
5/3	N/A Documentation	**Comment:** The documentation is good. A little heavy in parts and lighter in other parts but easy to identify in relation to the text.
		Response: No response necessary.

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Health

Topic: Obesity

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P1-3 (Topic Text)	**Comment:** 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.
		Response: No response necessary.
1/2	P1-3 (Topic Text)	**Comment:** 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.
		Response: No response necessary.
1/2	P1, L9-10	**Comment:** 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).
		Response: We have revised the sentence to reflect ambiguity in the literature regarding the link between obesity and the onset of puberty and have added the suggested reference (Aksglaede 2009). However, we did not incorporate discussion of pubertal assessment in order to maintain the focus of the indicator on obesity.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	P1, L9-10	**Comment:** 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)
		Response: We have revised the sentence to reflect ambiguity in the literature regarding the link between obesity and the onset of puberty. However, we did not incorporate discussion of pubertal assessment in order to maintain the focus of the indicator on obesity.
1/2	P1, L36-38	**Comment:** 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.
		Response: *Assuming the reviewer meant Page 1, Lines 40-42.* This reference is from a peer-reviewed journal (Flegal et al. 2010) and the statement was incorporated in earlier revisions to address limitations in the association between BMI and high adiposity. The authors feel it is important to address limitations in the BMI in the topic text. While many of the statements in this version of the topic have multiple citations prior to this statement, other statements later in the topic text may only contain one peer-reviewed reference. *Assuming the reviewer meant Page 2, Lines 36-38.* The language has been modified to reflect uncertainty in how air pollution may contribute to childhood obesity.
1/2	P2, L40-46	**Comment:** 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)
		Response: The AAP policy statement was incorporated into the discussion on characteristics of the built environment that reduce obesity.
1/2	P3, L1-11	**Comment:** 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.)
		Response This section of the topic text has been expanded based on peer review comments. As part of that expansion, we have incorporated information as well as the suggested reference on the benefits of green environments.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	P1-3 (Topic Text)	**Comment:** 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.
		Response The topic text covers many factors that may contribute to obesity, but generally does not prescribe possible solutions to the increasing rates of obesity. As such, the AAP Sports Medicine citation was not included. The topic text does acknowledge that elements associated with a sedentary lifestyle may be the primary drivers of obesity rates in the US. Behavioral modifications that could contribute to reduced obesity rates are beyond the scope of ACE3.
1/3	P1-3 (Topic Text)	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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.*
		Response We have reorganized the topic text section to better distinguish between defining obesity, addressing the public health concerns, and identifying environmental connections to obesity. For consistency across indicators, we are not utilizing subheadings in the topic text.
1/3	P1, L3-10 P10-14 (References section)	**Comment:** ***Public Health Concerns over Childhood Obesity*** ***(see some suggested rewording and additional references from lines 3-10 on pg 1)*** 2. 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. 3. 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. 4. 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. 5. 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. 6. 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):201-6. 7. 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. ***(reviewers has copied sections of the text into their review and inserted the***

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		above-listed references)
		Response We incorporated many of the suggested references into the reorganized text (Davis, Lee, Li, The, and Morrison references).
1/3	P1, L13	**Comment:** 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.
		Response The use of "insulin resistance" has been revised in the text, and is not listed in the clinical parameters. "Dyslipidemia" was not used as it was felt to be too high literacy for some of the readers of the report. The language used to describe lipid levels has been changed to reflect differences in the direction of change for HDL and LDL.
1/3	P1, L8	**Comment:** —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"
		Response "Dyslipidemia" was not used as it was felt to be too high literacy for some of the readers of the report. The language used to describe lipid levels has been changed to reflect differences in the direction of change for HDL and LDL.
1/3	P1-3 (Topic Text)	**Comment:** Note, there is nothing raised about the race/ethnic disparity in the health concerns of obesity.
		Response The intent of the topic text is to describe general issues associated with obesity. A reference to difficulties in interpreting BMI in different race/ethnic groups is included.
1/3	P1-3 (Topic Text) P3, L15-16	**Comment:** ***(relative to section: Emerging Environmental Exposure Perspective for Obesity)*** 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. These factors make up OBS2 so they really require a rationale. Therefore, if rural versus urban status were added the whole Topic Intro would

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		flow better. Poverty level could be presented last: o Trend over time o Trend by race/ethnicity o Trend (or current status) by rural and urban… but trend would be very interesting o 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.
		Response Location information for NHANES participants is not available in the NHANES public files; thus it is not possible to calculate prevalence of obesity (or any other NHANES variable) for urban children vs. rural children with the data available to EPA, and would require resources beyond those available for ACE3.
1/3	P1-3 (Topic Text) P10-14 (References Section)	**Comment:** **Suggested additional references** 1. 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. 2. 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. 3. 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. 4. 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. 5. 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. 6. 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):201-6. 7. 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. 8. 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response We incorporated many of the suggested references into the reorganized text (Davis, Lee, Li, The, and Morrison references).
2/1	P4, L14-22	**Comment:** 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.
		Response CDC states that the 2000 growth charts can be considered nationally representative. The 2000 update specifically addressed the use of data on infants that didn't incorporate appropriate race/ethnic representation. A sentence has been added to the text to address this concern.
2/2	P4-9 (Indicator OBS2)	**Comment:** Three things I found unclear— 1) 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.
		Response For readability to a broad audience, we have decided not to present numerical data in the overview paragraphs for each indicator.
2/2	P4-9 (Indicator OBS2)	**Comment:** Three things I found unclear— 2) 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.
		Response Within ACE3, we use current data only when we are making demographic comparisons. The reason for using a 4 year period with NHANES data is that it provides a sufficient number of observations to make comparisons between groups while taking into account geographic variation in sampling across NHANES years.
2/2	P4-9 (Indicator OBS2)	**Comment:** Three things I found unclear— 3) 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

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		children don't really have incomes, it is their family?
		Response We believe use of "all incomes" in this figure format is necessary and appropriate, because it is referring to children within a race/ethnicity category. Use of "all children" within a race/ethnicity grouping has potential to be confusing for many readers. In addition, the title of the figure makes clear that the grouping is by "family income."
2/2	P6 (Figure)	**Comment:** 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).
		Response After consideration and in the interest of being uniform throughout ACE we have decided to retain the current design of the graph.
2/2	P6, L4-5	**Comment:** 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).
		Response The second phrase (and sub-bullet that follows) provides evidence that the trends in obesity prevalence have leveled off in recent years. Other reviewers have noted that it is important to characterize the leveling off along with describing the overall trend between 1976 and 2008.
2/2	P4-9 (Indicator OBS1 and Indicator OBS2)	**Comment:** 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.
		Response In order to maintain readability to a wide audience, we have chosen not to include p-values in the text. We have included reports of statistical significance where applicable.
2/2	P7, L10-11	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response We feel "accounting" is clearer to the audience and is a proper statistical term.
2/3	N/A	**Comment:** The text is generally clear and straightforward.
		Response No response necessary.
2/3	P4, L8	**Comment:** Suggested revisions: Line 8. Replace "These indicators" at the beginning of the sentence with OBS1 and OBS2 indicators use….."
		Response The sentence structure has been revised.
2/3	P4, L15	**Comment:** 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….
		Response Changes were made to reflect sequence of events to identify obese children.
3/1	P6-9	**Comment:** 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.
		Response: We are not including sample size in the main figures, but have added sample sizes to the data tables in Appendix A of the report.
3/2	P8-9	**Comment:** Overall, I really like the tables, and I could see how I would use them.
		Response: No response necessary.
3/2	P8-9	**Comment:** 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

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		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.)
		Response: We have decided to refrain from including p-values in the table in order to maintain readability among audiences with varied levels of statistical understanding. We trust that researchers would go to the supplemental material for a more in-depth understanding of how an indicator was generated, and the accompanying statistical analyses. We have also included reports of statistical significance where applicable.
3/2	P8-9	**Comment:** 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.
		Response: We only indicate statistical significance for those comparisons where the resulting p-value is < 0.05.
3/2	P4-9 (Indicator OBS1 and Indicator OBS2)	**Comment:** 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.
		Response: See responses to above comments.
3/2	P4-9 (Indicator OBS1 and Indicator OBS2)	**Comment:** 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.
		Response: Within ACE3, we use current data only when we are making demographic comparisons. The reason for using a 4 year period with NHANES data is that it provides a sufficient number of observations to make comparisons between groups while taking into account geographic variation in sampling across NHANES years.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/3	P4-9 (Indicator OBS1 and Indicator OBS2)	**Comment:** 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.
		Response: We feel that the order of the text/figures/tables is consistent, and does not prevent understanding of the presented material.
3/3	P6-9	**Comment:** **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.
		Response: The layout of the figure has been changed and now has All Races/Ethnicities at the top.
3/3	P6 (Figure) P6, L8 P6, L5	**Comment:** **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. o 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.*
		Response: The second phrase (and sub-bullet that follows) provide evidence that the trends in obesity prevalence have leveled off in recent years. Other reviewers have noted that it is important to characterize that leveling off along with describing the overall trend between 1976 and 2008. Therefore, we have not separated out the

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		recent trend in childhood obesity data. However, we added reference in the sub-bullet to the age groups. For statistical testing, we used the same age groups shown in the data table, i.e. 2-5, 6-10 and 11-15, and 16-17. There was an error in the table of p-values, where a combined group of 11-17 years was shown; we have corrected this to provide the p-values for age groups 11-15 and 16-17.
3/3	P7 (Figure)	**Comment:** **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
		Response: For consistency across indicators, we have defined the race/ethnicity groups within the indicator text. The layout of the figure has also been changed and now has All Races/Ethnicities at the top.
3/3	P7 (Figure)	**Comment:** **Figure 2** is clear and attractive. (see note above: ALL category should be at the top of figure) ***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).*
		Response: Changes have been made to clarify "other" race/ethnic category.
3/3	P7, L9-14	**Comment:** ***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. o 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*

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		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.
		Response: A caveat was added to the existing structure of the bullet, but overall structure was retained (no sub bullet added). Sample sizes for each race/ethnic group have been added to the data tables.
4/1	P4-9 (Indicator OBS1 and Indicator OBS2)	**Comment:** 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.
		Response: No response necessary.
4/2	N/A (Overall Text)	**Comment:** 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 present 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).
		Response: The goal of the indicator is to introduce the idea of thinking of environmental contributors to obesity to a wider audience. Our intent was to summarize the trends in obesity, and highlight research that points to an environmental connection to the problem. Much of this research is only beginning to mature. It is not the intent of ACE to explicitly link trends in a health indicator to trends in exposure-related indicators. Epidemiological research is the appropriate way to look for those associations. Through these summaries ACE indicators and accompanying text may suggest important directions for children's environmental health research. Introductory text has been added to the ACE3 report discussing

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		these issues, which apply across the topics in the report.
4/2	N/A (Overall Text)	**Comment:** 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.
		Response: No response necessary.
4/2	P4-9 (Indicator OBS1 and Indicator OBS2)	**Comment:** Again, I agree that you have provided some great indicators. My above suggestion is still relevant for this question as well.
		Response: The goal of the indicator is to introduce the idea of thinking of environmental contributors to obesity to a wider audience. Our intent was to summarize the trends in obesity, and provide brief descriptions of research that point to an environmental connection to the problem. Much of this research is only beginning to mature. It is not the intent of ACE to explicitly link trends in a health indicator to trends in exposure-related indicators. Epidemiological research is the appropriate way to look for those associations. Through these summaries ACE indicators and accompanying text may suggest important directions for children's environmental health research. We have edited the phrasing of the principal objectives and inserted additional text in the report introduction to clarify the scope and intent of ACE3.
4/3	P4-9 (Indicator OBS1)	**Comment:** OBS1 is the most basic indicator. It is very appropriate to present here with respect to all of the goals outlined for ACE.
		Response: No response necessary.
4/3	P4-9 (Indicator OBS2)	**Comment:** 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.
		Response: The introduction provides background on environmental links to obesity. As with other indicators in ACE3, we provide race/ethnic/income break-outs as a matter of policy so that readers can identify disparities across a number of topics in environmental health. This is also described in the overall introduction to ACE.
4/3	P4-9 (Indicator OBS2)	**Comment:** 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.

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		My recommendation is for rural vs. urban sub-analysis (discussed above)
		Response: Location information for NHANES participants is not available in the NHANES public files; thus it is not possible to calculate prevalence of obesity (or any other NHANES variable) for urban children vs. rural children with the data available to EPA, and would require resources beyond those available for ACE3. However, we have expanded the built environment section of the topic text to highlight some of the differences in urban and rural communities. We have also added a sentence to the end of the background text to highlight the complexity of the obesity epidemic, and what these indicators provide.
4/3	P1-3 (Topic Text)	**Comment:** 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.
		Response: No response necessary.
4/3	P1-3 (Topic Text)	**Comment:** An interesting (framing) topic that is not raised is the issue about obesity negating the health benefits related to smoking cessation. One EPA issue tackled, only to be replaced with another, potentially more potent one.
		Response: Discussing any potential interplay between obesity and smoking cessation (among children 2-17) is beyond the scope of this indicator.
4/3	P1-3 (Topic Text)	**Comment:** 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.
		Response: Location information for NHANES participants is not available in the NHANES public files; thus it is not possible to calculate prevalence of obesity (or any other NHANES variable) for urban children vs. rural children with the data available to EPA, and would require resources beyond those available for ACE3. However, we have expanded the built environment section of the topic text to highlight some of the differences in urban and rural communities. We have also added a sentence to the end of the background text to highlight the complexity of the obesity epidemic, including the various interacting factors, and what these indicators provide.

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4/3	P1-3 (Topic Text)	**Comment:** 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.
		Response: We have added sentences to the end of the background text to highlight the complexity of the obesity epidemic, and what these indicators provide.
5/1	N/A (Overall Text)	**Comment:** Yes, the documentation appears to be complete and transparent.
		Response: No response necessary.
5/2	P15 (Table, Question 5)	**Comment:** Overall I think it is very complete. A few comments: 1) 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 nowhere 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.
		Response: The metadata are intended to provide information relevant to a data source, and thus may include information not directly relevant to indicators for a specific topic. Since NHANES is also the data source for the ACE3 biomonitoring indicators, the metadata include information relevant to biomonitoring. "Body Measurements," used in the generation of this indicator, are included in the description of data available from this database. As such, no change was made.
5/2	P15 (Table, Question 7)	**Comment:** Overall I think it is very complete. A few comments: 2) 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.
		Response: The next question in the metadata provides a link where you can get instructions where to get the data. The methods text identifies the specific files and variables necessary for calculation of the indicators.
5/2	P16 (Table, Question 5)	**Comment:** Overall I think it is very complete. A few comments: 3) P.16—5th 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

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		this indicator would be the question: Are the methods used to measure weight and height consistent throughout the lifespan of NHANES?
		Response: A sentence was added to indicate that measurements are comparable across time and space.
5/2	P17 (Methods)	**Comment:** 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.
		Response: Generally, we feel the content suggested by the reviewer for inclusion in the published report is too detailed for the general public.
5/2	P20, L5-8 (Methods)	**Comment:** 1) 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.
		Response: We feel this information requested for inclusion in the published report by the peer reviewer is too detailed for the general public.
5/2	P20, L34-36 (Methods)	**Comment:** 2) 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.
		Response: We feel this information is too detailed for the general public to include in the indicator text.
5/2	P25, L3-16 (Methods)	**Comment:** 3) 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.
		Response: We feel this information is too detailed for the general public to include in the indicator text. While the information in the published report may be too simplified to a professional audience, we provide further information that is available to anyone who wishes more detailed information regarding indicator calculation or statistical analysis.

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5/2	P25, L16 (Methods)	**Comment:** 4) 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).
		Response: We have added notes and explanations that there is no adjustment for multiple comparisons. There is precedent for this approach in CDC/NCHS documents, e.g. the annual Health Summary Statistics for U.S. Children reports presenting data from the National Health Interview Survey. Multiple comparisons can be implemented in various ways (e.g., alternate definitions of the extent of a comparison group). Since we provide the p-values, interested readers will be able to apply their own adjustments, e.g., by using a simple Bonferroni probability approach. Although we report large numbers of p-values in some cases, we did not use all these p-values to make our reporting decisions; instead we used the p-values to determine whether some of the patterns that we had already found were expected to have occurred "by chance." We have also streamlined the p-value table to reduce the number of comparisons by race/ethnicity and income. We have made the decision not to adjust for multiple comparisons as we feel it is important to identify all potentially important differences, and adjustment for multiple comparisons will increase the challenge in conveying findings of statistical testing to non-technical audiences. We clearly explain in the text that this may increase the probability that some of these differences may actually have occurred randomly. Bonferroni adjusted p-values are relatively easy to compute but tend to be overly conservative since they do not account for possible dependence between different tests.
5/2	P10-14 (References section)	**Comment:** 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

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		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.
		Response: Some of the suggested references were included in the revised text (AAP, Winterbottom, Aksglaede), along with other references that provide updated information on childhood obesity. It was not felt that the other references added significantly to the discussion provided in the topic text. The text is not intended to be comprehensive, but rather to identify key issues of interest.
5/3	P10-14 (References section)	**Comment:** See topic text section for additional suggested references.
		Response: No response necessary.
5/3	N/A (Overall Text)	**Comment:** The documentation is well done and appropriate for the audience, esp. given that it will be in an appendix format.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: No response necessary.
5/3	P17, L27-29 (Methods)	**Comment:** *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.*
		Response: Sample sizes have been added to each race/ethnicity data table.
5/3	P23, L10-29 (Methods)	**Comment:** *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.*
		Response: We believe the text is clear in context. "Body mass index" is used for reference to the obesity variable.
5/3	P23, L27 (Methods)	**Comment:** *Calculations of Indicator* **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.
		Response: This was corrected.
5/3	P8-9 (Tables)	**Comment:** 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.
		Response: We feel that the order of the text/figures/tables is consistent, and does not prevent understanding of the presented material.
General/3	N/A (Overall Text)	**Comment:** 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.

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		Response: No response necessary.
General/3	N/A (Overall Text)	**Comment:** 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.,1. 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.
		Response: Location information for NHANES participants is not available in the NHANES public files; thus it is not possible to calculate prevalence of obesity (or any other NHANES variable) for urban children vs. rural children with the data available to EPA, and would require resources beyond those available for ACE3. However, we have expanded the built environment section of the topic text to highlight some of the differences in urban and rural communities. We have also added a sentence to the end of the background text to highlight the complexity of the obesity epidemic, and what these indicators provide.

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Section: Health

Topic: Adverse Birth Outcomes

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	N/A Overall topic text	**Comment:** 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.
		Response: We added post-term birth to the list of items in paragraph 2 that we do not address in the text.
1/1	N/A Overall topic text	**Comment:** 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.
		Response: It is beyond the scope of ACE3 to discuss the mechanisms of how exposures may cause adverse health outcomes.
1/1	N/A Overall topic text	**Comment:** 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.

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		Response: Text was added to the end of the third paragraph.
1/1	P2, L16	**Comment:** 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.
		Response: The comment may be true for birth defects; however, there are still major questions that remain about which trimester is the most important for preterm and LBW. In addition, the critical exposure window is likely to differ for various exposures and modes of action. We have decided not to mention critical periods until more conclusive evidence is available.
1/1	N/A Overall topic text	**Comment:** 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.
		Response: We address general advantages and limitations of epidemiological studies in the report introduction.
1/1	Overall topic text	**Comment:** 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.
		Response: "Rate" seems to be the term most commonly used for preterm births as a percentage of all births and can be used here since the measure is per one year. While percentage is typically a prevalence, it is common to say "birth rate" and implies the rate per year. We changed the use of "prevalence" to "rate" where it occurred.
1/2	P1, L3-L14	**Comment:** 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.

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		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.
		Response: We revised the paragraph to improve clarity.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: We feel that mentioning high birth weight is appropriate for this brief list without also listing LGA, which is a related but distinct outcome.
1/2	P1, L20	**Comment:** 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.
		Response: We added a sentence in the first paragraph that discusses infants born at term with low birth weight.
1/2	P1, L20	**Comment:** Since preterm infants are a subset of LBWs, I tried to use this way of thinking about it in the subsequent paragraphs.
		Response: No response necessary.
1/2	P1, L20	**Comment:** Page 1, Line 20: "Preterm and low birth weight infants" should be changed to "LBWs including preterm infants…"
		Response: We believe the current text is clear and appropriate.
1/2	P1, L20	**Comment:** 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.
		Response: We believe the current text is clear and appropriate.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	P1	**Comment:** Would it be useful to add a line or two about the complications of term low birth weight infants since that is the indicator that is being used.
		Response: Infants born at term with low birth weight are not a group that shares certain distinct health outcomes. They have many of the same health outcomes as low birth weight infants born early, because their organ systems are immature. They are likely to be growth restricted, but that can occur at any gestational age. We did not address health effects of term low birth weight infants separately; however, the indicator text was revised to convey what can be learned from tracking this birth outcome.
1/2	P1, L34	**Comment:** 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.
		Response: The text was revised to include "through adulthood" but retained use of "child" instead of "infant."
1/2	P4, L24	**Comment:** 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 included. How preterm infants are defined (22 – 37 weeks gestation?) or how they are not defined at the lower limit.
		Response: There is no lower gestational boundary for preterm birth. Any live birth, regardless of how early, is considered a preterm birth. We have added "live" to the definition of preterm birth to make this clear.
1/2	P4, L24	**Comment:** 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?
		Response: There is no lower gestational boundary for preterm birth. Any live birth, regardless of how early, is considered a preterm birth. We have added "live" to the definition of preterm birth to make this clear.
1/2	P24, L15	**Comment:** 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.
		Response: We added text on how resuscitation of increasingly early infants might affect the rate of preterm birth.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	N/A Overall topic text	**Comment:** 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.
		Response: We discuss proximity to traffic density and cite the conclusion of the 2010 Panel on the Health Effects of Traffic-Related Air Pollution regarding preterm birth and low birth weight. Original studies in Manhattan found an association between chlorpyrifos and growth restriction, but a recent study by Barr et al. was not able to replicate it, therefore we decided not to include this association based on the current level of knowledge.
1/2	P1, L33	**Comment:** Page 1, line 33. The word "health" should be deleted.
		Response: We believe "health" is useful and have retained the current phrasing.
1/2	P1, L40	**Comment:** Page 1, line 40. I would change "increases" to "previous increasing preterm birth".
		Response: The text has been revised to increase clarity and readability.
1/2	P2, L2	**Comment:** Page 2.line 2. Change "preterm birth and low birthweight" to "preterm birth and growth restriction"
		Response: This is true but everywhere else we refer to "preterm birth and low birth weight" because these are the outcomes that are typically measured so we have retained the current phrasing.
1/2	P2, L2	**Comment:** Page 2 line 2. Delete the word "fetal"
		Response: The text has been revised.
1/2	P2, L24	**Comment:** Page 2, line 24. Change "that concluded" to "concluded that"
		Response: The text has been revised.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	P3, L5	**Comment:** Page 3, line 5. Define PFOS and PFOA
		Response: The text has been revised.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: No response necessary.
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: The National Center for Health Statistics uses 'rate' fairly routinely to describe the percentage of births that are preterm or low birth weight and "birth rate" is commonly used, so we have made changes to use this term consistently While percentage is typically a prevalence, this measure is per one year and implies the rate per the year in question.
2/2	N/A Overall topic text	**Comment:** Be clearer in Introductory paragraphs that very low birth weight as discussed there includes preterm infants, as opposed to the indicator where only term low birth weight infants are used. This is nicely discussed in the Indicator section.
		Response: We say "Infants may be born with a low birth weight because they were born early, because their growth while in utero has been restricted, or both." In addition, we added further description of infants born at term with low birth weight.
2/2	N/A Overall indicator text	**Comment:** 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 hospital chooses to fill out the birth certificate?

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: There is no lower gestational boundary for preterm birth. Any live birth, regardless of how early, is considered a preterm birth. We have added "live" to the definition of preterm birth to make this clear.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.
2/3	P5, L20-etc (Statistical Testing Section)	**Comment:** 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.
		Response: Although the number of births is not subject to sampling error, when used for analytic purposes (that is, the comparison of numbers, rates, and percentages over time, for different areas, or between different groups), the number of events that actually occurred can be thought of as one outcome in a large series of possible results that could have occurred under the same (or similar) circumstances. When considered in this way, the number of births is subject to random variation and a probable range of values can be estimated from the actual figures, according to certain statistical assumptions. We also discuss the role of statistical testing and caution that a non-statistically significant difference does not necessarily negate the importance.
3/1	N/A Overall presentation of indicator	**Comment:** The indicator presentation is effective as it simultaneously shows the time trends and the differences by racial/ethnic groups in the two outcomes. The text and descriptions are very clear and understandable to a broad audience.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: No response necessary.
3/1	P6, L1	**Comment:** 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%.
		Response: Changing the y-axis would distort the representation of differences by race/ethnicity.
3/1	N/A - Figures	**Comment:** 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?
		Response: This is outside the scope of ACE3; we have added text to the report introduction clarifying the scope and noting that comparing indicators is not the best way to evaluate possible associations.
3/1	P5, L 19-43	**Comment:** Could the data tables include a p-value or indicator of trends that were significant over time?
		Response: For readability, we have decided not to include p-values in the data tables, but we provide them in the documentation.
3/2	N/A Overall presentation of indicator	**Comment:** Aside from my edits suggested above, I think it was nicely written and quite clear. Define preterm birth!
		Response: Please see the above response.
3/3	P6, P7, P8 & P9 (Statistical Notes)	**Comment:** The "statistical" notes should be removed, per the comment in #2 regarding statistical significance.
		Response: Please see the above response regarding statistical testing of birth outcomes indicators.
3/3	P8, L3-L5	**Comment:** 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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: We chose to characterize other rates that changed by the same relative amount as staying constant, so to be consistent we characterized this one the same way.
4/1	P10-P11, Tables Birth1, Birth1a, and Birth1b	**Comment:** 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 has 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 prevalences 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?
		Response: In general, an interpretation of trends is beyond the scope of this report. We have edited the phrasing of the principal objectives and added additional text to the report introduction to clarify the intent and scope of ACE3. Regarding comparing to 1968, changes in how gestational age is estimated have occurred since then and comparisons with today's rates could be misleading.
4/1	P11-P13, Tables Birth2, Birth2a, Birth2b	**Comment:** Birth2. Birthweight 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 birthweight. It could be working as an intermediary variable and it could be introducing bias in our estimates.
		Response: We are aware of this ongoing debate but feel that as a surveillance tool, term low birth weight is a proper and commonly used way to monitor trends in growth restriction without the confounding issue of gestational age.
4/1	P10-P13, data tables	**Comment:** 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.
		Response: A discussion of how the data could be improved is beyond the scope of this report; we instead focus more on limitations of the data pertinent to the particular indicator presented.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
4/1	P10-P13, data tables	**Comment:** 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.
		Response: This is beyond the scope of the data used for these indicators and beyond the scope of this report.
4/2	N/A Overall text	**Comment:** 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 birthweight 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 gestaional age is determined? Sometimes obs will use an early ultrasound rather than LMP to determine gestational age.
		Response: There is no lower gestational boundary for preterm birth. Any live birth, regardless of how early, is considered a preterm birth. We have added "live" to the definition of preterm birth to make this clear. In addition, we added an explanation of changes over time in the way gestational age has been determined and how this might affect the rate of preterm birth.
4/3	N/A Overall indicator text	**Comment:** Both of the indicators of adverse birth outcomes meet the objectives as described above.
		Response: No response necessary.
5/1	P10, Data Tables	**Comment:** 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.
		Response: We have added percentages to the table.
5/1	P29, L4-L6	**Comment:** 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?
		Response: There is no restriction. It is all live births with a stated gestation period. For example, in 2007 there was no gestational age reported for about 7000 births; these births were excluded from the denominator.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
5/1	P29, L11-L13	**Comment:** Page 29, line 11-13: Similarly, how was the birth weight restricted for this analysis?
		Response: There is no restriction. It is all live births with a stated gestation period and birth weight.
5/1	P30, tables	**Comment:** 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.
		Response: The tables of p-values are meant to be a companion to the indicator data tables (such as Table Birth 1). The data tables indicate which group has the greater rate.
5/2	N/A Overall text	**Comment:** 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?
		Response: Please see the above response.
5/2	N/A overall text	**Comment:** Yes
		Response: No response necessary.

Special Features

Peer Review of February 2011 Draft ACE3 Indicator Documents
Peer Review Comments and EPA Responses

Section: Supplementary Topics

Topic: Birth Defects

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	N/A Overall Topic text	**Comment:** 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.
1/1		**Response:** No response necessary.
1/1	P1, L13	**Comment:** 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.
		Response: Estimates of economic impact of birth defects in the US are out of date. The last estimation using 1992 data calculated an impact of 8 billion annually (CDC 1995. Economic Costs of Birth Defects and Cerebral Palsy -- United States, 1992.). By adjusting to 2010$, an estimate could be made of around 12 billion dollars. However, this estimate is almost 20 years old and may not reflect the current national prevalence of birth defects. Text regarding the prevalence of birth defects by race/ethnicity has been added to the bulleted text below the indicator graph. In addition, a table containing the results of the statistical testing of birth defect rates between pairs of race/ethnicity groups (for the years 2005 to 2007) has been added to the Methods section.
1/1	N/A Overall text	**Comment:** 1-3. The relevant literature appears to be summarized appropriately.
		Response: No response necessary.
1/1	N/A Documentation	**Comment:** 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).
		Response: See response above.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/1	P1, L18 & L19	**Comment:** 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"
		Response: The suggested wording was added.
1/2	N/A Overall Topic Text	**Comment:** 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.
		Response: See response below.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: A paragraph on findings of birth defects and residential proximity to hazardous sites has been added.
1/2	N/A Overall topic text	**Comment:** 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).
		Response: As summarized in EPA's 2011 Draft Integrated Science Assessment for lead, earlier research has reported small associations between reported maternal occupational lead exposure and neural tube defects (Bound et al., 1997; Irgens et al., 1998), however, recent epidemiological studies relying on maternal measures of blood lead have not found an association (Brender et al., 2006; Zeyrek et al., 2009). Therefore, because of the limited findings, a discussion of the potential association of lead exposures and birth defects was not added to the document.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
1/2	N/A Overall topic text	**Comment:** 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.
		Response: A recent review by CDC (Manassaram et al., 2006) concluded that epidemiologic studies evaluating nitrates in drinking water and incidence of birth defects have been equivocal. Thus, nitrates were not discussed in this text.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: Human epidemiological studies were preferred over studies in animals due to rarity of birth defects and due to the difficulty extrapolating from high dose animal studies to human exposure levels. Text has been added to the report introduction discussing the greater focus on the epidemiological literature.
1/2	N/A Overall topic text	**Comment:** 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.
		Response: No response necessary.
1/2	N/A Overall topic text	**Comment:** 1.5. The organization of this section is 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		• 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: o Par 4: Epi studies of BDs associated with a variety of exposures o Par 5: Epi studies of BDs associated with solvents
		Response: The text was reorganized to provide greater clarity.
1/2	P1, L1	**Comment:** 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.
		Response: The text was edited as suggested.
1/2	P1, L19-L21	**Comment:** (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.
		Response: "Some" was inserted into the phrase as suggested. The remainder of the statement was rephrased based on the suggestion of Review 1 (see above).
1/3	N/A Overall topic text	**Comment:** 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

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		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.
		Response: We agree that birth defects may result in preterm birth. However, the CDC National Center for Health Statistics (NCHS) classifies birth defects as the primary cause of infant death ahead of low birth weight and prematurity. Therefore, this text has not been modified.
1/3	N/A Overall topic text	**Comment:** 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).
		Response: No response necessary.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: No response necessary.
1/3	N/A Overall topic text	**Comment:** 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.
		Response: No response necessary.
2/1	P4, L17	**Comment:** 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.
		Response: Text regarding the prevalence of birth defects by race/ethnicity has been added to the bulleted text below the indicator graph. In addition, a table containing the results of the statistical testing of birth defect rates between pairs of race/ethnicity groups (for the years 2005 to 2007) has been added to the Methods section.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/1	P4, L16-L17	**Comment:** 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."
		Response: These changes have been made.
2/1	P4, L16-L17	**Comment:** 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.
		Response: The text has been clarified.
2/2	N/A Overall indicator text	**Comment:** 2.1. Yes.
		Response: No response necessary.
2/2	P4, L5	**Comment:** 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.
		Response: This change has been made.
2/2	P4, L5 (and subsequent occurrences)	**Comment:** (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.
		Response: We believe that describing the Texas Birth Defects Registry as a monitoring program helps emphasize the active surveillance component of this program.
2/2	P4, L6, L7 and P4, L14	**Comment:** (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.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
		Response: The text has been revised.
2/2	P4, L6, L7 and P4, L14	**Comment:** (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.
		Response: The text has been revised.
2/2	P5, L5	**Comment:** (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.
		Response: This clarification is not deemed necessary.
2/2	P5, L6	**Comment:** (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.
		Response: We made alternate revisions to this text, based on consultation with statisticians and consistent with phrasing used elsewhere in the report. Based on consultation with statisticians, we chose not to replace "probability" with "likelihood."
2/3	N/A Overall indicator text	**Comment:** The indicators are well described.
		Response: No response necessary.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
2/3	N/A Overall indicator text	**Comment:** The rationale for applying statistical testing seems appropriate given the evidence of underreporting.
		Response: No response necessary.
3/1	N/A Overall data presentation	**Comment:** 3-1. Yes, in general, the figures, tables and text are appropriate.
		Response: No response necessary.
3/1	P5 or P6 (addition)	**Comment:** 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.
		Response: We feel that mentioning specific statistical tests in the summary text will be more information than most readers need to understand why statistical testing was done and what it can tell you. We also provide the source of data at the bottom of the figure.
3/1	P7, Table S5a	**Comment:** 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.
		Response: See response regarding race/ethnicity table and text above.
3/1	N/A Overall data	**Comment:** 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.
		Response: No response necessary.

Charge Question/ Reviewer #	Page/Line	Peer Review Comments and EPA Response
3/1	N/A Figures and Tables	**Comment:** 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
		Response: The orientation of the x-axis labels has been modified as suggested.
3/1	N/A Figures and Tables	**Comment:** I would change the width of the columns in the tables such that each row only uses one line
		Response: This change has been made.
3/2	Overall data text, and P7, Table S5a	**Comment:** 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.
		Response: Text regarding the prevalence of birth defects by race/ethnicity has been added to the bulleted text below the indicator graph. We have also provided rationale for these comparisons in the report introduction.
3/2	P7, Table S5a	**Comment:** 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.
		Response: A decision was made not to include p values in the data tables generally for this report. However, the statistical testing for trends is included in the discussion of the methods which will be posted online.
3/2	P7, Table S5a	**Comment:** 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.
		Response: No change needed.
3/2	N/A	**Comment:** 3.3 No suggestions for improvement; good job.
		Response: No response necessary.

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3/2	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.
3/2	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.
3/3	N/A Overall data presentation	**Comment:** The graphs are clear and illustrative – a challenge given the very large number of categories of birth defects.
		Response: No response necessary.
4/1	N/A Overall indicator text	**Comment:** 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.
		Response: No response necessary.
4/1	N/A Overall text	**Comment:** 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.
		Response: As stated in the indicator text, there is currently no national active surveillance system for birth defects. A portion of birth defects observed shortly after birth are recorded on birth certificates, however comparisons of birth defects recorded on birth certificates and birth defect registries have indicated that typically, less than half of birth defects are recorded on birth certificates (Boulet et al., 2011; Marengo 2010). In addition, less severe birth defects are often identified after discharge from the hospital and would not be captured on birth certificates. Sole reliance on national birth certificate data would grossly underestimate the prevalence of birth

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		defects. Some additional information on national estimates of birth defect prevalence rates has been added in the section "Comparing the Texas Birth Defects Registry with Other Data Sources".
4/1	N/A Overall text	**Comment:** 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.
		Response: No response necessary.
4/1	N/A Overall text	**Comment:** 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.
		Response: The inclusion of environmental data is beyond the scope of this indicator; however, additional text regarding prevalence of birth defects and possible relationships to proximity to contaminated lands was added to the document.
4/2	N/A Overall text	**Comment:** 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.
		Response: No response necessary.
4/2	N/A Overall text	**Comment:** 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

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		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: 1. (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. 2. (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).
		Response: The following text (with citations) was added in the indicator text (under "Data Presented in the Indicator"): "Trends in the rates of birth defects may be influenced by differences in clinical practice. For example, increasing trends in the prevalence of some birth defects could represent more accurate recording of birth defects and/or better diagnosis of subtle defects due to the use of more sensitive examinations and technology (CDC 2008; Langlois and Scheuele 2007; Langlois, Marengo and Canfield 2001; Botto et al., 2001)." We will consider presenting temporal trends for specific birth defects instead of broad anatomical groupings of defects for future editions of ACE.
4/3	N/A Overall indicator text	**Comment:** 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.
		Response: Information on maternal obesity was not available in the Texas data set; therefore, this additional analysis was not possible.
5/1	N/A Overall documentation	**Comment:** 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.
		Response: No response necessary.

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5/1	P3, L13	**Comment:** There is an extra period on line 13 of page 3
		Response: This has been corrected.
5/2	P12, Metadata	**Comment:** 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.
		Response: This is correct.
5/2	P12, Metadata	**Comment:** 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."
		Response: The suggested text was added.

5/2	P12, Metadata	**Comment:**
		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.

		Response: The suggested text was added.
5/2	P12, Metadata	**Comment:** Suggest changing "Records in the birth defects registry WERE matched…" to "Records in the birth defects registry ARE matched…"
		Response: This change has been made.

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5/2	P12, Metadata	**Comment:** 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."
		Response: This change has been made.
5/2	P12, Metadata	**Comment:** 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.
		Response: This change has been made.
5/2	P12, Metadata	**Comment:** 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".
		Response: This change has been made.
5/2	P12, Metadata	**Comment:** Change "mother's race/ethnicity" to "mother's race/ethnicity, mother's age group, or infant gender".
		Response: This change has been made.

5/2	P12, Metadata	**Comment:**
		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).

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		Response: The level of detail for county is not considered necessary for this report.
5/2	P15, Methods	**Comment:** 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."
		Response: The sentence was revised as suggested.
5/2	P15, Methods	**Comment:** Methods (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).
		Response: The equation for calculating birth defect prevalence rates has been corrected. The number of cases includes all reported cases including live births, stillbirth, miscarriage, and pregnancy terminations.
5/2	P15, Methods	**Comment:** Methods (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

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		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).
		Response: The method has been revised to use Poisson regression (adjusted for overdispersion) instead of a logistic regression, and all p-values have been re-calculated. In the previous logistic regression, cases were removed from the denominator (as suggested in this comment), as stated in the methods: "Using a logistic regression model, the logarithm of the odds that a given child has a particular type of birth defect is assumed to be the sum of explanatory terms for the three-year period and the mother's race/ethnicity. The odds that a given child has this type of birth defect is the probability that the child has this birth defect divided by the probability that the child does not have this birth defect."
5/2	P15, Methods	**Comment:** Methods (Statistical Comparisons): 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.
		Response: The sentence was revised as suggested.
5/2	P15, Methods	**Comment:** Methods (Statistical Comparisons): Although the wording of the Statistical Comparisons part is high level, I think that is appropriate for anyone who is interested in reading it.
		Response: No response necessary.
	P8, References	**Comment:** **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.

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		• 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.
		Response: Additional references will be incorporated where relevant; some of these references have not been added for reasons discussed in responses above.
5/3	N/A Overall text	**Comment:** Yes.
		Response: No response necessary.

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Section: Supplementary Topics

Topic: Contaminants in Schools and Child Care Facilities

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1/1	P16, References	**Comment:** 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
		Response: These additional citations have been reviewed and incorporated into the text as relevant. In particular: • Sexton et al. (2000): Cited on Pg.2 with the text "…certain groups of children are especially susceptible to such exposures." • Mir et al. (2010): Cited on Pg.6 with the text: "Strategies such as restrictions on the use of pesticides and adoption of IPM have been shown to be effective at reducing human exposure."

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		• Wilson et al. (2004): Cited on Pg.9 with the paragraph describing CTEPP study design/methodology: "The CTEPP study investigated the potential exposures of 257 preschool children, ages 1.5 to 5 years, and their primary adult child care providers to more than 50 anthropogenic chemicals, including pesticides, PAHs, PCBs, phthalates, and phenols. This regional study was conducted by EPA in North Carolina and Ohio in 2000–2001. Environmental (indoor and outdoor air, carpet house dust, and soil) and personal (hand wipe, solid and liquid food, drinking water, and urine) samples were collected for each child in the study at home and at the child care center over a 48-hour period." • Wilson et al. (2001): Cited on Pg.1 with text: "The behaviors of very young children (e.g., crawling, hand-to-mouth activity) increase their exposure to contaminants in dust, on surfaces, or in toys and other objects." • Lambrinidou et al. (2010): Cited on Pg.2 in addition to the other references about drinking water. • Chiang et al. (2008): Although this article makes some important contributions to investigating arsenic and lead exposure in Chinese schoolchildren, we do not believe that there is direct relevance to the text in this section that is not covered by the references already cited. • Newman (2010): Cited on Pg.3 with the text: "PCBs are also found in caulk and paint used in building structures before 1980, which may mobilize into the surroundings from removal efforts, natural weathering, or deterioration over time, and contribute significantly to PCB levels in indoor air and dust in schools." • Herrick (2010): Cited on Pg.3 with the text: "PCBs are also found in caulk and paint used in building structures before 1980…" • Herrick et al. (2007): Cited on Pg.3 with the modified text: "PCBs…may mobilize into the surroundings from removal efforts, natural weathering, or deterioration over time, and contribute significantly to PCB levels in indoor air and dust in schools." • Peper et al. (2005): Although this article makes an important contribution in exploring personal exposure levels to PCBs in school buildings, the age range of subjects included is 37-61 years. Since children's exposure levels and health outcomes were not considered in this study, we have decided not to include it as a reference in this section.
1/1	N/A Overall text	**Comment:** 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.

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		Response: After a careful review of the NIOSH/EPA SENSOR database, we have decided that in its current state we cannot incorporate this data within this particular section. Although when reporting pesticide measurements, states have an option to categorize them as occurring in schools or child care facilities, states are not required to report this information and furthermore, stratification of the data set by this particular measurements type is not available for the data set online. Due to the nature of this section which focuses on children's exposure in schools and child care facility environments, we believe that this limitation hinders the ability to incorporate the data from SENSOR into that of this particular section.
1/1	N/A Overall text	**Comment:** 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.
		Response: The measure based on data from the California study specifically reports the amount of pesticides applied to schools in California, and therefore we consider it of minimal concern that agricultural pesticides are not measured. The other measures in this section are based on data sets that do measure levels of agricultural pesticides found in schools (such as diazinon).
1/2	N/A Overall text	**Comment:** 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.
		Response: We agree that lead is an important contaminant to consider as an indicator for children's health. The ACE3 report has extensively covered lead and reported on indicators for children's exposure to lead in other sections (i.e., Biomonitoring, Environments and Contaminants). Therefore, we have not reported on lead as an indicator in this section. However, we have modified the lead section in this topic to address additional surveillance statistics on lead's presence in schools and child care facilities specifically. We also agree with the concern that contaminants in schools and child care facilities lack systematic monitoring/collection and are not available nationwide. This concern is addressed in this section, such as with the text: "Data on school or child care environmental exposures are not systematically collected" and this is clearly an area that requires additional attention.
1/2	N/A Overall text	**Comment:** 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

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		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.
		Response: In following with the organization of other sections of this report, where the presentation of each topic begins with background text for the topic and its indicators, followed by a figure that presents the data for each indicator, we have decided not to incorporate an additional figure/table into the background text for this section.
1/2	N/A Overall text	**Comment:** 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.
		Response: We agree that lead is an important contaminant to consider as an indicator for children's health. The ACE3 report has extensively covered lead and reported on indicators for children's potential exposure to lead in other sections (Biomonitoring, Environments and Contaminants). Therefore, we have not reported on lead as an indicator in this section. However, we have modified the lead section in this topic to address additional surveillance statistics on lead's presence in schools and child care facilities specifically.
1/3	N/A Overall text	**Comment:** The topic text is very choppy, hard to follow and written at a level way too 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.
		Response: We have made substantive changes to the organization, language, flow, and clarity of this section based on this comment as well as later comments by this reviewer to increase the readability for our target audience.
1/3	P1, L3-L10	**Comments:** 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.
		Response: We have revised the introductory paragraph to read: "The indoor and outdoor environmental quality of schools and child care facilities plays an important role in affecting children's health and academic performance. Depending on the type of facility and its particular characteristics (i.e., age, usage, and maintenance), children may be exposed to contaminants from a variety of indoor and outdoor

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		sources. Potential indoor exposure sources include building materials and furnishings (such as paint, treated wood, furniture, carpet, and fabrics), products used for building maintenance (such as cleaning products and pesticides), and products used for hobbies, science projects, and arts and crafts projects or within the learning environment (such as paint, markers and correction fluid). Potential outdoor exposure sources include air pollution from nearby traffic and industry. In addition to these specific exposures, children may also experience unsatisfactory environmental conditions such as inadequate lighting, ventilation, indoor air quality, or noise control. These exposures potentially impact the comfort and health of students, which may adversely affect their academic performance and increase their risk of both short- and long-term health problems."
1/3	P1, L10-L12	**Comments:** 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 than 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.
		Response: We have addressed reviewer comments by making several substantive edits to the text. As a result, this paragraph has been removed and incorporated into other parts of the text, which has been noted in other responses to reviewer comments.
1/3	P1, L20-L28	**Comment:** 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.
		Response: We have addressed these concerns and added more text to this particular paragraph. The text now reads: "School and child care environments share many characteristics influencing children's exposure to indoor environmental contaminants, such as the sources and types of potential environmental contaminants. Both environments also tend to house a large number of occupants in a small confined space, so that without proper ventilation a large number of children can be at risk for potential exposure to indoor contaminants. However, there are also a number of important differences between the two. Children in child care facilities are generally much younger than those in schools, sometimes as young as a few weeks old. The behaviors of very young children (e.g., crawling, hand-to-mouth activity) increase their exposure to contaminants in dust, on surfaces, or in toys and other objects. Younger children may also spend more time in child care facilities, some as many as 10 hours per day, 5 days a week. Also, compared with schools, child care facilities can be located in a much wider variety of settings, including office buildings, individual homes, and religious buildings.

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		As a result, the indoor and outdoor environments can differ widely between child care facilities and may not be directly under the control of those running the child care itself. Furthermore, child care facilities are more often operated independently, while schools are frequently part of a school district with centralized facilities management. This has important implications for strategies to address environmental problems in these facilities."
1/3	P1, L30-L40	**Comment:** 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.
		Response: We have revised the text to address these concerns. We have moved the original Paragraph #4 to Paragraph #2 and have revised to text to read as follows: "These potential exposures are of particular concern because children generally spend most of their active, awake time at schools and child care facilities. Children are especially sensitive to contamination, for several reasons. First, children are biologically more vulnerable than adults since their bodies are still growing and developing. Second, children's intake of air and food is proportionally greater than that of adults. For example, relative to body weight, a child may breathe up to twice as much air as adults do; this increases their sensitivity to indoor air pollutants. In particular for younger children, the inhalation and ingestion of contaminated dust is a major route of exposure due to their frequent and extensive contact with floors, carpets, and other surfaces where dust gathers, such as windowsills, as well as their high rate of hand-to-mouth activity. Lastly, children have many years of future life in which to develop disease associated with exposure."
1/3	P1, L39-L43	**Comment:** 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.
		Response: This paragraph has been revised to address this comment. The text now reads: "Children may be exposed to a variety of contaminants in school and child care settings, such as lead, asbestos, polychlorinated biphenyls (PCBs), pesticides, brominated flame retardants, phthalates, and perfluorinated chemicals. Exposure to indoor contaminants can occur through multiple routes, such as dermal (through

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		the skin), inhalation, and direct and indirect ingestion. These types of indoor environmental contaminants are associated with a variety of adverse health outcomes, as well as outcomes related to educational performance for which impaired health is a suspected cause.[9] These adverse health effects may be short-term (headache, dizziness, nausea, allergy attacks, or respiratory problems) or longer-term and more serious (asthma, neurodevelopmental effects, or cancer). Children exposed to indoor air pollution also miss more days of school due to illness. A child's overall academic performance can suffer as a result of such an illness or absence. For example, exposure to indoor air pollutants has been associated with decreased concentration and poor testing outcomes." **Comment:** 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.
1/3	P2, L5-L12	
		Response: This paragraph has been revised to address this comment. The paragraph now reads: "There is evidence that many schools and child care facilities in the United States have significant and serious problems with indoor environmental contaminants and certain groups of children are especially susceptible to such exposures. Children with allergies, asthma, and other respiratory problems are especially susceptible to the effects of indoor air pollution. Asthma attacks and allergies are often triggered by indoor allergens (pollen, dust, cockroaches), as well as by mold."
1/3	P2, L26-P4, L4	**Comment:** 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.
		Response: We have reviewed each paragraph for all the specific indoor contaminants. This reviewer's comments have been addressed and the following edits have been made: 1) organizing each paragraph in a similar format; 2) simplifying or

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		explaining complex terminology; 3) addressing specific comments for the lead and asbestos sections. Although we recognize the importance of highlighting the potential health risks by discussing them in the opening of each section, we have decided to follow the format that has been used throughout this ACE3 report in discussing the contaminant source, potential for exposure, and then the health effects of concern.
1/3	P4, L6-L17	**Comment:** "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.
		Response: We have reviewed this particular section and considered the reviewer's comments. We have decided to continue using the terminology "school siting" because it is a commonly used phrase found in the literature that might be used as a keyword to locate more information about the topic. However, we have made several edits to the text, including a sentence that defines the phrase so that it will be understood by the reader. We have also made several edits to this section to address the other comments by the reviewer. We have concluded that it is beyond the scope of this report to provide specific information regarding which schools are built on or near contaminated lands. This text now reads: "School siting (selecting a site, or location, for a new school) is a complex process that often requires assessment of several considerations, such as whether to renovate an old school or to build a new one, cost of land and land preparation, and the availability of infrastructure including roads and utilities.EPA has recently developed voluntary guidelines for school siting as a way to support states, tribes, communities, local officials, and the public in understanding and appropriately considering environmental and public health factors when making school siting decisions. These siting guidelines address issues such as the special vulnerabilities of children to hazardous substances or pollution exposures, modes of transportation available to students and staff, the efficient use of energy, and the potential use of the school as an emergency shelter."
1/3	P4, L19-P6, L7	**Comment:** 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.
		Response: We have reviewed this section and edited it to simplify or explain complex terminology. The text now reads: "Pesticides are used in the indoor and outdoor environment to prevent, destroy, repel, or otherwise control pests such as rodents, insects, unwanted plants, and microbials (such as bacteria). They can be sold in many different forms, such as sprays, powders, crystals, or balls, and thus their application inside or outside of schools and child care facilities may lead to several

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		potential routes of exposure for children. For example, application of pesticides in the indoor environment has been shown to contaminate untreated surfaces, including kitchen counters and toys, indoor air, and dust. Once applied, pesticide residues may take anywhere from a few hours to several months or years to completely break down (degrade). Pesticide residues in the indoor environment are less exposed to factors that enable its degradation, and therefore are more persistent than those in the outdoor environment. This persistence means that pesticide exposures can remain a concern for a long period of time, even if the area is no longer being treated. For example, an assessment of pesticide residues in dust of inner city homes found a high prevalence of the pesticide chlorpyrifos two to three years after its indoor use was banned. DDT also continues to be measured in indoor dust several decades after its use was banned in the United States. Furthermore, the persistence of pesticides in the environment after application creates not only an opportunity for children to be exposed directly to the residues, but also the potential for residue migration, leading to contamination of untreated areas. As a result, exposures may occur long after application and through a variety of routes such as inhalation and indirect ingestion of dust. Outdoor pesticide applications on school property, as well as on nearby agricultural fields, lawns, or house perimeters, may contaminate nearby schools and child care facilities. Several studies demonstrate increased levels of pesticides in indoor air and dust following pesticide applications in an adjacent outdoor area. This often occurs when outdoor air contaminated with pesticide residues mixes with the indoor air (through natural drifting into the building or being brought in through HVAC systems), or residue particles are tracked in on the shoes and clothing of people entering the building."
1/3	P6	**Comment:** A concluding paragraph for the introductory section again highlighting the importance of this issue and its connection to children's health is needed.
		Response: We have applied the format that has been used throughout this ACE3 report and follow the topic definition and summary of scientific findings relevant to children's environmental health immediately with a discussion of the indicators for that topic.
2/1	N/A Overall indicator text	**Comment:** 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.
		Response: We have reviewed these suggested data and concluded that in their current states, they cannot be incorporated into these indicators. For example, the NIOSH sensor data does not currently allow for stratification of the data set to identify those

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		specific to schools and child care facilities. Due to the nature of this section which focuses on children's exposure solely in these environments, we believe that this limitation hinders the ability to incorporate these data into this section. We also agree with the reviewer's comments that personal exposure data would be more relevant than using measurements of pesticide presence; however, an appropriate data set reporting these data was not found when selecting these measusres.
2/2	N/A Overall indicator text	**Comment:** 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?
		Response: We have addressed several of these comments and added clarification to the description of each measure. Our process for selecting indicators is outlined in the Introduction section of the ACE3 report; our selection of what indicators to report is primarily limited by the availability of appropriate data. In particular for lead, the ACE3 report has extensively covered this topic and reported on indicators for children's exposure to lead in other sections (Biomonitoring, Environments and Contaminants). Therefore, we have not reported on lead as an indicator in this section. However, we have modified the lead section in this topic to address additional surveillance statistics on lead's presence in schools and child care facilities specifically.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: We believe that the potential risks for each contaminant has been adequately reviewed in the background text for this section which reviewed each contaminant, its exposure sources, and its potential risks to children's environmental health. Both surveys varied in time when samples were taken, due to the large scale of each survey; therefore, these data are representative of potential exposures year-round.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: We have reviewed this particular text and considered this suggestion. However, we have decided not to change the discussion of each measure, due to their relation in

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		measuring potential exposures in child care facilities. We have separate discussions on each measure and the contaminants that they measure, and we believe that this is an adequate way to discuss the data for each measure.
2/3	N/A Overall indicator text	**Comment:** 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.
		Response: We have revised this sentences and it now reads: "Measure S4 displays the annual amount (pounds per year) of pesticides…" We have reviewed the text for Indicator School1(now Measure S4) but have decided that it is out of the scope of this report to discuss the potential for expanding this state-wide program to a nationwide scale of reporting pesticide application in schools. Our goal overall for this report is to present indicators that represent nationwide samples of U.S. children; however, the Supplementary Topics section is designed to report on topics where minimal (or no) nationwide data are available, but that represent topics that still warrant environmental health concerns for children. We have also concluded that an extrapolation from pesticide applications in California to the rest of the nation would be too complex and unsupported by adequate data to address in this report.
3/1	N/A Overall data presentation	**Comment:** 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.
		Response: In following with the organization of other sections of this report, where the presentation of each topic begins with background text reviewing the scientific literature on the various potential exposures and health effects, we have decided to leave the text as is. We believe that it is important to provide a full scope of the issues relevant to the topic at hand prior to presenting the data on the measures that we have selected.
3/2	N/A Overall indicator text	**Comment:** 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.
		Response: Our process for selecting indicators is outlined in the Introduction section of the ACE3 report; our selection of what indicators to report is primarily limited by the availability of appropriate data. In particular for lead, the ACE3 report has extensively covered this topic and reported on indicators for children's potential

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		exposure to lead in other sections (Biomonitoring). Therefore, we have not reported on lead as a measure in this section. However, we have modified the lead section to address additional surveillance statistics on lead's presence in schools and child care facilities specifically.
3/3	N/A Overall indicator text	**Comment:** 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.
		Response: In the table for indicator Child Care1 (now Measure S2), we have clearly identified which data comes from regional data sources, and which come from national data sources. Since each of these report on the same pesticides, and have no overlap in reporting, we believe that it is best to present these in the same table. For indicator Child Care2 (now Measure S3), we have changed the table to clearly identify that the data comes from a regional data source.
4/1	N/A Overall Indicator text	**Comment:** 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.
		Response: After careful consideration we have decided to leave the text as is. We believe that it is important to provide a full scope of the issues relevant to the topic at hand prior to presenting the data on the indicators that we have selected. Pesticides data from NHANES are not available for children younger than age 6 years. Even with the stratification by age, the data could not be classified by pesticide measurements at schools or child care facilities versus pesticide measurements at home and other source (i.e., parks). Therefore, we have decided not to include these data into that of our indicators at this time.
4/1	N/A Overall Indicator text	**Comment:** 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.
		Response: We have addressed several limitations in the discussion of the data used for this measure and its source and we believe that this is sufficient. Suggestions for how to improve the data is beyond the scope of this report.
4/1	N/A Overall Indicator text	**Comment:** c.) I am certain that these indicators do not do this.
		Response: We have edited the phrasing of this objective and inserted additional text in the report introduction to clarify the scope and intent of ACE3 and in particular, the Supplementary Topics section. We agree that these measures may be limited in their ability to track and understand the potential impacts of these contaminants on

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		children's' health on a national basis, due to the limitations of data availability. However, we believe that these topics represent important aspects to be considered, and therefore have included them as Supplementary Topics .
4/2	N/A Overall Indicator text	**Comment:** a) 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.
		Response: We believe the text is clear that the two surveys were conducted only one time. We are unaware of any efforts to collect similar data on a periodic or continuing basis. Due to the limitations in data availability on a nationwide level, we are unable to provide national indicators on these particular topics. We agree that indicators on a national scale would be an important contribution to understanding children's environmental health, were such data to be made available in the scientific literature.
4/2	N/A Overall Indicator text	Comment: b) 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.
		Response: We agree with the concern that there are minimal data available nationwide for the presence of many of these environmental contaminants in schools and child care facilities. We have reported measures on the data that are available and we believe that this gives a partial snapshot of the potential exposure to these types of contaminants in schools and child care facilities. We agree, however, that a larger more representative sample for the environmental contaminants discussed in this section would provide a basis for improved measures, were such data to become available. We have also edited the phrasing of this objective and inserted additional text in the report introduction to clarify the scope and intent of ACE3 and in particular, the Supplementary Topics section. We believe that contaminants in schools and child care facilities are important aspects of children's environmental health, and therefore have included them as Supplementary Topics .
4/2	N/A Overall Indicator text	**Comment:** c) 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

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		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.
		Response: Due to the limitations in data availability on a nationwide level, we are unable to provide national indicators on these particular topics. We agree that collection of such data on a national scale would be an important contribution to understanding children's environmental health.
4/3	N/A Overall Indicator text	**Comment:** 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.
		Response: We have substantially revised each section based on reviewer comments, and have addressed previous comments that has resulted in adding text which discusses this connection in more detail. We further believe that the potential risks for each contaminant have been adequately reviewed in the background text for this section which reviewed each contaminant, its exposure sources, and potential risks to children's environmental health and thus this information is not repeated in the text for each indicator.
4/3	N/A Overall Indicator text	**Comment:** 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).
		Response: We have addressed several limitations in the discussion of the data used for this measure and its source and we believe that this is sufficient. We agree that these measures may be limited in their ability to track and understand the potential impacts of these contaminants on children's' health on a national basis, due to the limitations of data availability. However, we believe that contaminants in schools and child care facilities are important aspects of children's environmental health, and therefore have included them as Supplementary Topics . We do not believe that it would be appropriate to address Objective C at this time for these topics, due to the minimal availability of nationwide data reporting on these particular settings for children. We have added text to the report introduction to clarify the intent of the Supplementary Topics section.
5/1	N/A Overall Indicator text	**Comment:** A new section is needed on limitations to the current data and general recommendations on improving future data collection analysis and including additional data.

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		Response: We have addressed several limitations in the discussion of the data used for this measure and its source and we believe that this is sufficient.
5/2	N/A Documentation	**Comment:** The documentation appears adequate for the indicators.
		Response: No response necessary.
5/3	N/A Documentation	**Comment:** 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.
		Response: No response necessary.