U.S. EPA's responses to public comments submitted March 8 – April 21, 2011, on draft indicator documents for *America's Children and the Environment*, Third Edition

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EPA response to April 19, 2011 comments from Cynthia F. Bearer, Children's Environmental Health Network.

To whom it may concern,

The Children's Environmental Health Network appreciates the opportunity to comment on the proposed Third Edition of *America's Children and the Environment* (ACE3).

The Children's Environmental Health Network (CEHN) is a national multi-disciplinary organization whose mission is to promote a healthy environment and to protect the fetus and the child from environmental health hazards. The Network's Board and committee members include internationally-recognized experts in children's environmental health science and policy who serve on key Federal advisory panels and scientific boards. We recognize that children, in our society, have unique moral standing.

The Network was created to promote the incorporation of basic pediatric facts such as these in policy and practice:

- Children can be more susceptible and more vulnerable than adults to toxic chemicals.
- Children are growing. Pound for pound, children eat more food, drink more water and breathe more air than adults. Thus, they are likely to be more exposed to substances in their environment than are adults.
- Children have higher metabolic rates than adults and are different from adults in how their bodies absorb, detoxify and excrete toxicants.
- Children's systems, including their nervous, reproductive, digestive, respiratory and immune systems, are developing. This process of development creates periods of vulnerability. Exposure to toxicants at such times may result in irreversible damage when the same exposure to a mature system may result in little or no damage.
- Children behave differently than adults, leading to a different pattern of exposures to the world around them. For example, they exhibit hand-to-mouth behavior, ingesting whatever substances may be on their hands, toys, household items, and floors. Children play and live in a different space than do adults. For example, very young children spend hours close to the ground where there may be more exposure to toxicants in dust, soil, and carpets as well as low-lying vapors such as radon, mercury vapor or pesticides.
- Children have a longer life expectancy than adults; thus they have more time to develop diseases with long latency periods that may be triggered by early environmental exposures, such as cancer or Parkinson's disease.

The world in which today's children live has changed tremendously from that of previous generations. One of these changes is the phenomenal increase in substances to which children

are exposed. Synthetic chemicals are ubiquitous in our environment worldwide, and traces of these compounds are found in all humans and animals. For the majority of the thousands of new chemicals introduced into children's environments since World War II, little is known about the health effects on children. As reported by the EPA, 83,000 industrial chemicals are currently produced or imported into the United States. The Centers for Disease Control and Prevention's National Human Exposure Report has amply demonstrated that such chemicals often are ubiquitous, appearing in the vast majority of blood and urine samples taken at random from the general population in the U.S. Many of these are readily passed across the placenta to the fetus or to the infant via breast milk.

Thus, we praise the U.S. Environmental Protection Agency (EPA) for continuing and expanding *America's Children and the Environment (ACE).*

I. General Comments

As presented in the online publication, *America's Children and the Environment, Third Edition (ACE3)*, two of ACE3's three goals are to "inform discussions among policymakers and the public about how to improve federal data on children and the environment" and "to help policymakers and the public track and understand the potential impacts of environmental conditions on children's health and, ultimately, to identify and evaluate ways to minimize environmental impacts on children."

The Network believes an important aspect of achieving those two goals is a clear discussion in the report about not just what is presented within -- existing information that the Agency deems quantifiable and reliable -- but what is **not** known. Most members of the public, and even policymakers, assume "safety." Based on our years of contacts with the public, until they are informed otherwise, most Americans assume that a product or a compound has been fully tested for safety, including for the safety of their children.

The Network urges the addition of a brief section of the report that describes for a lay audience the extent of our knowledge -- or, more accurately, lack of it -- about the impact of children's exposures to the thousands of chemicals newly-introduced and ubiquitous in their environments. These information gaps are one reason, the Network hopes, that the Agency has called for reform of the Toxic Substances Control Act. Including such a section in this report will help to inform the public and policymakers of one key reason for reforming this outdated statute.

> **Response:** The limited information on health effects of many environmental contaminants has been briefly addressed in the introduction to the report.

II. Comments on Proposed Draft Indicators for ACE3

CEHN offers the following comments on the proposed draft indicators for ACE3:

Environments and Contaminants:

Food Contaminants --

- **Pesticides:** ACE3 proposes using the "Percentage of apples, carrots, grapes, and tomatoes with detectable residues of organophosphate pesticides, 1998–2008" as the sole indicator of food contaminants (see page 5). While tracking organophosphates is an important step in better understanding and responding to environmental food contaminants, there are a number of other pesticides and pesticide categories of concern that also should be included in ACE3. These include, at least, carbamates and pyrethroids.

  Response: We chose to limit the indicator presentation to one class of pesticides to maintain clarity of the presentation. We agree that carbamates and pyrethroids are additional classes of interest and will consider these for future editions.

Climate Change

- The Network commends the Agency for the inclusion of climate change and its impact on children in this report. Children are the first and worst hit by climate change, as indicated by studies done in the developing world. A WHO report estimated that 85% of the deaths occurring attributed to climate change in these countries are young children. U.S. children, like their counterparts around the world, will be more vulnerable to climate change's heat waves, water contamination, natural disasters, changing disease vectors, and social and economic disruption, than adults.

  Response: No response necessary.

Biomonitoring –

- **Expand Ages Studied:** As proposed in ACE3, data for vast majority of the listed compounds measure detectable levels of contaminants in women of child-bearing age, not children. EPA should consider expanding the scope of its biomonitoring data to include information drawn directly from newborns and young children through such mechanisms as cord blood, breast milk and meconium. The Network recognizes that ethical issues may complicate the collection of such samples, but we believe that such complications are not and should not be a bar. The environment, diet and behavior of the very youngest children differs dramatically from adults and even from children just a few years older. The Network urges the Agency to coordinate with relevant sister agencies to generate and present this data.

  Response: While we recognize the utility of such measures, they are not available in the NHANES database which is the best nationally representative data available and used for our biomonitoring indicators. We have prepared an introduction for the Biomonitoring section that discusses the limited data for young children and lack of measurements in breast milk.

Special Features

- **Contaminants in Schools and Child Care Facilities --** Although most U.S. children under age six spend up to 40 hours a week in child care settings, little has been done to protect young children from environmental health hazards in child care and preschools. Data collected from school settings, such as the national survey of radon levels discussed in AC3, should also be captured for pre-K child care settings, including commercial and home-based child care facilities, where the youngest children spend significant time.

  Response: Although some nationwide data do exist for environmental contaminants in child care settings and schools, such as that for radon discussed in the background text of this section, these data are not systematically collected on a routine basis. We agree there is a need to capture such data on a routine basis, particularly if such exposures are to be incorporated into reports like ACE and other assessments of children's environmental health issues..

II. Recommendations for Additional Indicators for ACE3

CEHN also recommends the following indicators be added to ACE3:

- **Environments and Contaminants: Mercury and PCBs:** The vast majority of states have issued fish advisories regarding the consumption of fish high in contaminants such as mercury and polychlorinated biphenyls. Children, especially the infant and the fetus, are at greatest risk from harm due to consumption of contaminated fish. The Network urges the inclusion of information about the range of fish advisories issued and a link to finding more information about advisories in one's own locality.

  Response: Discussion of state fish advisories (including web links) is included in the Mercury text.

- **Environments and Contaminants: Children's Toys & Products** – Children are growing, developing organisms, whose days are spent exploring their world through touch, taste, and movement. This natural curiosity and wonder is often exhibited by infants and toddlers putting household item in their mouths. Given this known developmental and behavioral pattern, the Network urges the EPA to add indicators regarding residues and contaminants on children's toys and products, including but not limited to phthalates and Bisphenol A.

  Response: Children's toys and products have been referenced where data is available, throughout the report. Data necessary for developing an ACE indicator addressing these issues are not available.

- **Biomonitoring: Child Body Weight Standard** – The multitude of environmental hazards facing children must be understood within the context a child's life. This includes their smaller body mass as compared to an average adult male. EPA should establish and use standard children's body weight as a calculating factor, instead of relying on standards associated with an average adult male (70kg-body weight).

  Response: Children's smaller body mass as a factor in differential vulnerability is discussed in the report introduction. Children's body weights are not used in calculation of any ACE indicators: biomonitoring data are reported as concentrations in blood or urine; and most Environments and Contaminants indicators are generally reported as presence of contaminants above a stated level.

- **Biomonitoring: Residues from Treated Wood –** Millions of board feet of treated wood in playground sets, picnic tables, benches and decks contain potentially hazardous levels of arsenic due to the use of Chromated Copper Arsenate (CCA). CCA wood has not been on the market for several years, but structures built before the ban of CCA wood exist and are aging. Some studies have indicated both that the arsenate compound can leach out of the wood as it ages and that children can be exposed to potentially harmful levels of this compound. EPA should expand the ACE3 biomonitoring data set to include children's exposure to this compound.

  Response: Arsenic was considered as a possible Biomonitoring indicator; however, there were also many other topics of interest for this section, and the number of Biomonitoring indicators has already been substantially increased from the 2003 edition of ACE.

- **Special Features: Community Impact of Industrial Facilities** -- Many children live and attend school or childcare in communities negatively impacted by environmental contaminants associated with industrial development and waste. In order to better understand and respond to these exposures, EPA should consider implementing a system of fence-line monitors on industrial sites. Such a monitoring system also would facilitate better communication guidelines and evacuation protocols in the event of industrial chemical incidents.

  Response: No response necessary.

The Children's Environmental Health Network appreciates the opportunity to comment on ACE3. We commend the Agency for maintaining and expanding this valuable source of information, and we are ready to assist EPA with the completion of the updated draft.

You may contact me or the staff of CEHN with any questions or requests for additional involvement. My phone number is 410-404-1372 and CEHN's Director of Training and Policy, Carol Stroebel, can be reached at 540-678-4111.

Sincerely,

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EPA responses to April 21, 2011 comments from Richard Becker, American Chemistry Council

The attached comments on the draft report are lengthy and detailed. While it is widely recognized that health and well-being can be impacted by a broad range of environmental influences, including physical, chemical, biological and social factors, the draft ACE report narrowly focuses on environmental exposures. This exclusive focus on exposure is particularly problematic as it may lead to the incorrect conclusion that exposure to chemicals (e.g. phthalates) at any level is not only cause for concern, but also a direct source of negative health effects. In doing so, the report ultimately provides the reader with an incomplete picture of the current state of science concerning children's health in general.

It is troubling that the draft ACE report seems to make such little effort to provide a complete overall picture of child health in the United States. For example, the draft report does not refer to The Health and Well-Being of Children: A Portrait of States and the Nation 2007 [http://mchb.hrsa.gov/nsch07/] which concludes the health and well-being of children in the U.S. is improving overall with 84.4% of children in the United States listed as being in excellent or very good health, an increase from 83% in 2003. In this periodic report, the U.S. Federal Interagency Forum on Child and Family Statistics reports on a number of contextual measures describing the changing population, family, and environmental context in which children are living, as well as a spectrum of indicators that depict the well-being of children in the areas of economic security, health, behavior and social environment, and education. Another report that has not been referenced or cited as a resource is entitled America's Children in Brief: Key National Indicators of Well-Being, 2010 [http://www.childstats.gov/pdf/ac2010/ac_10.pdf], a study that provides U.S. federal government data detailing declining rates across a range of health spectrums, including infant mortality rate, birth rate for adolescents, and rate of cigarette usage among teenagers. The report also notes preterm birth rate declined for the second straight year, from 12.8 percent in 2006 to 12.7 percent in 2007 to 12.3 percent in 2008. Additionally, the report states that "the percentage of children with current asthma increased slightly from 2001 to 2008" and "in 2007–2008, 19 percent of children ages 6–17 were obese, not statistically different from the percentage in 2005–2006." The report goes on to state that

Poor eating patterns are a major factor in the high rate of obesity among children. In 2003–2004, on average, children's diets were out of balance, with too much added sugar and solid fat and not enough nutrient-dense foods, especially fruits, vegetables, and whole grains. The average diet for all age groups met the standards for total grains, but only children ages 2–5 met the standards for total fruit and milk. [America's Children in Brief: Key National Indicators of Well-Being, 2010 (pg. 17)].

Overall, the authors of the draft ACE report fall short in meeting the standards of practice for an objective and comprehensive scientific discussion of health effects, what is known and not known about risk factors and causal determinants, and rates of illnesses. Throughout the draft report, the authors seek to associate chemicals with the induction of adverse effects in children, and in doing so selectively cite one or a few publications in the literature which

purport to establish such an association. There is little or no attempt to present a balanced summary of the scientific literature, or to describe the scientific limitations of positive studies with respect to whether or not they achieve the scientific standard of causality. As a result, much of the discussion in the draft document is highly misleading and inconsistent with the standards EPA has set for developing and disseminating objective scientific work products. The Agency information quality guidelines [http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf] require EPA work products to be unbiased, accurate and reliable. Agency guidance clearly states: "… application of these principles involves a "weight-of-evidence" approach that considers all relevant information and its quality, consistent with the level of effort and complexity of detail appropriate to a particular risk assessment." [ibid] It is important to stress that the principles EPA has adopted require evaluations such as those contained in the draft ACE report to be "comprehensive, informative, and understandable" and present "peer-reviewed studies known to the Administrator that support, are directly relevant to, or fail to support any estimate of public health effects and the methodology used to reconcile inconsistencies in the scientific data." [http://www.law.cornell.edu/uscode/42/300g-1.html]. Therefore, the use of selective citations is not only biased, but is also in direct contravention of Agency policy that requires the totality of relevant and reliable studies to be assessed using a weight of evidence evaluation process.

Response:

We appreciate the reviewer's concerns regarding the broad scope of factors that affect children's health, and we agree that determining causal relationships between environmental exposures and adverse health outcomes requires the consideration of a multitude of other factors. However, the goals and objectives of ACE (as outlined in the report Introduction) are not intended to accomplish such determinations and so we believe that our current approach to addressing factors that may influence children's environmental health is appropriate. We do include discussions of factors other than environmental contaminant exposures in the background text for each Health topic, and have expanded this text in many cases.

We are aware of The Health and Well-Being of Children: A Portrait of States and the Nation 2007 (corrected website: http://mchb.hrsa.gov/nsch/07main/) and the annual America's Children reports (to which EPA contributes). For some indicators ACE incorporates similar data sets, methodology, or indicator calculations as used in these reports. These two reports are essential components in assessing various facets of children's health and well-being generally, and we believe that ACE's contribution to this effort is in its focus on environmental health specifically. This, as stated in ACE's objectives, is intended to inform discussions among policymakers and the public on how to improve data and track trends on children's health and the environment.

The quote provided from EPA's information quality guidelines pertains to Agency risk assessments; ACE is not intended to serve as a risk assessment, and text regarding this point has been included in the report introduction. A comprehensive review of the

literature and weight-of-evidence determinations are beyond the scope of ACE. The purpose of the background text provided for each topic is to briefly summarize key findings from the literature that are informative as to possible relationships between environmental contaminants and children's health outcomes. Studies reporting associations and studies that do not find exposure-outcome associations are included. Where available, authoritative reviews of the literature with weight-of-evidence findings are cited and their findings summarized. Suggestions for additional references were solicited from peer reviewers, and numerous references have been added based on those suggestions. Expanded introductory text prepared for the draft report gives more context and explanation of the scope of ACE3.

Comments on the Draft Indicator Document Entitled *Health: Birth Outcomes*

The draft Indicator Document entitled Health: Birth Outcomes provides a discussion of changes in rates of preterm birth and low birth weight in the United States based on analyses of what are described as "the best national data sources available" for characterizing the relationship between environmental contaminants and children's health. The national data source utilized and discussed is the National Vital Statistics System (NVSS) operated by the Centers for Disease Control and Prevention (CDC), which is a compilation of the birth registries in all 50 states. Birth certificates in the United States include vital statistics for both birth weight and length of gestation. Although the database is a valid resource for gathering information on birth weight and length of gestation (preterm versus full term) in infants born in the United States, the draft Indicator Document on birth outcomes is too brief and selective to be complete. The fact that the NVSS data is being used in an attempt to establish a link between birth outcome and environmental contaminants, such as chemicals, and then to imply that the rates of low birth weight and/or preterm birth in the United States are rising as a result of environmental contaminant exposure is misleading.

Response:
The indicators are not being used to attempt to establish a link between birth outcomes and environmental contaminants; they are used to report a time series of the rates of preterm birth and term low birth weight. The background text provides the rationale for consideration of adverse birth outcomes as a children's environmental health issue. The introduction to the Health section of the draft ACE3 report provides context for the presentation of the health outcomes indicators.

Also, the use of selective citations of published literature without applying the weight of the scientific evidence for the factors that influence birth outcomes is a flaw in the methodology applied in drafting the document.

As an example of the use of selective citations, the draft Indicator Document relies on a CDC database, yet fails to discuss CDC's current research into the causes of preterm birth. The CDC website (www.cdc.gov) has a section devoted to preterm birth and active research areas. There

it is stated that the "reasons for preterm births remain unclear." Then, included at the site are a list of CDC research areas into causes for preterm birth where the following are listed: investigations into vitamin D deficiency as a cause of preterm birth; genetic factors for preterm birth; social factors that influence preterm birth rates; and clinical factors, such as prenatal care, and their relationship to preterm birth rates. Also described is the need to standardize gestational age reporting on birth certificates, as inaccuracy in the reporting is known to occur and has a significant effect on the estimates of preterm birth rates in the United States. None of the research areas listed by CDC are focused solely on the relationship of environmental chemical exposure and preterm birth. In fact, a recent CDC report (October 2008; MacDorman and Mathews, NCHS Data Brief) [www.cdc.gov/nchs/data/databrefs/db09.pdf] states that preterm birth rates have shown a decline in recent years. As a result, at least with respect to the issue of preterm birth rates and chemical exposure, the weight of the scientific evidence does not indicate that chemical exposure is a significant factor responsible for increases in the rate in the United States. The draft Indicator Document, however, fails to discuss these other areas of research as well as the CDC's own statements regarding preterm birth rates.

With respect to the discussion of low birth weight as an adverse health outcome and the link to chemical exposures, the draft Indicator Document fails to discuss the breadth of the scientific literature on this topic. There has been a great deal of research showing that factors such as poverty, poor nutrition, short intervals between pregnancies, multiple births, and maternal age are strongly associated with an increased risk of low birth weight for babies born at term. Although there are some studies discussing a role for chemical exposures in affecting birth weight, there is no consensus among scientists that any particular chemical is associated with an increased risk of low birth weight in pregnant women. Implying that certain chemicals are risk factors for low birth weight based on citations of selected studies does not place appropriate focus on the most relevant risk factors for low birth weight. The draft Indicator Document should emphasize that scientific data supports a role for some very important social and environmental factors other than chemical exposure when assessing the risks for low birth weight in the United States today.

Response:

The background text does address the major factors that have been associated with adverse birth outcomes, such as multiple births, maternal age, obstetric practices, SES, etc. prior to discussing the potential role of air pollutants and other environmental contaminants.

The text does not draw conclusions regarding the relative contribution of environmental contaminants to adverse birth outcomes; it rather briefly summarizes key findings from the literature that are informative as to possible relationships between environmental contaminants and children's health outcomes. A comprehensive review of the literature and weight-of-evidence determinations are beyond the scope of ACE. Where available, ACE relies on authoritative reviews of the literature and reports their conclusions regarding the strength of the evidence for a causal role of specific environmental factors

in the development of childhood diseases and disorders. In the case of adverse birth outcomes, weight of evidence conclusions from the U.S. Surgeon General (for ETS) and the National Toxicology Program (for lead) are included. We have reviewed the text for other environmental contaminants and edited as necessary to convey that no weight-of-evidence conclusion is being drawn.

The NCHS data brief cited in this comment (MacDorman and Mathews 2008) (http://www.cdc.gov/nchs/data/databriefs/db09.pdf) finds that, in contrast to the reviewer's statement, the percentage of preterm births "increased rapidly" (from 11.6% in 2000 to 12.7% in 2005), which corresponds with the data presented in the draft ACE3 indicator.

Finally, the draft Indicator Document fails to provide a discussion of the effect of dose or level of exposure on the risk for adverse birth outcomes such as low birth weight or preterm birth. The issue of dose is alluded to by the findings cited relating to PCB consumption but it is not then discussed in the overall context of chemicals as risk factors for adverse birth outcomes. The lack of discussion of the importance of level of exposure or dose to the interpretation of the cited chemical exposure studies is a significant flaw in the draft document. This is because of the complex nature of the relationship between adverse birth outcomes and factors such as genetics and maternal characteristics (age, ethnicity, diet), factors that appear to be more significant influences on the incidence rates of adverse birth outcomes.

Response:
Text has been revised to give a qualitative characterization of exposure levels in the cited studies.

Comments on the Draft Indicator Document Entitled *Health: Obesity*

The draft Indicator Document entitled Health: Obesity provides a discussion of changes in rates of childhood obesity in the United States based on analyses of what are described as "the best national data sources available" for characterizing the relationship between environmental contaminants and children's health. The national data source utilized and discussed is the National Health and Nutrition Examination Survey (NHANES) which is a nationally representative survey of health and nutritional status of the civilian, non-institutionalized United States population that is conducted yearly by the National Center for Health Statistics of the CDC. Approximately 5000 people are interviewed each year and physical exams are also conducted, which include measurement of both height and weight of all participants. Although the NHANES database is a good resource for gathering information on the incidence of obesity, as measured by elevated body mass index (BMI) in the United States, the draft Indicator Document on obesity is too selective to be complete. The fact that the NHANES data is being used to attempt to establish a link between childhood obesity and environmental contaminants, such as chemicals, and then to imply that obesity rates in children in the United States are rising as a result of environmental contaminant exposure is misleading and not

consistent with the available science concerning the factors that have influenced childhood obesity rates in the United States. Additionally the use of selective citations of published literature without applying the weight of the scientific evidence for childhood obesity incidence and the related causes is a flaw in the methodology applied in drafting the document.

The draft Indicator Document correctly identifies the most important factors that are thought to contribute to the increase in obesity in the United States, including childhood obesity, i.e., increased caloric intake and lack of exercise. The average American, adults as well as children, eats a diet high in calories, well above the necessary caloric intake for maintaining a healthy weight. This, combined with the more sedentary lifestyle that is common in the United States in recent decades, is the most important factor in the large increase in obesity that has been observed. [Testimony of William H. Dietz, Director at CDC (http://www.cdc.gov/washington/testimony/2009/t20091216.htm)] Although there are some limited data linking exposure to certain chemicals with changes in body weight and fat mass in animal models of obesity, these effects are most often observed with high doses of chemical intake. It is important to remember that routine toxicological testing of the chemicals found in products that humans are routinely exposed to include assessments of animal body weight and food consumption, which are indicative of the ability of a chemical to induce obesity. More importantly, the draft Indicator Document has again used only selective citations to support the link between environmental chemicals and obesity. When the scientific literature as a whole is examined, it is clear that very few chemicals have been shown to increase body weight and food consumption even at very high doses. Instead, it is seen that in animals that are genetically obese, or are induced to become obese through altered dietary intakes (i.e., high fat diets), some chemicals have adverse health effects at doses lower than doses that might produce similar effects in non-obese animals. This is evidence for obesity as a risk factor for exacerbating many types of toxicity, not for an independent effect of chemical exposure to induce obesity.

> **Response:**
> NHANES data are not being used to attempt to establish a link between childhood obesity and environmental contaminants; they are used to report a time series of prevalence of obesity among children. The text characterizes the research showing an association between chemical exposures and obesity as a “possible role,” and states that obesity is due primarily to an imbalance between caloric intake and physical activity.

The authors discuss the link of endocrine disruption to obesity and imply that chemicals which may disrupt endocrine systems might be responsible for induction of obesity in children. There are no reliable scientific data to support this link. Endocrine disruption describes a mechanism of action by which exposure to a substance induces an adverse effect, such as birth or developmental defects, adverse neurological effects, cancer, or reproductive dysfunctions. Chemicals have long been assessed for these adverse effects through traditional toxicological testing methods, and, where they have shown to cause such adverse effects, those chemicals have been classified and managed accordingly pursuant to existing hazard classification

standards on the basis of normal endpoints of concern and pursuant to available chemical risk management programs. The suggestion that chemicals that affect endocrine function have been associated with a myriad of human health effects, including obesity and diabetes, is misleading and is not representative of the weight of the scientific evidence. Both the Global Assessment of the State-of-the-Science of Endocrine Disruptors prepared by the International Programme for Chemical Safety of the World Health Organization, and Implications of Endocrine Active Substances for Human Health and Wildlife: Executive Summary, prepared by the Scientific Committee on Problems in the Environment (SCOPE) and the International Union of Pure and Applied Chemistry (IUPAC) concluded that there is no firm evidence that exposures to endocrine active substances at levels measured in the general population are affecting human health. At the same time, these groups acknowledge the potential that such effects could be occurring and that further investigation is warranted. Those reports also find some clear instances of adverse effects occurring in wildlife, but, for the most part, these appear to be only at elevated exposures. In contrast, the discussion of endocrine disruption in the draft Indicator Document seems to imply that there is widespread scientific consensus that the current environment in the United States exposes children to levels of chemicals sufficient to lead to an increase in the rate of obesity, a position that is inconsistent with the analyses by various scientific groups.

Response:
The text does not "imply that there is widespread scientific consensus that the current environment in the United States exposes children to levels of chemicals sufficient to lead to an increase in the rate of obesity," and rather uses conditional language indicating that such relationships are hypothesized and not established. The text has been revised to further clarify this point, including revisions to text describing particular research findings.

The draft Indicator Document also implies that environmental chemicals may be responsible for the growing problem of Type II diabetes in the United States. Like the incidence of obesity in the United States population, the incidence of Type II diabetes has also increased. Scientific evidence clearly supports a link of the increased rate of obesity to the increase in Type II diabetes, particularly in adults. However, scientific evidence does not support any role for environmental chemicals as an independent risk factor for Type II diabetes in either adults or children. The citation of only a few selected studies to imply that such a relationship is scientifically based is misleading and without merit.

Response:
The draft topic text describes research findings suggesting a potential role for chemical exposures in diabetes. The text has been edited to insure that there are no implications of established relationships.

Comments on the Draft Indicator Document Entitled *Health: Respiratory Diseases*

The draft Indicator Document entitled Health: Respiratory Diseases provides a discussion of the incidence and causes of asthma and respiratory disease in children in the United States based on analyses of what are described as "the best national data sources available" for characterizing the relationship between environmental contaminants and children's health. The national data source utilized and discussed is the National Health Interview Survey (NHIS) which is an annual, large scale household interview survey study conducted by the CDC in a representative sample of the civilian, non-institutionalized United States population from 1997 to the present. The survey from 1997 to 2005 included 12,000 to 14,000 children, while since 2006 the survey has included 9,000 to 10,000 children. In the survey, parents have been asked whether their child had ever been diagnosed with asthma. Two additional databases were used to investigate the rate of hospital visits or emergency room visits for children due to asthma or other respiratory diseases. These databases were the National Hospital Ambulatory Medical Care Survey (NHAMCS) and the National Hospital Discharge Survey (NHDS), both of which were developed by the National Center for Health Statistics of the CDC. The NHAMCS has collected data on physician diagnoses for visits to hospitals and outpatient departments beginning in 1992 while the NHDS reports physician diagnoses for hospital discharges beginning in 1965. Both surveys exclude federal and military hospitals and report patient demographic information. Although these databases are valid resources for gathering information on rates of asthma and asthma-related hospitalizations for children in the United States, the discussion in the draft Indicator Document is too brief and selective to adequately establish a link between chemical exposure and asthma in children.

The fact that survey data is being used in an attempt to establish a link between asthma and environmental chemical contaminants, and then to imply that incidence rates in children in the United States are rising as a result of chemical exposure, is misleading. While available data indicate that the incidence of childhood asthma has increased in the United States, as well as other areas of the industrialized world, over the last two decades, the surveys do not provide any information demonstrating that chemical exposure is the critical factor. Moreover, evidence suggests that in the United States, the rates of childhood asthma have begun to level off.

> **Response:**
> The survey data are not being used to attempt to establish a link between asthma and environmental contaminants; they are used to report a time series of prevalence of current asthma and the prevalence of asthma attacks among children. The text summarizes key findings from the literature that are informative as to possible relationships between environmental contaminants and children's health outcomes.

Additionally, the use of selective citations of published literature without applying the weight of the scientific evidence for specific chemicals is a flaw in the methodology applied in drafting the document.

The draft Indicator Document appropriately points to studies on certain environmental contaminants, such as particulate matter, lead, ozone, nitrogen dioxide, carbon monoxide, and sulfur dioxide, all chemicals commonly associated with air pollution, that have been linked with respiratory irritation and even exacerbation of asthma in adults as well as children. However, the discussion fails to provide a context for the levels of these chemicals that are currently found in the environment of the overwhelming majority of children in the United States. The document fails to distinguish between the hazard posed by chemicals and the risks that are actually observed, which are dependent on the dose of the chemical not just the presence in the environment. The consideration of the dose required to produce effects is of particular importance in the context of other chemicals mentioned in the draft document, such as formaldehyde. Moreover, although respiratory diseases have been linked to high levels of air pollution or exposure to air pollution, they appear to be related as well to other risk factors such as poverty, poor housing conditions, and genetics. It is not clear whether certain chemicals in the environment are independent risk factors for respiratory disease, particularly at low doses.

Some portion of the increase in the rates of childhood asthma may be due to improved recognition and diagnosis, but not all. This rise in asthma has been particularly prominent in children and even more so in those living in urban environments, and has occurred in all developed countries around the world. The reasons for this increase in asthma are not known and there are likely to be multiple contributing factors. There is clear evidence that both genetics and the environment can be important factors in asthma. With regard to specific environmental exposures, there is evidence that exposure early in life to both allergens and irritants may play a pivotal role in the development of allergy and asthma. In fact, the analysis provided in the draft Indicator Document supports an important role for genetics in the risk of developing asthma based on differences in ethnicity as well as gender.

> **Response:**
> A variety of factors that may contribute to asthma are discussed in the topic text, including poverty, poor housing conditions, and genetics. Where available, the text has relied on authoritative reviews of the literature regarding environmental contaminant exposures and respiratory conditions - including EPA's Integrated Science Assessments for criteria pollutants, and the HEI review of traffic-related emissions.

It should be noted that the section of the draft Indicator Document that discusses emergency room visits and hospital admissions for respiratory diseases is inconsistent with the findings with regards to incidence of asthma. As already mentioned above, there has been an increase in the incidence of asthma in children over the last two decades, with increases still being seen, although smaller, in the last decade. Yet, contrary to the expected pattern for emergency room visits and hospitalizations for respiratory diseases, which would be expected to increase as well, the draft Indicator Document describes a decrease in both emergency room visits for asthma and an even larger decrease in hospitalizations for respiratory diseases in children. This finding would suggest that the factors that influence the rate of emergency room visits and

hospitalizations due to respiratory disease are different from those that affect the incidence rate changes for asthma itself. This difference has not been explained nor discussed.

Response:
We are unaware of any studies that have provided an explanation for the decreases in ER visits and hospitalizations for asthma. Possible explanations could include improved asthma management, decreasing exposure to air pollution and/or allergens, or changes in the health care system – however, it would not be appropriate for us to speculate on this in an EPA report. We have added text explaining the difference between statistics on the percentage of children who have asthma (current asthma prevalence) and those on outcomes for children with asthma (asthma attack prevalence, ER visits, hospitalizations). We have also noted that the percentage of children with current asthma who had asthma attacks (asthma attack prevalence divided by current asthma prevalence) has declined.

It is important to note that the draft Indicator Document fails to apply proper weight-of-the-evidence methodology in its discussion of asthma and respiratory diseases and the link to chemical exposure. Instead of applying the weight of the scientific evidence to the discussion in the draft Indicator Document, selected citations are presented, citations that do not represent the majority of the evidence for any particular environmental chemical. Failure to discuss the body of the scientific evidence to support the discussion of childhood asthma incidence and the link to chemicals in the environment is a serious flaw in the current draft document.

Response:
A comprehensive review of the literature and weight-of-evidence determinations are beyond the scope of ACE. The purpose of the background text provided for each topic is to briefly summarize key findings from the literature that are informative as to possible relationships between environmental contaminants and children's health outcomes. Studies reporting associations and studies that do not find exposure-outcome associations are included. Where available, the text has relied on authoritative reviews of the literature regarding environmental contaminant exposures and respiratory conditions - including EPA's Integrated Science Assessments for criteria pollutants, and the HEI review of traffic-related emissions.

Comments on the Draft Indicator Document Entitled *Health: Neurodevelopmental Disorders*

The draft Indicator Document entitled Health: Neurodevelopmental Disorders provides a discussion of the incidence and causes of several neurodevelopmental disorders in children in the United States based on analyses of what are described as "the best national data sources available" for characterizing the relationship between environmental contaminants and children's health. The national data source utilized and discussed is the National Health Interview Survey (NHIS) which is an annual, large scale household interview survey study conducted by the CDC in a representative sample of the civilian, non-institutionalized United

States population from 1997 to the present. The survey from 1997 to 2005 included 12,000 to 14,000 children while since 2006 the survey has included 9,000 to 10,000 children. In the survey, parents have been asked whether their child has ever been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), Attention Deficit Disorder (ADD), autism, mental retardation, or a learning disability; these neurodevelopmental disorders are then the focus of the draft Indicator Document discussion. Although the NHIS database is a valid resource for gathering information on incidence rates of certain types of neurodevelopmental disorders in the United States, the discussion in the draft Indicator Document is too brief and selective to be complete.

The fact that the NHIS data is being used to attempt to establish a link between neurodevelopmental disorders and environmental contaminants, such as chemicals, and then to imply that incidence rates in children in the United States are rising as a result of environmental contaminant exposure is misleading. Additionally, the use of selective citations of published literature without applying the weight of the scientific evidence for individual disorders and specific chemicals or classes of chemicals is a flaw in the methodology applied in drafting the document.

Response:

NHIS data are not being used to attempt to establish a link between neurodevelopmental disorders and environmental contaminants; they are used to report a time series of prevalence of neurodevelopmental disorders among children. The background text provides the rationale for consideration of neurodevelopmental disorders as a children's environmental health issue.

The text has been extensively revised and draws upon numerous additional references. However, a comprehensive review of the literature and weight-of-evidence determinations are beyond the scope of ACE. The purpose of the background text provided for each topic is to briefly summarize key findings from the literature that are informative as to possible relationships between environmental contaminants and children's health outcomes. Studies reporting associations and studies that do not find exposure-outcome associations are included. Where available, authoritative reviews of the literature with weight-of-evidence findings are cited and their findings summarized. The phrasing used in summarizing the literature is intended to convey findings of relevance to children's environmental health while also conveying the limitations and lack of causal findings.

The draft Indicator Document appropriately points to certain environmental contaminants, such as lead and methylmercury, that are known to be associated with neurological damage in children and developing organisms. However, the discussion fails to provide a context for the low levels of these chemicals that are currently found in the environment of the overwhelming majority of children in the United States. The document fails to distinguish between the hazard posed by chemicals and the risks that are actually observed, which are dependent on the dose of the chemical not just the presence in the environment.

Response:
The text generally distinguishes between epidemiological findings observed at exposure levels typical for the current U.S. general population vs. those at levels much higher levels. We have also added discussion of these issues to the report introduction.

With respect to individual neurodevelopmental disorders, although the draft Indicator Document specifically states that "widespread environmental contaminants" can damage a child's brain and nervous system, the document uses selective citations to support its discussion of the individual disorders that are discussed in more detail. The document does not reflect the entire body of data available on each of the specific disorders and the large number of studies that have been performed on individual chemicals that might pose a hazard to human health.

Response:
The text is not intended to be a comprehensive review of the literature. Instead, it is intended to briefly summarize evidence related to particular environmental contaminants or particular disorders that suggest a possible relationship relevant to children's environmental health. The text is careful to not use wording that indicates conclusion of a causal relationship except when citing a comprehensive review has reached such a conclusion. Text on other potential causal factors has been expanded (e.g. maternal smoking, alcohol).

With respect to the section on ADHD, although there is literature discussing a potential relationship between chemical exposure and the disorder in children, a cause and effect relationship has not been proven even for lead, one of the most studied environmental contaminants. Implying that environmental contaminant exposure is an independent risk factor for development of ADHD is misleading and not consistent with the weight-of-the-evidence on this topic. Moreover, the statistical analyses presented provide proof that exposure to chemicals is not likely the most important consideration when examining the incidence rate of ADHD in the United States. For example, gender and race are shown to be highly correlated with incidence of ADHD in children in the United States. The draft Indicator Document reports that boys are much more likely to be diagnosed with ADHD than girls and that race affects the relationship, with Caucasian race and black race associated with significantly higher incidences of this disorder. Both gender and racial differences implicate genetics as a critical concern for assessing incidence rates of ADHD. Children living in poverty were also more likely to be diagnosed with ADHD than children living in homes with larger incomes. Such relationships of poverty to disease incidence usually are related to factors such as proper nutrition and parental influences. As a result, focusing the discussion in the draft Indicator Document on environmental chemicals as opposed to these other well-established influences (genetics, socioeconomic status) is misleading and is in direct conflict with the statistical analyses presented in the document.

Response:

The interpretation of the prevalence data as offering "proof" regarding relative importance of environmental contaminants is highly speculative. The relative importance of environmental contaminants in ADHD is unknown and cannot be dismissed simply on the basis of demographic differences in prevalence. Further, the text does not propose or imply that environmental contaminants are the most important consideration. The literature indicates that genetics alone cannot explain all incidence of ADHD, and that some portion of prevalence attributed to genetic factors may represent gene-environment interactions. Text providing context regarding other potential risk factors has been expanded.

With respect to the general disorder referred to as "learning disability," the section similarly reflects the bias of the authors. The discussion implies that exposures to chemicals are "causing" or contributing to learning disabilities (LDs). Such implication is contrary to current scientific consensus, which holds that the causes and incidence of LDs are not known with any degree of certainty, due to the varied operational definitions, the diverse constellations of symptoms, and limited relevant research. Further, the authors fail to communicate that it is difficult to determine the prevalence rate for LDs and whether or not the rates are increasing over time because of the variations in the definition of an LD and the ever-evolving approaches to diagnosis and estimation of prevalence. What is known about chemicals and LDs is that there are a number of chemical compounds (lead, mercury, ethanol, cocaine) that are known or suspected developmental neurotoxicants in humans under conditions of sustained overexposure, some of which cause cognitive deficits. The effects of relatively high exposure levels of lead and mercury on learning impairment are well established. While some have postulated that other chemicals, such as pesticides, PCBs, solvents and hormonally active agents may cause LDs in children, these hypotheses are far from being proven. Several epidemiological studies of neurodevelopmental effects in children have focused on PCB exposure and have reported evidence of a relationship to child development or learning. Reviewers have noted, however, that these studies have numerous methodological problems, particularly, limitations in estimating PCB exposure and sample selection, thereby reducing confidence in the results. Scientists have also noted that because learning and development are influenced by many factors, it is not possible to conclude with any degree of certainty that exposure to PCBs is one of those factors (Schantz, S.L. 1996. Neurotoxicol. Teratol. 18:217-227).

Response:

The ACE3 text does not indicate that causes of learning disabilities are known (see paragraph 2 on page 4 of the review draft). The text has been revised to clarify the available research findings regarding particular environmental contaminants and learning disabilities. The first section of the background text provides general findings regarding potential cognitive effects of exposure to certain environmental contaminants, and the subsequent Learning Disabilities section discusses more specific findings relevant to LD and school performance – focusing primarily on lead. Text has been revised to clarify these points.

Regarding the neurodevelopmental effects of PCBs, the literature has expanded significantly since 1996. The draft text cites more recent review articles by S.L. Schantz and other authors that support a concern for PCB exposure as a contributing factor in neurodevelopmental deficits. The text does not particularly emphasize a relationship between PCBs and learning disabilities, though two relevant studies are noted.

There is a wide range of incidence rates for LD reported in the scientific and medical literature – rates ranging from 1% to 30% of the general population -- which is the result of variations in the definition of LD and the source of case ascertainment. The estimates for children are similarly variable. The National Institutes of Health (NIH) estimated for 1993 that nearly four million school-age children in the United States have an LD, while the CDC estimated 1.4 million in 1991-1992. The reason the CDC reports a much lower number of children affected by LD may be due to a more restrictive definition. Finally, based on special education services of students 6 to 21 years of age, the U.S. Department of Education reported that nearly 4% of students in 1999 were learning disabled. Yet, the draft Indicator Document concludes that there has been no statistically significant change in the overall incidence rate for LD in children in the United States over the time period from 1997 to 2008. In fact, the rate of LD in boys actually appears to have declined after accounting for the confounding effects of race, age and family income, another important finding of the statistical analysis that is not given weight in the discussion of environmental contaminants and LDs.

Response:
We believe that the pattern of the data do not indicate any clear trends in learning disabilities over time. The CDC data presented in the ACE3 indicator do not restrict the definition of learning disabilities, as the estimates are based on parental responses to the question "Has a representative from a school or a health professional ever told you that <child's name> had a learning disability?"

It is also important to discuss that neurodevelopmental effects such as delayed speech, cognitive and attention deficit disorders, hyperactivity, and lowered IQ have been associated with poverty, social disadvantage, child abuse and neglect, malnutrition, and parental disinterest. Because many of these outcomes are included among LD functional deficits, they are considered by some to be possible risk factors or contributory factors for LD itself. However, epidemiological studies that include specific cases of LD children are rare. The varied definitions of LD and the diverse constellation of symptoms it encompasses make understanding the causes of the disease very difficult. Where it was once thought that LD was caused by a single neurological problem, it is now recognized that it involves difficulty in bringing together information from various brain regions. Damage to the brain resulting in learning impairment may occur at any time in a person's life; however, it is much more likely to occur at certain crucial points during prenatal development or before the child is three years old, when the brain is still rapidly developing. The reverse is also true in that the developing brain has much greater plasticity, so the damage may be more likely to be reversible.

Response:
We have noted potential influences of socioeconomic status in the introductory text and the neurodevelopmental text, including interactions of environmental contaminants and SES.

With respect to autism and a link to environmental chemicals, the discussion is also misleading. The draft Indicator Document specifically states that the incidence or prevalence of autism has risen sharply. The document provides a discussion of incidence rates and cites rates reported by the CDC, for example. However, the authors neglect to discuss that fact that the CDC has stated there is great uncertainty about the true incidence and prevalence of autism in the United States, overall rates as well as rates in different geographic regions and different subpopulations (CDC. 2001. Autism among Children. NCEH Pub No. 01-084; http://www.cdc.gov/ncbddd/dd/ddautism.htm). The prevalence of autism and the question of whether it is actually increasing over time have generated considerable debate in the scientific and public health communities. The authors of the draft Indicator Document fail to objectively communicate this. Some studies have attempted to determine whether the reported increase is real or an artifact of improved diagnosis, misdiagnosis or other factors. In another study (Taylor et al. 2003. Arch. Dis. Childhood 88:666-670), it was reported that the purported rise in prevalence of autism may not be real at all, but due to factors such as increased recognition, a greater willingness on the part of educators and families to accept the diagnostic label, and better recording systems.

Response:
We believe the text is clear that a substantial portion of the increased prevalence has been explained by factors such as increased recognition, and a substantial portion has not. We have edited the text to indicate that the sharp increase is in reported prevalence, as distinguished from the unknown actual trend in prevalence. We reviewed the Taylor et al. article; the main points from this paper are already included in the text, i.e. that increased recognition, etc., play some part in the reported increased in prevalence. The literature on this point has advanced substantially since 2003.

With respect to risk factors and the development of autism, the discussion in the draft Indicator Document is incomplete. It fails to mention that it is generally agreed among medical experts that there is an unknown genetic component to autism and autism spectrum disorders (ASDs). Hypothesized contributory non-genetic risk factors, such as vaccines, diet, drugs, infections, and chemicals in the environment remain unproven. Investigations to date have not established a cause and effect relationship between exposure to substances in the environment and autism; the CDC has concluded that the current scientific evidence does not support the hypothesis that vaccines cause autism. Regardless of the lack of understanding about the causes and even the rates of autism and ASDs, the authors of the draft Indicator Document imply that environmental chemicals are related to an increased incidence in autism.

Response:
We believe the text is clear that genetic factors are an important component for autism and ASDs, and does not indicate or imply a proven role for any environmental factors. The text does discuss research findings and hypotheses that may imply an important role for environmental contaminants, and the limited findings available for particular environmental contaminants.

Finally, it is important to note that the draft Indicator Document fails to apply proper weight-of-the-evidence methodology in its discussion of neurodevelopmental disorders. Instead of applying the weight of the scientific evidence to the discussion in the draft Indicator Document, selected citations are presented, citations that do not represent the majority of the evidence for any particular disorder type or any particular environmental contaminant. Failure to discuss the body of the scientific evidence to support the discussion of neurodevelopmental disorder incidence and the link to chemicals in the environment is a serious flaw in the current draft document.

Response:
A comprehensive review of the literature and a weight-of-evidence determination is beyond the scope of ACE. The purpose of the text is to briefly summarize key findings from the literature that are informative as to possible relationships between environmental contaminants and children's health outcomes. Studies reporting associations and studies that do not find exposure-outcome associations are included. Where available, authoritative reviews of the literature with weight-of-evidence findings are cited and their findings summarized.

Comments on the Draft Indicator Document Entitled *Environments and Contaminants: Drinking Water*

The draft Indicator Document entitled Environments and Contaminants: Drinking Water provides a discussion of contaminants that may be found in drinking water sources that are associated with increased risk of disease in children in the United States based on analyses of what are described as “the best national data sources available” for characterizing the relationship between environmental contaminants and children’s health.

The draft Indicator Document acknowledges that “disinfection of drinking water to reduce water-borne infectious disease is one of the major public health advances of the 20th century.” However, it discusses the possible health effects associated with the disinfection byproducts without emphasizing that it is essential that disinfection not be compromised in attempting to control these byproducts in water. Globally, waterborne diseases are one of the most serious threats to children’s health. The World Health Organization (WHO) estimates 1.6 million people, mostly in developing countries die each year as a result of unsafe water supply, sanitation and hygiene; WHO estimates that most of the burden of disease is borne by children. If not for proper drinking water disinfection, most commonly chlorination, America’s children

also would be threatened by waterborne diseases. That is why when evaluating the potential health effects of drinking water disinfection byproducts, the WHO perspective is essential: The health risks from these byproducts at the levels at which they occur in drinking water are extremely small in comparison with the risks associated with inadequate disinfection. Thus, it is important that disinfection not be compromised in attempting to control such byproducts. [WHO International Programme on Chemical Safety, 2000].

Further, in its "National Primary Drinking Water Regulations: Stage 2 Disinfectants and Disinfection Byproducts Rule," the EPA states that "…maximizing health protection for sensitive subpopulations requires balancing risks to achieve the recognized benefits of controlling waterborne pathogens while minimizing risk of potential [disinfection byproduct (DBP)] toxicity."

Response:

We agree that disinfection of drinking water is critical to ensuring children's health. This is why we point out in the indicator text that disinfection of drinking water is one of the major public health advances of the 20th century. Furthermore, we address microbial contaminants as the first type of drinking water contaminant that can present health risks to children, and we also note that children are a vulnerable group as their immune systems are less developed than those of most adults. Indicator E7 and E8 present data on total coliforms (E7 for violations of the health-based standard and E8 for monitoring and reporting violations) for community water systems. The indicators are meant to present information about a wide variety of drinking water contaminants that might be important for children's environmental health; the aim of the indicators is not to compare risks and impacts associated with exposure to various contaminants in order to make a determination about which one is more or less important.

In addition to failing to stress the importance of maintaining an appropriate level of drinking water disinfection, the draft Indicator Document fails to properly apply the weight of scientific evidence to what is claimed to be the possible effects of exposure to the disinfection byproducts. More specifically, contrary to EPA's assertion that "Long-term exposure to disinfection byproducts has been associated with bladder cancer and possible reproductive effects" (lines 19-20, page 2), the weight of scientific evidence does not support such associations.

Regarding chloroform and other trihalomethanes (bromoform, bromodichloromethane and dibromochloromethane), US EPA considers the Maximum Contaminant Level of 80 μg/L for "Total Trihalomethanes" to be protective of human health, including susceptible populations, such as children. When considering any potential association of exposure to disinfection byproducts and bladder cancer, US EPA stated in its National Primary Drinking Water Regulations: Stage 2 Disinfectants and Disinfection Byproducts Rule

…the existing epidemiological evidence has not conclusively established causality between DBP exposure and any health risk endpoints, so the lower bound of potential risks may be as low as zero.

Further, the overall weight of evidence for an association between exposure to disinfection byproducts and most reproductive or developmental effects, including congenital anomalies/birth defects, neural tube defects and respiratory anomalies, is mixed, inconsistent or weak. [According to a report by The Sapphire Group, Inc. (2004; reference available upon request)].

Response:
A comprehensive review of the literature and weight-of-evidence determinations are beyond the scope of ACE. The purpose of the background text provided for each topic is to briefly summarize key findings from the literature that are informative as to possible relationships between environmental contaminants and children's health outcomes. Studies reporting associations and studies that do not find exposure-outcome associations are included. Where available, authoritative reviews of the literature with weight-of-evidence findings are cited and their findings summarized.

Our text does indicate a lack of causal conclusions regarding associations between exposure to disinfection byproducts and reproductive and developmental effects: for example, "Recent reviews of published studies, however, found that due to inconsistent findings among multiple studies, there was not enough evidence to conclude that there is an association between exposure to disinfection byproducts and birth defects" (Drinking Water draft indicator document, page 2, lines 23-25; phrasing has been modified and additional review articles cited in final ACE3 report). We have added text to the statement regarding disinfection byproducts and bladder cancer and reproductive effects to read "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" to indicate the limitations in the epidemiological evidence.

Comments on the Draft Indicator Document Entitled *Biomonitoring: Phthalates*

The draft Indicator Document entitled Biomonitoring: Phthalates provides an overview of the uses and applications of phthalates, the various routes of exposure to phthalates, and the proposed health risks phthalates pose to children in the United States based on analyses of what are described as "the best national data sources available" for characterizing the relationship between environmental contaminants and children's health.

Since the second edition of the America's Children and the Environment report, the draft Indicators in the newly named "Biomonitoring" section [This section was formerly labeled "Body Burden".] has increased from three [These three substances included lead, mercury, and

Cotinine] substances to nine. The list was expanded to include Polychlorinated biphenyls (PCBs), Polybrominated diphenyl ethers (PBDEs), Perfluorochemicals (PFCs), Perchlorate, Phthalates, and Bisphenol A]. While it is perfectly reasonable to assume that new substances will be added to the report as biomonitoring studies expand, and as research progresses, EPA has provided little to no explanation as to why it considers phthalates to be indicators of children's environmental health. Additionally, the draft Indicator Document fails to make the distinction between exposure levels that are considered safe by regulatory agencies and those that could result in adverse health effects. As written, the report may lead some to conclude that exposure to phthalates at any level are of concern and may contribute to the health effects described throughout this section.

Although the draft Indicator Document identifies phthalates as "25 different manmade chemicals," the document continually fails to differentiate between the various chemicals that make up the class. This is particularly problematic considering the varying characteristics of the specific chemicals and the resultant risk profiles associated with them. More specifically, the assertion that "Phthalates are suspected endocrine disruptors" is simply false. While "some" phthalates are suspected endocrine disruptors, there are just as many that have not been linked to endocrine disruption. Further, the chapter only presents biomonitoring data for three of the 25 phthalates, di-2-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBzP). Therefore, the section would be more appropriately titled "Biomonitoring: DEHP, DBP, and BBzP."

> **Response:**
> The entire topic text section is meant to give an overview of the studies regarding phthalate exposures and associated health outcomes that may be of interest for children's health. We feel that we adequately explain why phthalates is a topic area that is included in the report.
> We have revised the text to make clear that only some phthalates have been associated with adverse health outcomes. For example, the statement referred to in the comment (on page 2 of the document) now reads "Some phthalates are suspected endocrine disruptors."

The confusion caused by the various types of phthalates can be seen in the draft Indicator Document's failure to properly identify the sources of exposure for the different phthalates. In this section there are a number of instances where the exposure pathway of various phthalates is mischaracterized. Some of these instances include:

- The document states that "phthalates" are found in personal products, while only diethyl phthalate (DEP) is currently used in such products.
- The document mischaracterizes the implications of the Consumer Product Safety Improvement Act of 2008 (CPSIA) by stating that it "banned" six phthalates. While it is true that DBP, BBP, and DEHP are prohibited in toys and child care articles, DnOP, DINP,

and DIDP are only temporarily prohibited from toys and child care articles that can be mouthed.

- The document also states erroneously that DEHP is used in "auto upholstery…toys, and food packaging." The FDA has concluded that phthalates, including DEHP, are not used in food packaging. [The draft section "Environments and Contaminants: Food Contaminants" (page 3) also incorrectly states that phthalates are used in food packaging]. Additionally, it is no longer used in toys or in auto interiors.

  Response:
  We have made the change regarding DEP. We have clarified the implications of the CPSIA. We have made changes regarding food packaging, etc. as suggested in the detailed comments provided by ACC.

In addition to the failure to properly associate specific phthalates with pathways of exposure, the draft Indicator Document also fails to provide an accurate depiction of the current state of the science regarding the risk profile associated with phthalates. Some of these inaccuracies concern biological mechanism for exposures, including:

- Phthalates are rapidly metabolized in the body. There is no evidence to suggest that they are stored in breast milk or elsewhere.
- The available evidence indicates that phthalates in dust are not biologically available. Levels in dust do not correlate with the metabolite levels found in the inhabitants.
- As a class of compounds, the phthalates have low volatility. The potential for inhalation exposure is very low for all but the smallest members of the class (DEP, DMP).
- Phthalates are not readily absorbed through the skin.

  Response:
  We have made the suggested change to the sentence regarding breast milk. We agree that there are few studies that have looked at whether phthalate levels in dust correlate with levels found in the inhabitants. However, phthalate levels in dust are an important potential route of exposure. Two studies, by Becker et al. and Fromme et al., are specifically cited in the detailed comments from ACC. In the Becker et al. study, the authors concluded that a failure to show a correlation between levels found in dust and urinary levels in children may have been due to the wide range of ages included in the study (3-14 years). They proposed that very young children may be more highly exposed to DEHP in dust since they spend more time on or near the floor and that evaluation of very young children might show such a correlation. Their study included too few young children to evaluate this possibility. Furthermore, the expert panel convened for the preparation of NTP's DEHP monograph concluded that the lack of correlation between dust levels and urinary levels in this study may be due to the contribution of other exposure media. The Fromme et al. study did not include correlation of levels in dust with biomonitoring data. Therefore, we cannot conclude that the levels present in dust cannot be related to biomonitoring levels and the statement "The phthalates that may

be present in dust can be ingested by infants and children through hand-to-mouth activities" is appropriate. We have made the change suggested (in the ACC detailed comments) to the sentence describing inhalation exposure to read "Other minor routes of phthalate exposure include inhalation, drinking contaminated water, and absorption through the skin."

EPA responses to comments submitted by Asa Bradman, University of California - Berkeley

Comment:
Possible considerations to add to the America's Children and the Environment (ACE)indicators: Pesticide use and pest problems in California Child Care (see http://apps.cdpr.ca.gov/schoolipm/childcare/pest_mgt_childcare.pdf)

Response:
We reviewed the suggested document, but did not identify information applicable for indicator development.

Comment:
Possible considerations to add to the America's Children and the Environment (ACE)indicators: Housing quality indicators based on the HUD housing survey and census data.

Response:
We did not consider such potential indicators to be a priority for ACE3. Data on children in physically inadequate housing are reported in the interagency America's Children report.

EPA responses to comments submitted by Heather L. Brumberg, MD, MPH, FAAP, New York Medical College

Health: Neurodevelopmental Disorders

These are important indicators. The potential association between ADHD and prematurity was not mentioned, but noted recently by the EPIPAGE study: Delobel-Ayoub et al. Pediatrics 2009, Aarnoudse-Moens et al. Pediatrics 2009, and the EPICure study: Johnson et al. J Am Acad child Adolesc Psychiatry 2010. On the other hand, Heinonen et al. in BMC Pediatr 2010 recently found the association not with prematurity but small for gestational age. Due to the lack of clarity in the literature and the rising rates of neurodevelopmental disorders as well as rising rates of prematurity, it might be interesting to relate these to both prematurity and low birth weight, and then examine environmental exposures effects. Similarly autism spectrum disorders were noted to be associated with prematurity by multiple studies including the ELGAN study: Limeropoulos et al. 2008 Pediatrics article, Johnson et al. J Pediatr, and Kuban et al. 2009 J Pediatr.

> **Response:** We have added text noting the possible contributions of adverse birth outcomes to neurodevelopmental disorders, and particularly ADHD.

Health: Adverse Birth Outcomes

I would caution that more and more data is emerging suggesting that even birth at term (37 or 38 weeks) do not have as good outcomes as 39 weeks gestation. It is increasingly clear that those "early term" infants are at risk for morbidities noted in recently published papers including those by Tita et al. New England journal of Medicaine 2009, Clark et al. AJOG 2009, Moster et al. JAMA 2010, Bailit et al. AJOG 2010. As the chapter has alluded to, I believe it is difficult to separate out mortality and morbidities and prematurity and low birth weight overlap so much. For example a heart problem in a low birth weight baby described is likely a patent ductus arterious which is also more common in preterm infants. In the background section, line 26-32 describing low birth weight morbidities could use a reference from a neonatal text book in addition to the cited one of a patient information page from JAMA. Line 40-42 should also consider poorer maternal health (maternal obesity, hypertension, diabetes) relating to the delivery of an infant early due to maternal reasons. Lines 27-36 might be worthwhile to reference the World Trade Center study by Perera et al. EHP 2005. Under the Overview of the NVSS Natality Data section, perhaps prematurity may be broken down into smaller categories such as the late preterm (34-37 weeks) and very preterm <32 weeks. Interestingly the late preterm group which there is mounting evidence have higher risk of mortality/morbidities is the major contribution to rising rates of prematurity while extremely prematurity rates have remained fairly stable over time. Should an increasing environmental exposure be contributing, perhaps this may be a high yield group to examine? Under the Age, Race, and Ethnicity section, it is not clear why maternal age of 40 or greater was chosen when traditionally advanced

maternal age has been defined as >35 years of age where issues such as a higher risk of having an infant with Trisomy 21.

> **Response:** We have added mention of “early term” infants and cited three references. We changed the wording to reflect the point about prematurity and low birth weight. We believe the current reference adequately supports the text about low birth weight morbidities. Poorer maternal health is mentioned near the end of that paragraph with “other factors” that affect preterm birth and low birth weight. We have added the Perera et al., 2005 study as well as other studies of PAHs and LBW/IUGR.
> Tracking preterm birth defined as <37 weeks is common practice that we retain. However, we added text to reflect that not all infants born before 37 weeks have the same risk of adverse outcomes. We feel that a cut point of either age 35 years or 40 years would work, but have retained 40 because while it is true that women >35 have a greater risk of adverse outcomes such as preterm birth, even women 30-34 have a higher rate of preterm birth compared to women 25-29. The rate increases with age and there is no specific age at which the preterm birth rate jumps up, so a somewhat arbitrary cut point must be chosen.

Special Features: Birth Defects

Why is the Texas the best congenital malformations registry? Could multiple states' congenital malformations registries be pooled?

> **Response:** No judgment is made in the document that the Texas birth defects registry is "the best" birth defects registry. However, the Texas Birth Defects Registry is one of the top active surveillance birth defect registries in the U.S., covers nearly 10% of births in the U.S., and has been cooperative in sharing data for this report. Estimates of 21 birth defects, pooled from 24 registry programs with varying case ascertainment methods, have been published by CDC in collaboration with the National Birth Defects Prevention Network (NBDPN). The Texas registry data reports on a broader range of birth defects, including some with relatively high prevalence that are not reported by the NBDPN. Text describing the NBDPN has been added.

EPA responses to April 21, 2011 comments from Laura Brust, High Molecular Weight Phthalate Esters Panel of the American Chemistry Council

The High Molecular Weight Phthalate Esters Panel of the American Chemistry Council appreciates the opportunity to provide comments on the draft of the Agency's Third Edition of America's Children and the Environment (ACE). The Panel represents the North American manufacturers of high molecular weight phthalates. [High molecular weight phthalates are diesters of phthalic anhydride based on alcohols with nine or more carbon atoms]. The Panel believes that the information in the draft report is not "presented in an accurate, clear, complete, and unbiased manner," as required by EPA's information quality guidelines, because it is not specific to the different types of phthalate esters. The report should be revised to clarify that the data presented are applicable to specific phthalates and not to phthalates as a class.

The draft Biomonitoring: Phthalates section presents biomonitoring data for only three of 25 phthalates – dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), and di(2-ethylhexyl) phthalate (DEHP). Therefore, the section would be more appropriately titled "Biomonitoring: DBP, BBP, and DEHP." The draft section identifies phthalates as "25 different manmade chemicals," but continually fails to differentiate between the various chemicals that make up the class. In so doing, the Agency ignores the divergent physical and chemical characteristics of the specific chemicals and the resultant hazard and risk profiles associated with them. Consequently, the draft section makes general statements, such as that on Page 2 (Line 20), that "Phthalates are suspected endocrine disruptors." While a few phthalates cause adverse reproductive and developmental effects in rodents, [The exposures estimated from the Centers for Disease Control data for DBP, BBP, and DEHP are below the safe levels established by EPA and, more recently, by European regulatory agencies. Recent reviews by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction and the European Chemicals Bureau have concluded that typical childhood exposures are not of concern] others, such as the high molecular weight phthalates diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and dipropylheptyl phthalate (DPHP), show only weak effects at very high doses or are inactive.

Response:

We have revised the text to make clear that only some phthalates have been associated with adverse health outcomes. For example, the statement referred to in the comment (on page 2 of the document) now reads "Some phthalates are suspected endocrine disruptors." While we understand the suggestion to rename the topic, our report is meant to reach a broad audience—one that may require some introduction to phthalates before delving into the specific compounds. Note that this format is consistent across the report topics. For example, a similar approach has been taken with the perfluorochemicals topic.

EPA response to Comments submitted by Alycia Halladay, PhD, Autism Speaks

Under "Health: Neurodevelopmental Disorders", page 5 – the discussion of the factors accounting for the rising prevalence in autism should be accompanied by research at Columbia University which uses the California DDS system to identify and quantify factors which contribute to this change. Dr. Peter Bearman and his colleagues have estimated that approximately 50% of the increase in prevalence is unexplained. Full articles can be found here: http://www.understandingautism.columbia.edu/papers/

> **Response:** We have expanded the sentence to include increased parental age, and have added several references - including three articles by Bearman and colleagues.

Under "Health: Neurodevelopmental Disorders", page 5, line 7: Two different epidemiological studies have linked pesticide exposure during pregnancy to an increased risk of ASD. These studies should be included here.

> **Response:** We reviewed these studies (D'Amelio et al. 2005 and Roberts et al. 2007) and determined that their findings were too limited and narrow to warrant inclusion.

Under "Health: Neurodevelopmental Disorders", page 5, line 7: "many" should be changed to "some". Also, the CNV burden is higher in simplex families compared to multiplex families. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1933261/?tool=pubmed

> **Response:** The change to "some" has been made.

Under "Health: Neurodevelopmental Disorders", page 5, line 12: the reference provided examined all CNVs, both inherited and denovo. As currently written, it implies that only de novo CNVs were found in synaptic patterning genes.

> **Response:** We reviewed the sentence and determined that this point provided more detail than needed for this text; therefore, the sentence was deleted.

Under "Health: Neurodevelopmental Disorders", page 5, line 15, insert "Some" before "Children"

> **Response:** The revision has been made.

Under "Health: Neurodevelopmental Disorders", page 5, lines 22-35: Additional studies have studied large databases for association between thimerosal containing vaccines and autism and have reported no association.

> **Response:** We did not make a change to this paragraph, as we do not intend to address the breadth of the literature on this point; citing the IOM conclusion is sufficient.

Under “Health: Neurodevelopmental Disorders”, page 5: The report does not review or include scientific evidence linking altered immune status with ASD, both in epidemiological and clinical reports. Changes in the immune system during pregnancy could contribute to the etiology or trigger ASD symptoms. Many environmental chemicals are known to affect the immune system, and these findings are relevant to the ACE report.

Response: We chose not to make this addition, given the limited literature.

Under “Health: Neurodevelopmental Disorders”, the role of epigenetics in autism is being more closely studied. Preliminary studies have identified epigenetic regulation on many genes of interest relating to autism. In addition, many disorders with similar behavioral phenotypes, including Rett Syndrome and Prader-Willi Syndrome, are caused by improper methylation of genes during conception and development. This should be mentioned in this section as a possible mechanism of gene/environment interactions.

Response: We chose not to make this addition, given the limited nature of the findings specific to autism at this point.

Under “Health: Neurodevelopmental Disorders”, page 9, lines 7-11. The Autism and Developmental Disorders Monitoring network (ADDM) is mentioned on page 9, however, this report relies on the National Health Interview Survey as the main source of prevalence. The ADDM is an active prevalence study, which utilizes data at 11 network sites, capturing diagnosis data on over 300,000 children at age 8. The records are individually reviewed by developmental specialists and the network re evaluates data from 8 year olds a regular basis. Changes in prevalence over time are more accurately represented by ADDM data compared to a single phone interview in the NHIS survey. It is recommended that the ADDM data published in 2010 serve as indicators for prevalence of ASD.
http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5810a1.htm

Response: We carefully considered the use of ADDM data for this indicator; however, we determined that the NHIS is more consistent with the ACE criteria - including regular updates that are gathered consistently over time, and availability of data. We agree regarding the importance of the ADDM data, which is why we provide the estimates in the text.

EPA responses to April 21, 2011 comments from the Polycarbonate/BPA Global Group of the American Chemistry Council

Re: America's Children and the Environment, Third Edition (ACE3) – Biomonitoring: Bisphenol A (BPA)

Dear Sir or Madam:

The Polycarbonate/BPA Global Group of the American Chemistry Council (ACC)[1] respectfully submits these comments on the Environmental Protection Agency's Draft Indicators for America's Children and the Environment, Third Edition (ACE3). The Polycarbonate/BPA Global Group represents the leading global manufacturers of BPA and polycarbonate plastic. For many years the group has sponsored scientific research to understand whether BPA has the potential to cause health or environmental effects and to support scientifically sound policy. These comments specifically focus on the Biomonitoring: Bisphenol A (BPA) section and are in addition to comments on other ACE3 sections submitted separately by ACC.

Please do not hesitate to contact me if I can be of further assistance to clarify any comments or if additional information is needed. I can be reached at (202) 249-6624 or by e-mail at steve_hentges@americanchemistry.com.

Regards,

Steven G. Hentges, Ph.D.
Polycarbonate/BPA Global Group

[1] The American Chemistry Council represents the leading companies engaged in the business of chemistry. Council members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. The Council is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $674 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies are among the largest investors in research and development.

Comments of the Polycarbonate/BPA Global Group on the Environmental Protection Agency's Draft Indicators for America's Children and the Environment, Third Edition (ACE3)

April 21, 2011

1. Selection of Bisphenol A as a Children's Health Indicator is Not Supported by the Weight of Scientific Evidence

a. Environmental contaminants selected as children's health indicators require a clear link to children's health

As stated on the ACE3 website, an indicator is a "*quantitative depiction of an important aspect of children's environmental health*."[2] The same website further states that ACE is "*EPA's compilation of children's environmental health indicators and related information, drawing on the best national data sources available for characterizing important aspects of the relationship between environmental contaminants and children's health*."[2] These concise statements make it clear that an environmental contaminant must be clearly linked to children's health to qualify as an ACE indicator.

The importance of a clear link to children's health is further highlighted by two of the main purposes of ACE, which are to "*inform discussions among policymakers and the public about how to improve federal data on children and the environment*" and, most importantly, "*help policymakers and the public 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*."[2] These purposes would be difficult to realize by focusing on environmental contaminants that are not clearly linked to children's health, and such a focus might well be counter-productive by applying attention and resources to substances that have no significant bearing on children's health.

Consistent with the need for a clear link to children's health, the "Body Burden" section of the current ACE webpage[3] states "*the measures in this section do not account for many environmental contaminants that are important to children but … for which information is lacking to evaluate health significance. For example, data are now available for a number of other environmental contaminants … [h]owever, no information is available to show how these concentrations relate to health risks.*" Environmental contaminants should be carefully selected as indicators only when adequate information is available to evaluate health significance and relate concentrations to health risks. Lack of information to evaluate and, most importantly, lack of health risks both should disqualify a substance from selection as a children's health indicator.

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[2] See http://www.epa.gov/ace/ace3draft/index.html.
[3] See http://www.epa.gov/ace/body_burdens/bb_background.html.

Response: The intent of ACE is to provide indicators that address potential factors that may affect children's environmental health. The report does not represent or require a weight-of-evidence determination. The scope and intent of the report have been clarified in expanded introductory text prepared for the full report. In particular, the scope of ACE goes beyond substances with known effects on children's health; established causal relationships are not necessary for inclusion of an issue in ACE. This information in the final report provides readers with appropriate context to recognize the extent of current scientific understanding regarding the potential of an environmental contaminant to affect children's health. BPA is included in the report to convey the extent of our current knowledge and to encourage continued research in this area.

b. The weight of scientific evidence does not provide a clear link between bisphenol A and children's health risks

Bisphenol A (BPA) is one of the best tested substances in commerce. The scientific literature is replete with many hundreds of studies on BPA and this extensive data has been comprehensively reviewed in recent years by many government agencies worldwide. In contrast, the ACE3 text that provides the rationale for designation of BPA as a children's health indicator is less than two pages in length and includes only 37 citations. Although the number of citations is limited, the ACE3 text does acknowledge that "*the effects of low-dose exposure to BPA in lab animals are debated within the scientific community*," meaning there is no scientific consensus that BPA is a human health risk.

Although there are many comprehensive government assessments of BPA, the ACE3 citations refer only to one, specifically from the National Toxicology Program (NTP), which concluded there was "some concern," "minimal concern" or "negligible concern" for certain developmental effects. However, not mentioned is that these conclusions were primarily based on laboratory animal studies that, according to NTP, "*provide only limited evidence for adverse effects on development and more research is needed to better understand their implications for human health*." In other words, no actual health risks were identified by NTP.

The ACE3 text also notes that "*epidemiological data on the effects of BPA in human populations are limited*." Similarly, but with a more complete conclusion, NTP noted that there was "*insufficient evidence to determine if bisphenol A causes or does not cause reproductive toxicity in exposed adults*" or "*developmental toxicity when exposure occurs prenatally or during infancy and childhood.*" As with laboratory animal studies, the available epidemiological studies do not identify actual human health risks, and due to significant study design limitations, are generally incapable of doing so.

The ACE3 text further notes that "*the primary route of human exposure to BPA is believed to be through diet, when BPA migrates from food and drink containers*." In light of this generally accepted belief, it is quite remarkable that the text makes no mention whatsoever that food contact products are regulated by the Food and Drug Administration (FDA) and that FDA is

currently conducting an assessment of the safety of BPA from these products. In its last significant update (January 2010), FDA stated that "*studies employing standardized toxicity tests have thus far supported the safety of current low levels of human exposure to BPA*" and "*BPA is not proven to harm children or adults*." As stated by Dr. Joshua Sharfstein, who at the time was the principle deputy commissioner of FDA, "*if we thought it was unsafe, we would be taking strong regulatory action*." Based on its current view that BPA is safe for use in products that contact food, FDA has not taken or proposed any regulatory action on BPA.

In addition to reviewing existing scientific information on BPA, FDA is also conducting research in its own laboratory – the National Center for Toxicological Research – to answer key scientific questions and clarify uncertainties. To date, FDA's researchers have published four studies from their ongoing research in the peer-reviewed scientific literature.[4,5,6,7] Collectively, these new studies provide additional strong support for FDA's current view that BPA is safe for use in food contact products.

> **Response:** Weight-of-evidence determinations are beyond the scope of ACE. The purpose of the background text provided for each topic is to briefly summarize key findings from the literature that are informative as to possible relationships between environmental contaminants and children's health outcomes. The conclusions by the National Toxicology Program on reproductive and developmental effects of BPA, as well as other peer-reviewed articles described in the topic text, justify the inclusion of BPA as an indicator in the ACE3 report. Information on NTP levels of concern is provided in the topic text, and general information on reconciling information from animal studies and epidemiological studies is provided in the report introduction. The pharmacokinetic papers of Doerge et al., and the Volkel et al. article describing BPA measurements in urine of infants have been incorporated into the revised text, along with more recent papers from the FDA laboratory by Doerge et al. and Fisher et al. The Twaddle et al. reference was not included as it was a methods article and not directly relevant to the information presented in this indicator. We have added text concerning FDA's regulatory authority for BPA to the first paragraph.

c. The ACE3 text intended to support selection of BPA as an indicator is incomplete and misleading

The FDA research also helps to highlight some of the significant limitations presented by the very short and incomplete text in the draft ACE3 document on BPA. For example, the second to last paragraph (page 2, lines 16-26) states that "*children, particularly developing fetuses and*

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[4] Doerge, D. R., Twaddle, N. C., Woodling, K. A., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. Toxicology and Applied Pharmacology. 248(1):1-11.

[5] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. Toxicology and Applied Pharmacology. 247(2):158-165.

[6] Doerge, D. R., Vanlandingham, M., Twaddle, N. C., and Delclos, K. B. 2010. Lactational transfer of bisphenol A in Sprague-Dawley rats. Toxicology Letters. 199(3):372-376.

[7] Twaddle, N. C., Churchwell, M. I., Vanlandingham, M., and Doerge, D. R. 2010. Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague-Dawley rats using liquid chromatography with tandem mass spectrometry. Rapid Communications in Mass Spectrometry. 24(20):3011-3020.

infants, are likely to be more sensitive to the effects of BPA due to their developmental stage." The paragraph then goes on to state that infants and children are exposed to higher levels of BPA compared with adults and are less effective at metabolizing BPA.

At the outset, it should be noted that this paragraph (and numerous other places in the document) incorrectly states that BPA is found in human urine. In fact, many studies have shown that what is present in urine is not BPA itself but rather a metabolite of BPA that has been shown to be non-estrogenic and has no known biological activity. This distinction is very important since it illustrates what is known from many human and laboratory animal pharmacokinetic studies, which is that humans very efficiently metabolize and eliminate BPA from the body.

The evidence presented to support the assertion that infants are exposed to higher levels of BPA is a single study on premature infants in neonatal intensive care units, which is of questionable relevance for the vast majority of infants. Recent data on infants of 1-2 months age does not support the assertion that infants are exposed to higher levels of BPA.[8]

More importantly, recent data from FDA's research indicates that neonatal monkeys at a very young age do have ample capability and capacity to metabolize BPA, comparable to adults.[4] This study, along with other laboratory animal studies, does not support the assertion that infants are more sensitive to the effects of BPA. Although not designed to evaluate metabolism, the cited study on premature infants does not support the assertion that infants are less effective at metabolizing BPA. As stated by the authors, "*more important, our findings suggest that even premature infants have some capacity to conjugate BPA*." Similarly, the study on infants of 1-2 months of age showed that BPA in urine is predominately in the form of conjugated metabolites, indicating that very young infants are able to metabolize and eliminate BPA from the body.

> **Response:** The BPA topic text presents a balanced and concise summary of current research and concerns associated with BPA but a comprehensive review of the literature is beyond the scope of ACE. Additional and updated references were included in the revision, including several references suggested in these comments. We have clarified the text surrounding BPA metabolites to note that they are non-estrogenic, but feel that the existing characterization of BPA measurements in urine accurately describes what is measured. We have also edited the text to clarify the findings regarding metabolism in young animals and their possible relevance to humans and have removed the statement that children are likely to be more sensitive to the effects of BPA.

2. Bisphenol A Biomonitoring Data and the Derived Children's Health Indicators Are Presented With No Useful Health Context

The draft ACE3 document on BPA provides an extensive description of how the two indicators were statistically derived from biomonitoring data. Completely missing is any

[8] Völkel, W., Kiranoglu, M., and Fromme, H. 2011. Determination of free and total bisphenol A in urine of infants. Environmental Research. 111(1):143-148.

information to provide a meaningful context to understand the health significance of the biomonitoring data or the indicators. This is a significant flaw that should be corrected if the indicators are adopted.

a. Current exposure levels are far below safe intake limits

In isolation, biomonitoring data is only an indicator of exposure to a substance and does not directly provide any indication of the health significance of the exposure, which is of fundamental importance for an ACE3 children's health indicator. As stated by the Centers for Disease Control and Prevention (CDC) in regard to its BPA biomonitoring data, "*Finding a measurable amount of BPA in the urine does not mean that the levels of BPA cause an adverse health effect.*"[9]

Ample information is available in the peer-reviewed scientific literature and from government sources to provide the health context that is needed. The same CDC biomonitoring data that is used to derive the indicators has been used to estimate daily intake of BPA.[10,11] Comparison of estimated daily intakes with established health-based exposure guidance values provides a simple and meaningful context for the health significance of the biomonitoring data. For example, both EPA and the European Food Safety Authority have established health-based exposure guidance values for BPA in the form of a Reference Dose (RfD) and Tolerable Daily Intake (TDI), respectively. In both cases, the value is 50 µg/kg bodyweight/day, which is approximately 3 orders of magnitude above the estimated daily intakes associated with the median concentrations of BPA metabolites in urine reported in CDC's biomonitoring data and the derived indicators.

In a related analysis, the same health-based exposure guidance values have been converted into a "biomonitoring equivalent," which is an estimate of the urinary concentration that is equivalent to a health-based exposure guidance value.[12] The biomonitoring equivalent for BPA was calculated as 2.6 mg/g creatinine, which is approximately 3 orders of magnitude above the median concentrations of BPA metabolites in urine.

In addition to providing useful health context for the BPA biomonitoring data and derived indicators, these analyses also indicate that the levels of BPA metabolites reported in urine are not indicative of a health risk. Consistent with the discussion above, these analyses also indicate that there is no link between the proposed children's health indicator values and an actual human health risk.

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[9] See http://www.cdc.gov/exposurereport/BisphenolA_FactSheet.html.

[10] LaKind, J. S. and Naiman, D. Q. 2008. Bisphenol A (BPA) daily intakes in the United States: Estimates from the 2003-2004 NHANES urinary BPA data. Journal of Exposure Science and Environmental Epidemiology. 18(6):608-615.

[11] LaKind, J. S. and Naiman, D. Q. 2010. Daily intake of bisphenol A and potential sources of exposure: 2005-2006 National Health and Nutrition Examination Survey. Journal of Exposure Science and Environmental Epidemiology. In Press.

[12] Krishnan, K., Gagné, M., Nong, A., Aylward, L. L., and Hays, S. M. 2010. Biomonitoring equivalents for bisphenol A (BPA). Regulatory Toxicology and Pharmacology. 58(1):18-24.

Response: A general discussion regarding the presentation of the biomonitoring indicators has been provided in the introduction to this section in the full ACE3 report. This text notes that in most cases information on health risks associated with levels of chemicals in blood or urine typical for the general population is limited. EPA has not developed reference doses or other guidance values in biomonitoring units, thus there is no clear basis for providing conclusions on the health significance of the BPA levels presented in the indicators; and as noted in the text and comments above, the question of what levels of BPA exposure are harmful are debated within the scientific community. The indicators nevertheless are informative regarding trends in population exposure; for example, it will be interesting to observe whether there are reductions in urinary BPA over time following recent reformulations of various BPA-containing consumer products.

b. Spot urine sample biomonitoring data is of very limited value as a health indicator for individuals

It is well known that BPA has a very short half-life in the body. Consequently, the level of BPA metabolites measured in urine will vary considerably both within a day and between days as a function of short-term exposure patterns. This has recently been demonstrated in a CDC study that monitored levels of BPA metabolites over 7 days.[13] As concluded by these researchers, BPA biomonitoring data based on spot urine samples may adequately reflect a population's average exposure to BPA, provided the sample size is sufficiently large and samples are randomly collected throughout the day. However, the concentration of BPA metabolites in a single spot sample is not a reliable measure of an individual's exposure due to high variability both within a single day and across days.

Since the CDC biomonitoring data is based on single spot samples, the data and the children's health indicator values derived from this data are not suitable for application to individuals. As a minimum, this limitation should be discussed to reduce the potential for the indicator values to be misused by application to individual urine biomonitoring values. More importantly, due to this severe limitation, the children's health indicators should not be adopted at all if they are intended as indicators for individuals.

Response: We agree with the comments regarding the limitations of spot samples for assessing an individual's exposure, and believe that the focus on population characterization is clear in our presentation of the data. The expanded introduction for the Biomonitoring section provides further context for understanding the data. Text regarding individual variability in urine samples has been revised, and the Ye et al. reference has been incorporated.

[13] Ye, X., Wong, L.-Y., Bishop, A. M., and Calafat, A. M. 2011. Variability of urinary concentrations of bisphenol A in spot samples, first-morning voids, and 24-Hour collections. Environmental Health Perspectives. In Press.

EPA responses to March 28, 2012 comments from Alan Kantz, Global Advisors on Smokefree Policy

Comments on America's Children and the Environment, Third Edition Draft

Global Advisors on Smokefree Policy (GASP) is a non-profit dedicated to serving and educating the public on smoke- and tobacco-free public policies. We provide guidance and expert technical assistance to address public health concerns on the sales, marketing, and use of tobacco. We consult with colleagues and the public at large to resolve smoking-related issues.

While reviewing the draft of America's Children and the Environment, Third Edition ("Report"), we noticed some omissions regarding secondhand smoke:

In Biomonitoring: Cotinine, on page 1, lines 20-23, the Report should expand the list of chronic diseases caused by environmental tobacco smoke (ETS) to include diabetes and other chronic diseases linked to ETS exposure. More broadly, the Report needs to mention that with the increasing use of smoking non-tobacco products or products where tobacco is one of many ingredients, e.g. hookah smoking, cotinine levels may not be a reliable indicator of secondhand smoke exposure.

Response: We did not identify sufficient references to support addition of these points.

In Environments and Contaminants: Criteria Air Pollutants, on page 3, lines 31-37, the Report needs to include tobacco smoke and ETS in the list of major sources of carbon monoxide exposure, and note that these point sources can escape detection in large-scale monitoring programs.

Response: In this section, we are addressing pollutants in ambient air rather than sources in indoor environments, which are addressed elsewhere in the report.

In Environments and Contaminants: Indoor Environments, on page 1, lines 42-44, the Report needs to mention the new health concern "thirdhand smoke" (THS) as another vector through which outdoor pollution can penetrate indoor environments. THS is ETS that adheres to materials like carpet, walls, furniture, plastic, cloth, hair or skin, and continuously gases off noxious carcinogenic vapors. In some situations, a smoker or a nonsmoker in close proximity to outdoor smoking may inadvertently transport THS on their person from the outdoor environment to an indoor environment. For example, a mother who smokes outside to avoid exposing her children to ETS may still expose them to THS when she carries and feeds them after smoking, since THS is on her clothing and hair. THS in a situation like this one is distinct from indoor ETS produced by indoor smoking.

Response: Discussion of "thirdhand smoke" has been added. "Furthermore, children may be exposed to toxic residues that remain from ETS in dust and on surfaces inside the home for weeks or months after smoke has cleared from the air. These residues, referred to as "third-hand smoke," may be re-emitted into the gas phase or may react with other compounds to form secondary pollutants. The risk of exposure to third-hand smoke may be particularly high for infants, due to their close proximity to contaminated objects such as blankets, carpets, and floor surfaces, and their frequent hand-to-mouth activity."

On page 2, lines 20-21 of the same section, carbon monoxide should be listed as a component of ETS to maintain consistency with other places ETS is mentioned in the Report (e.g. Biomonitoring: Cotinine, page 1, lines 4-6).

Response: We have modified the text in both Indoor Environments and Cotinine regarding the components of ETS; carbon monoxide is now included in both places.

On page 2, lines 22-24 of the same section, the Report needs to list THS as another way ETS can enter the air. Here is a possible rewrite of the sentence:

ETS is released into the air directly from the burning of tobacco, when cigarette or pipe smokers exhale the tobacco smoke they have directly inhaled, and from smoke embedded in surfaces including walls, cloth, hair, and skin that gasses off over time.

The Report should also note that THS can harm children, particularly infants, without entering the air. For instance, babies crawling on carpeting in a smoking-permitted home may be exposed to THS embedded in the carpet through both skin and oral contact.

Response: Please see the response above.

On page 5 of the same section, EPA needs to supplement Indicator E5, infant and early childhood exposure to ETS in the home, by also tracking exposure to ETS outside the home with a new indicator. This will aid future Reports by providing more complete information on childhood exposure to ETS to supplement the information on cotinine levels tracked under Indicator B5.

Response: Data are not available for an indicator of ETS exposure outside the home.

Thank you for considering these changes. If you have any questions, please contact me at akantz@njgasp.org or (908) 273-9368.

Regards,
Alan Kantz

Program Manager

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EPA responses to comments submitted by: Lisa K. Marengo, Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services

I have noted some errors in your DRAFT Indicator for Third Edition of America's Children and the Environment; Special Features: Birth Defects.

The first error is found on page 5, line 3 and is a misquote of my report entitled Comparison of Texas Birth Defects Registry and Texas Vital Records Data for Selected Birth Defects Readily Diagnosed at Delivery (your reference 58). I never said that "the most obvious birth defects, such a as missing limbs are only identified 43% of the time". Limb defects were not even analyzed in my report. What I reported was "For the readily diagnosed birth defects examined, 36-42% of Registry cases had their defect reported on their birth or fetal death certificate." The birth defects listed on the birth certificate that were examined included: anencephaly; spina bifida; omphalocele or gastroschisis; cleft palate alone or cleft lip with/without cleft palate; and any congenital anomaly. I have attached my report for your reference.

> **Response:** This has been corrected. The example of missing limbs has been replaced by spina bifida and cleft palate.

The second error is in the table under Data Summary on on page 15, line 22: The number of live births for 2002-2004 should read 1,131,**1**84 not 1,131,584.

> **Response:** This had been corrected.

Thank you for the opportunity to review this report.

EPA response to comments of the Phthalates Esters Panel of the American Chemistry Council

Comments of the
Phthalate Esters Panel
of the American Chemistry Council
on
America's Children and the Environment, Third Edition

Draft Indicators
Biomonitoring: Phthalates
March 2011

To Whom It May Concern:

The Phthalate Esters Panel of the American Chemistry Council appreciates the opportunity to provide comments on the draft of the Agency's Third Edition of America's Children and the Environment (ACE). The Panel represents the North American manufacturers of phthalates which are the subject of one section of the draft report. I have enclosed specific comments on the draft Biomonitoring: Phthalates section. As a general comment, however, the Panel believes that it is inappropriate, and in violation of EPA's information quality guidelines, to include phthalates among the indicators of children's health in the draft report, since the low levels of phthalates found by the Centers for Disease Control (CDC) are unlikely to contribute to the environmental risks faced by children.

> **Response:** The intent of ACE is to provide indicators that address potential factors that may affect children's environmental health. The scope and intent of the report have been clarified in expanded introductory text prepared for the current draft. In particular, the scope of ACE goes beyond substances with known effects on children's health; established causal relationships are not necessary for inclusion of an issue in ACE. This information in the draft report provides readers with appropriate context to recognize the extent of current scientific understanding regarding the potential of an environmental contaminant to affect children's health.
>
> A 2006 report from the National Toxicology Program (NTP) concluded that infants and children may be more highly exposed than adults to one phthalate (DEHP) and that there is enough evidence to justify some concern for effects of DEHP exposure on the reproductive tract of male infants and children. Additionally, the NTP concluded that there is some concern for adverse effects of DEHP exposure on the development of the male reproductive tract in male offspring of pregnant women exposed to levels of DEHP commonly detected in the general population. For these reasons, we feel that the inclusion of phthalates in the ACE report is well-supported.

Although previous ACE reports have included discussions of biomonitoring results,[14] the analysis has been limited to substances for which data are available to evaluate their significance to trends in children's health.[15] This is not the case for the phthalates included in the draft report – dibutyl phthalate (DBP), butyl benzyl phthalate (BBzP), and di(2-ethylhexyl) phthalate (DEHP). Despite a four-page introduction that attempts to summarize the available health effects information, the report has not, and cannot, relate biomonitoring levels to children's health trends described elsewhere in the draft report or to environmental risks overall. To the extent one seeks to conclude anything from the biomonitoring data for these three phthalates it is that the exposures estimated from the CDC data are below the safe levels established by EPA and, more recently, by European regulatory agencies.

The biomonitoring data do suggest that children's exposure to DBP, BBzP, and DEHP is widespread, but there is no basis to suggest that this low level exposure is a health concern or that it should be used as an indicator of overall children's health. In fact, reviews by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction and the European Chemicals Bureau have concluded that the typical childhood exposures are not of concern.[16]

If, on the other hand, EPA wishes to estimate reductions in exposure to DBP, BBzP, and DEHP as a result of the restrictions imposed by the 2008 Consumer Product Safety Improvement Act (CPSIA), the data are not yet available to make such a comparison. The current CDC data – both the 2005-06 data set described in the draft report and the 2007-08 data that have recently become available – are based on samples taken before the CPSIA restrictions took effect in early 2009.

> **Response:** Please see above response regarding findings from the National Toxicology Program. A primary purpose for presenting time series of biomonitoring data is to determine whether any increases or decreases are occurring. This can be informative as to whether interventions such as the 2008 Consumer Product Safety Improvement Act are reducing exposure to phthalates; to do so, levels occurring prior to its enactment must be quantified. Updates to the phthalate indicators will present data that might indicate whether the enactment of CPSIA has been effective for reducing exposures. Available information is insufficient to determine whether the urinary metabolite levels depicted in the indicators present a risk to children's health, and the indicators are not intended to relate exposures to health outcomes. The purpose of the background text provided for each topic is to briefly summarize key findings from the literature that are

[14] The first ACE report in 2000 included a section on Biomonitoring that included a discussion of CDC data on lead concentrations in children's blood. In the Body Burden section of 2003 version of the ACE report, EPA discussed lead, mercury, and cotinine concentrations in blood.

[15] ACE 2003, at 51.

[16] These reviews have expressed concern about the use of some phthalates in children's toys (since restricted by the CPSIA) and the potential for exposure to DEHP among neonates receiving medical treatment.

informative as to possible relationships between environmental contaminants and children's health outcomes. The topic text provides background information about why phthalate exposure may be relevant to children's environmental health, based on peer-reviewed scientific literature. Expanded introductory text provides further context for understanding what can be learned from biomonitoring indicators.

Draft Indicators

EPA gives no explanation for why it considers biomonitoring levels of the three phthalates to be indicators of children's environmental health. In presenting the biomonitoring data, the draft report makes no attempt to compare the levels to those considered safe by regulatory agencies. As written, the report may lead some to conclude that any exposure to these phthalates is of concern and that these substances may contribute to the health effects described elsewhere in the draft.

Response: The text provides a summary of the health-effects literature that suggests potential concerns for children's health from exposure to these three phthalates, and does not indicate that there are established causal relationships with adverse health outcomes. The expanded biomonitoring introduction provides readers with appropriate context to recognize the extent of current scientific understanding regarding the potential of an environmental contaminant to affect children's health. Reference doses that apply to some of the phthalates are provided in intake units (ug/kg/day) rather than biomonitoring units, and thus the indicator values cannot be directly compared to levels considered "safe." 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.

Biomonitoring: Phthalates

Since the chapter only discusses biomonitoring data for three phthalates, it should be titled *Biomonitoring: DBP, BBzP, and DEHP*.

Response: The report is meant to be accessible to a wide audience. We believe that titling the section as "Phthalates" and including a more detailed description of what is being measured in the following text ensures clarity.

Page 1, Lines 4-5

Revise sentence to read "*<u>Some</u> phthalates are also used as additives in many personal care products, such as cosmetics.*"

Only diethyl phthalate (DEP) is currently used in fragrance formulations. According to a recent survey conducted by the Food and Drug Administration (FDA), dibutyl phthalate (DBP) no longer is used in nail polish to a significant degree.

Response: We have revised the sentence to read "Some phthalates are also present in cosmetics, nail polish, hair products, skin care products, and some medications."

Lines 13-14

Revise sentence to read *"Phthalates are also used in wall coverings, tablecloths, floor tiles, furniture upholstery, carpet backings, shower curtains, garden hoses, rainwear, pesticides, ~~some toys,~~ shoes, automobile upholstery, ~~food packaging,~~ medical tubing, and blood storage bags."*

The Consumer Product Safety Improvement Act (CPSIA) has restricted DBP, butyl benzyl phthalate (BBzP), and di(2-ethylhexyl) phthalate (DEHP) from use in toys, and di-n-octyl phthalate (DnOP), diisononyl phthalate (DINP), and diisodecyl phthalate (DIDP) from use in toys that can be mouthed, since February 2009.

In a summary of recent surveys of food packaging and pharmaceuticals provided to CPSC's Chronic Hazard Advisory Panel, representatives of the FDA indicated that they were unable to find evidence of phthalate use.[17]

Response: We have rephrased the sentence to state that phthalates "are or have been used" in these products.

Line 16

Revise sentence to read "*~~Phthalates are~~ Diethyl phthalate (DEP) is also used in cosmetics, ~~nail polish~~, hair products, and skin care products, ~~and some medications~~*."

See comment on lines 4-5.

Response: This sentence comes before our description of the various phthalates and therefore we have kept the reference to phthalates more broad. Also, we have changed the language to make clear that phthalates are currently present in some nail polishes (rather than currently used in the manufacturing). We have rephrased the sentence to read, "Some phthalates are also present in cosmetics, nail polish, hair products, skin care products, and some medications."

Lines 18-21

Revise sentence to read *"The Consumer Product Safety Improvement Act of 2008 (CPSIA) banned the use of ~~six phthalates~~ DBP, BBzP, and DEHP in toys and child care articles at concentrations greater than 0.1 percent: . . ."*

[17] Video of the FDA presentations can be viewed at http://www.cpsc.gov/about/cpsia/chap0710.html.

The interim CPSIA restrictions for DnOP, DINP, and DIDP apply to toys that can be mouthed and child care articles.

> **Response:** We have rephrased to "The Consumer Product Safety Improvement Act of 2008 (CPSIA) banned the use of three phthalates in toys and child care articles at concentrations greater than 0.1 percent: di-2-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBzP). CPSIA also restricts the use of di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP), and di- n-octyl phthalate (DnOP) in toys that can be mouthed and child care articles."

Line 31
Delete sentence *"Phthalates stored in a mother's body can enter her breast milk."*

Elsewhere in the draft section (Page 6, Lines 12-14), EPA correctly notes that phthalates are rapidly metabolized and removed from the body. Consequently, they are not "stored" in breast milk or elsewhere in the body.

> **Response:** We have removed the word "stored" from the sentence. We feel it is important to keep the text regarding lactational exposure; therefore, the sentences now read "Phthalates in a mother's body can enter her breast milk. Ingestion of that breast milk and infant formula containing phthalates may also contribute to infant phthalate exposure."

Lines 33-34
Revise sentence to read *"Although ~~The~~ phthalates ~~that~~ may be present in dust ~~can be ingested by~~ the levels cannot be related to those found in infants and children present in the residence ~~through hand-to-mouth activities~~."*

The available evidence indicates that phthalates in dust are not biologically available.[18] Levels in dust do not correlate with the metabolite levels found in the inhabitants.

> **Response:** In the Becker et al. study, the authors concluded that a failure to show a correlation between levels found in dust and urinary levels in children may have been due to the wide range of ages included in the study (3-14 years). They proposed that very young children may be more highly exposed to DEHP in dust since they spend more time on or near the floor and that evaluation of very young children might show such a correlation. Their study included too few young children to evaluate this possibility. Furthermore, the expert panel convened for the preparation of NTP's DEHP monograph concluded that the lack of correlation between dust levels and urinary levels in this

[18] Becker K *et al.* DEHP metabolites in urine of children and DEHP in house dust. *Intl J Hyg and Environ Health* 207: 409-417 (2004); Fromme H *et al.* Occurrence of phthalates and musk fragrances in indoor air and dust from apartments and kindergartens in Berlin (Germany). *Indoor Air* 14(3): 188-195 (2004).

study may be due to the contribution of other exposure media. The Fromme et al. study did not include correlation of levels in dust with biomonitoring data. Therefore, we cannot conclude that the levels present in dust cannot be related to biomonitoring levels and our statement "The phthalates that may be present in dust can be ingested by infants and children through hand-to-mouth activities" is accurate.

Lines 34-36
Revise sentence to read *"Finally, infants and small children can be exposed to phthalates by sucking ~~on toys and other~~ objects made with phthalate-containing plastics."*

As indicated in the prior paragraphs, the CPSIA has restricted DBP, BBzP, and DEHP from use in toys and child care articles, and DnOP, DINP, and DIDP from use in toys that can be mouthed and child care articles.

> **Response:** Although phthalate use has been restricted in newer toys, children can come into contact with toys manufactured before the CPSIA.

Lines 38-39
Revise sentence to read *"Other <u>minor</u> routes of phthalate exposure <u>may</u> include inhalation, drinking contaminated water, and absorption through the skin."*

As a class of compounds, phthalates have low volatility. The potential for inhalation exposure is very low for all but the smallest members of the class – DEP and dimethyl phthalate (DMP). Phthalates are not readily absorbed through the skin.

Drinking water exposure to phthalates is very low. According to EPA's most recent occurrence data,[19] only 11 percent of nearly 28,000 drinking water systems reported detecting DEHP – one of two phthalates subject to a drinking water standard. Only 3 percent reported one or more detections of 3 micrograms/liter (μg/L) or higher and only 1 percent reported ever exceeding the maximum contaminant limit of 6 μg/L.

> **Response:** The text has been revised to, "Other minor routes of phthalate exposure include inhalation, drinking contaminated water, and absorption through the skin."

Lines 40-41
Revise sentence to read *"People living near phthalate-producing factories ~~or hazardous waste sites~~ may be exposed to phthalates released into the air or ground water where they live."*

[19] EPA Office of Water. Contaminant Occurrence Support Document for Category 2 Contaminants for the Second Six- Year Review of National Primary Drinking Water Regulations. EPA-815-B-09-011 (October 2009). Available at http://water.epa.gov/lawsregs/rulesregs/regulatingcontaminants/sixyearreview/second_review/index.cfm#summary.

Phthalates are readily absorbed by sediment and tightly bound. Once released from sediment they are quickly broken down. There is little chance for exposure at waste sites.

> **Response:** The Agency for Toxic Substances and Disease Registry (ATSDR) includes well-water near hazardous waste sites as a potential route of exposure in its toxicological profiles for some phthalates. Although they also note that biodegradation is expected to occur under aerobic conditions, the dominant fate of some phthalates is determined by local environmental conditions.

Page 2, Lines 3-5
Revise sentence to read *"This can be a very significant route of exposure, especially for premature infants in intensive care units~~, whose small size and fragile physical condition may increase their risk of adverse health effects from phthalate exposure~~."*

Despite the widespread use of DEHP in blood bags and tubing in neonatal care units for many years, the European Commission's Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) recently indicated that "there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans."[20] One small follow-up sponsored by the National Institutes of Health, "did not show long-term adverse outcome related to physical growth and pubertal development in adolescents previously exposed to DEHP in the neonatal period."[21]

> **Response:** The change was made as suggested.

Line 20
Revise sentence to read *"<u>Some</u> phthalates are suspected endocrine disruptors."*

The evidence for male development effects is based on exposure in laboratory animal tests to high doses of a few of the phthalates. It is incorrect to suggest that all phthalates cause such effects in rodents.

> **Response:** The change was made as suggested.

Lines 24-25
Revise sentence to read "Male laboratory animals exposed to <u>high doses of some</u> phthalates have been known to display elements of 'phthalate syndrome,'"

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[20] SCENIHR. Opinion on the Safety of Medical Devices Containing DEHP-Plasticized PVC or Other Plasticizers on Neonates and Other Groups Possibly at Risk. (February 6, 2008).

[21] Rais-Bahrami K *et al.* Follow-up study of adolescents exposed to di(2-ethylhexyl) phthalate (DEHP) as neonates on extracorporeal membrane oxygenation (ECMO) support. *Environ Health Perspect* 112: 1339-40 (2004).

See comment on line 20.

Response: The change was made as suggested.

Lines 28-30
Revise sentence to read *"A number of animal studies have found associations between <u>exposure to certain</u> phthalates ~~exposure~~ and changes in male hormone production, altered sexual differentiation, and changes to reproductive organs, including hypospadias."*

See above comments.

Response: The change was made as suggested.

Lines 38-41
Revise sentence to read *"Prenatal exposure to some phthalates at typical U.S. population levels has been associated with ~~male reproductive effects, as indicated by~~ changes in physical measures of the distance between the anus and the genitals in male infants <u>in one study</u> ~~where a shorter distance is a marker of feminization~~. <u>The significance of a reduction in this distance is unclear.</u>"*

There is no evidence of reproductive effects in the Swan studies. The significance of the anogenital distance observations is unclear and the results from the Swan studies have not been replicated. Both NTP's Center for Risks for Human Reproduction and the European Chemicals Bureau have ignored these studies in their assessments of the phthalates included in the Swan studies.

Response: A human study was recently published that associated anogenital distance with decreased semen quality and low sperm count. We have rephrased to include discussion of this study and to better clarify the significance of anogenital distance observations to "In one study, prenatal exposure to some phthalates at typical U.S. population levels was associated with changes in physical measures of the distance between the anus and the genitals (anogenital distance) in male infants. A shorter anogenital distance has been associated with decreased fertility in animal experiments and a recent human study reported that a shorter anogenital distance in men was associated with decreased semen quality and low sperm count."

Lines 41-42
Revise sentence to read *"One study found that boys born to women <u>working in the hairdressing industry or as cleaners</u> ~~exposed to phthalates at work~~ were more likely to be born with hypospadias."*

The study by Nassar *et al.* did not measure actual exposure to phthalates, but used job classification in the "hairdressing and beauty industry" or as "cleaners" as a surrogate for

phthalate exposure.[22] The authors indicated that about 30 percent of the study population did not provide occupational data and that "this may have biased results." It is inappropriate to suggest an association between hypospadias and phthalate exposure.

> **Response:** We have removed the text regarding hypospadias and the Nasser et al. reference.

Lines 42-44
Revise sentence to read *"Another study observed an association between increased concentrations of phthalate metabolites concentrations in breast milk and altered reproductive hormone levels in newborn boys, although the findings were not consistent with those in laboratory animals."*

The study, while small, found no relation between phthalate levels in breast milk and incidence of cryptorchidism. The LH levels reported in the study were within normal limits. The reported findings for MEP and MMP are inconsistent with the animal evidence.

> **Response:** In this paragraph, we are only discussing human studies and therefore do not relate findings to animal studies. However, we have rephrased the statement to clarify the study's findings to "Another study reported an association between increased concentrations of phthalate metabolites in breast milk and altered reproductive hormone levels in newborn boys. The same study did not find an association between breast milk phthalate metabolite concentrations and cryptorchidism."

Lines 45-46
Delete sentence *"Childhood levels of certain phthalate metabolites have been weakly associated with pubic hair development in a group of 6-8 year old girls."*

Metabolites were measured in single spot urine samples in the study by Wolff *et al.*[23] Despite the fact that phthalate metabolite levels were grouped into categories (low and high) and divided into quartiles, the reported association with pubic hair development was still very weak.

> **Response:** We have removed the sentence as suggested.

Page 3, Lines 1-3

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[22] Nassar N *et al.* Parental occupational exposure to potential endocrine disrupting chemicals and risk of hypospadias in infants. *Occup Environ Med* 67: 585-589 (2010).

[23] Wolff MS *et al.* Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. *Environ Health Perspect* 118 (7): 1039-46 (2010).

Revise sentence to read *"A recent study found negative associations between urinary phthalate metabolite concentrations and thyroid hormone levels and growth in children, although the metabolite levels were not adjusted for creatinine concentrations."*

The estimates of exposure by Boas *et al.*[24] were based on a single spot urine sample, and likely do not correspond to actual exposures. Most of the statistically significant findings disappear when the metabolite levels are adjusted for creatinine production.

> **Response:** The sentences regarding this study have been removed.

Lines 6-7

Revise sentence to read *"A review article of published studies concluded that there is an association between ~~indicators of phthalate exposure~~ the presence of PVC in the home and risk of asthma and allergies in children."*

Phthalates were not measured in this study by Jaakkola *et al.*[25] No association with phthalates can be estimated from this study.

> **Response:** We have rephrased this text to read "Finally, some researchers have hypothesized that phthalate exposure in homes may contribute to asthma and allergies in children. Two research groups have conducted studies, primarily in Europe, and reported associations between surrogates for potential phthalate exposure in the home and risk of asthma and allergies in children."

Lines 12-13

Revise sentence to read *"Some studies suggest that typical population-level prenatal exposure to DEHP is associated with shorter pregnancy duration, while at least one other study suggests an association with a longer pregnancy term . . ."*

Other researchers (Adibi *et al.* 2009)[26] have suggested the opposite association - that exposure lengthens pregnancy.

> **Response:** We have added this reference and changed the sentence to read "A handful of studies have reported associations between prenatal exposure to some phthalates

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[24] Boas M *et al.* 2010. Childhood exposure to phthalates: associations with thyroid function, insulin-like growth factor I, and growth. *Environ Health Perspect* 118 (10): 1458-64 (2010).

[25] Jaakkola JJ *et al.* The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. *Environ Health Perspect* 116(7): 845-53 (2008).

[26] Adibi *et al.* Maternal urinary metabolites of di-(2-ethylhexyl) phthalate in relation to the timing of labor in a US multicenter pregnancy cohort study. *Am J Epidemiol* 169: 1015–1024 (2009)

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."

Lines 13-14
Delete *". . .as well as alterations of thyroid hormone levels in pregnant women."*

Huang *et al.* (2009)[27] estimated exposure from a single spot urine sample. Although calculated, the creatinine-adjusted metabolite levels were not used in the comparison to thyroid hormone levels.

> **Response:** We have removed the phrase as suggested. However, in a later paragraph we cite Huang et al. and state "Human health studies have reported associations between exposures to DBP and altered reproductive hormone levels in newborn boys, and shifts in thyroid hormone levels in pregnant women." The use of spot urine samples and the choice regarding whether to use creatinine adjustment are methodological details that do not need to be reported in this text. We note also that the concern with spot urine is that it may lead to exposure misclassification, which would bias findings toward the null. It is thus noteworthy that these studies do find associations.

Lines 22-23
Delete sentence *"Finally, there is a growing concern that exposure to phthalates may lead to neurodevelopmental problems in children."*

Although there have been a couple of studies suggesting an association, one can hardly characterize the results as a growing concern.

> **Response:** We have revised this sentence to read "Exposure to some phthalates has been associated with neurodevelopmental problems in children in some studies."

Lines 23-25
Revise sentence to read *"One study found an association between prenatal exposure to phthalates and decrements in an infant's overall quality of responsiveness, attention to visual and auditory stimuli, and quality of movement*. <u>The authors note, however, that 'the clinical or preclinical utility of a single assessment of infant behavior shortly after delivery is unclear.'</u>"

Maternal exposure was based on a single spot urine sample taken during pregnancy in Engel *et al.* (2009).[28] The authors noted that "the clinical or preclinical utility of a single assessment of infant behavior shortly after delivery is unclear."

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[27] Huang PC *et al.* Associations between urinary phthalate monoesters and thyroid hormones in pregnant women. *Human Repro* 22 (10): 2715-22 (2007).

Response: We have revised the text to incorporate additional studies with findings associating phthalate exposure to neurodevelopmental effects, conducted in children at older ages. Evaluating the strengths and weaknesses of individual studies is beyond the scope of ACE. As a general matter, we agree that studies of older children are likely to be more meaningful than assessments in infancy.

Lines 25-28

Revise sentence to read *"A follow-up study of the same group of children at ages 4 to 9 years found an association between prenatal phthalate exposure and behavioral deficits ~~commonly found in children with clinically diagnosed attention-deficit/hyperactivity disorder (ADHD) and conduct disorder~~."*

Exposure estimates of the children were based on a single spot urine sample from their mothers while pregnant. Engel *et al.* (2010)[29] acknowledged that the findings do not represent clinically significant differences in behavior.

Response: We have clarified the sentence to read "Two studies of a group of New York City children ages 4 to 9 years reported associations between prenatal exposure to certain phthalates and behavioral deficits, including effects on attention, conduct, and social behaviors." Findings of associations need not represent clinically significant differences to be of relevance for children's health.

Lines 28-30

Revise sentence to read *"Another study ~~found~~ <u>suggested</u> that children with higher levels of phthalate metabolites <u>(based on a single spot urine sample)</u> in their urine were more inattentive and hyperactive, and displayed more symptoms of ADHD compared with those who had lower levels."*

Kim *et al.* (2009)[30] measured metabolites measured in a single spot urine sample and do not appear to have been adjusted for creatinine levels.

Response: The use of spot urine samples and the choice regarding whether to use creatinine adjustment are methodological details that do not need to be reported in this text. We note also that the concern with spot urine is that it may lead to exposure misclassification, which would bias findings toward the null. It is thus noteworthy that

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[28] Engel SM *et al.* Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. *Neurotox 30: 522-528 (2009).*

[29] Engel SM *et al.* Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect* 118 (4): 565-71 (2010).

[30] Kim BN *et al.* Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. *Biological Psychiatry* 66 (10):958-63 (2009).

these studies do find associations. This text has been revised and updated to "Studies conducted in South Korea of children ages 8 to 11 years reported that children with higher levels of certain phthalate metabolites in their urine were more inattentive and hyperactive, displayed more symptoms of ADHD, and had lower IQ compared with those who had lower levels."

Lines 36-38
Revise sentence to read *"These three phthalates were chosen because they are commonly detected in humans and their potential connection to adverse children's health outcomes is ~~well supported by the scientific literature~~ <u>suggested by animal studies</u>."*

> **Response:** Some human studies have shown associations between phthalate exposure and adverse children's health outcomes. However, we acknowledge that the human data is more limited. Therefore, we have revised the sentence to read "These three phthalates were chosen because their metabolites are commonly detected in humans and their potential connection to adverse children's health outcomes is supported by the scientific literature..."

Lines 43-45
Revise sentence to read *"DEHP is currently the only phthalate plasticizer used in PVC medical devices such as blood bags and plastic tubing. DEHP is also used in flooring, wallpaper ~~auto upholstery~~, <u>and</u> raincoats~~, toys, and food packaging~~."*

FDA has concluded that DEHP is not used in food packaging. It is no longer used in toys; its use in auto interiors also has been eliminated.

> **Response:** The sentence was revised to clarify that DEHP has been used in the past in toys, food packaging, and auto interiors to read "DEHP is also currently used in flooring, wallpaper, and raincoats and has been used in toys, auto upholstery, and food packaging."

Page 4, Lines 5-7
Delete Reference 61.

The finding of an association between phthalate exposure and early breast development (telarche) by Colon *et al.* (2000)[31] is inconsistent with the preponderance of data indicating that none of the phthalates demonstrates significant estrogenic activity. The authors failed to compare the levels found in the girls in Puerto Rico (where the incidence of telarche is the highest reported) and levels found elsewhere.

[31] Colon I *et al.* Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ Health Perspect* 108(9): 895-900 (2000).

Response: This reference has been removed as suggested.

Page 5, Lines 20-22
"Indicators PHTL1 and PHTL2 use data from all cycles of NHANES for which data have been reported (the 1999–2000 cycle through the 2005–2006 cycle) to show the trend over time for women ages 16 to 49 years and children ages 6 to 17 years."

More recent biomonitoring data (2007-08) are now available from CDC.

Response: These data have been added to the indicator.

Lines 26-28
Revise sentence to read *"The primary urinary metabolites of DBP ~~are~~ is mono-n-butyl phthalate (MnBP) and the primary metabolite of diisobutyl phthalate (DIBP) is mono-isobutyl phthalate (MiBP)."*

MnBP is a metabolite of DnBP; MiBP is a metabolite of diisobutyl phthalate (DiBP). If EPA plans to combine these two products, it should indicate so clearly.

Response: We have clarified this in the text.

Page 7, Lines 7-9
"A birthrate-adjusted distribution of women's urine phthalate metabolite levels is used in calculating this indicator, meaning that the data are weighted using the age-specific probability of a woman giving birth."

Weighting introduces an unnecessary level of complexity. A more straightforward approach would be to present the data for the two age groups separately or to focus on the group with the higher probability of giving birth.

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. 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 Research 111 (1):149-155.

Lines 23-27

Revise sentence to read *"NHANES only provides phthalate metabolite data for children ages 6 years and older, which means that the indicator is not able to capture the exposure of premature infants, some of whom may have high levels of phthalate exposure due to the use of medical equipment containing phthalates; . . ."*

Exposure from medical equipment is not typical among infants.

Response: The change was made as suggested.

Lines 25-27
Delete *". . . or young children, whose play and mouthing behaviors may increase their exposure to phthalates in toys and house dust."*

As noted elsewhere, dust does not appear to be a significant contributor to exposure. The phthalates are no longer used in toys.

Response: Please see above response regarding exposure from toys and dust.

Page 9, Lines 4-6
"Between 2001–2002 and 2005–2006, the median level of the DEHP metabolites (MEHP, MEOHP, and MEHHP) in women ages 16 to 49 years increased from 33.5 to 37.9 µg/g creatinine, although this increase was not statistically significant. "

Differences that are not statistically significant should not be included in the discussion.

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. For this particular bullet, our characterization has changed due to addition of 2007-2008 data, and removal of creatinine adjustment (as recommended by peer reviewers).

EPA responses to comments submitted by James TerBush, www.BioSpotVictims.org

To whom it may concern,

Thank you for the opportunity to comment on the EPA's draft indicators for America's Children and the Environment, Third Edition (ACE3). BioSpotVictims.org, a non-profit organization which seeks to educate the public on the dangers of pet pesticide products, would like to express concern over the failure of ACE3 to consider pet pesticide products as an indoor environmental contaminant that poses significant health risks to children.

According to the EPA, tens of thousands of pets are reportedly harmed each year by pet pesticide products, particularly spot-ons, which contain a high concentration of pesticide and are applied to the backs of pets as a spot or stripe to prevent fleas and ticks. Adverse reactions from these products range in severity from skin irritation to chemical burns, seizures, and even death of the pet.

Last year, after conducting a year-long investigation into pet spot-on incidents (which had been prompted by a sharp increase in reported incidents, and national media exposure), the EPA announced the results of its investigation:

http://www.scientificamerican.com/article.cfm?id=small-dogs-susceptible-flea-poison

The EPA found that pet spot-on incidents were mainly due to labeled dosages that were too large for small pets, and product labels that had inadequate instructions and warnings. It also found that stricter regulations are needed to evaluate pet pesticide products before and after they are registered.

Incredibly, the EPA reached many of the same conclusions when it evaluated the safety of pet pesticide products in 1996:

http://www.biospotvictims.org/004003-032.pdf

Pet spot-on products have been on the market for well over a decade, but concerns over children's exposure to these products have largely gone unnoticed until recently.

In July 2009, Dr. Gail Krowech, a toxicologist at California's Office of Environmental Health Hazard Assessment, gave a presentation to California's Scientific Guidance Panel entitled Potential Designated Pesticides:

http://oehha.ca.gov/multimedia/biomon/pdf/0709IprodioneOcthilinoneFipronil.pdf

Here are some of Dr. Krowech's comments concerning fipronil, the main active ingredient in Frontline flea and tick products:

"Widely used tick and flea treatment for dogs and cats"

"Residues found in 40% of U.S. homes studied in 2005-2006"

"Potential hand-to-mouth exposure from contact with treated pets"

"Particular concern for children"

"Use is increasing"

"Potential concerns for cancer, hormone disruption, and developmental neurotoxicity"

According to a recent study of acute illnesses associated with exposure to fipronil, pet care products (Frontline) were related to more than one-third of cases and accounted for the majority of childhood cases (64%):

http://www.biospotvictims.org/2010_fipronil_clinicaltox.pdf

According to another study, which investigated fipronil residues on gloves worn while petting dogs after Frontline application, exposure to Frontline-treated pets pose human health risks:

http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list_uids=12361121&dopt=AbstractPlus

In October 2009, Nicholas Halbach, a veterinarian and member of EPA's Pesticide Environmental Stewardship Program (PESP), submitted the following comments to the FIFRA Scientific Advisory Panel, which had met to consider the EPA's draft guidelines for its Standard Operating Procedures (SOP) for Residential Pesticide Exposure Assessment:

http://www.biospotvictims.org/EPA-HQ-OPP-2009-0516-0038.pdf

Here are some of Dr. Halbach's comments:

"The steady rise of reported toxicities to spot-on products with pets underscores the potential health implications of chronic human exposure."

"Over 60% of U.S. households have one or more dogs and/or cats. Consequently, for many individuals spot-on treated pets may pose a single greatest source of chronic pesticide exposure."

"Spot-on products present a novel use of novel chemicals with undetermined endpoints in health effects. The range of active ingredients includes chemicals listed as both possible carcinogens and suspected endocrine disruptors."

In its review of the draft SOP guidelines, the FIFRA Scientific Advisory Panel expressed concern that EPA's risk assessment methodology did not adequately protect pregnant women, fetuses, and children. Furthermore, it was critical of EPA's definition of "toddlers" as children aged 3-6.

The Panel stated, "using the toddler label for ages 3-6 is simply misleading and confusing. In addition, exposure factor data collected from 3-6 year olds might lead to underestimation of exposures to 2-3 year olds since hand-to-mouth and object-to-mouth behavior generally decline with age. Children with developmental delays, such as those with intellectual disabilities and/or autism, may still exhibit mouthing behavior at age 6. Finally, at least one Panelist is concerned that the Agency's questionable 'toddler' age selection is an indication that actual infant and toddler exposures have not been adequately examined."

Here are the minutes from the FIFRA Scientific Advisory Panel meeting:

http://www.biospotvictims.org/EPA-HQ-OPP-2009-0516-0054.pdf

Similar concerns had been expressed three years earlier by a group of EPA scientists and risk managers. They sent a letter to the EPA Administrator, stating that "EPA could betray the public trust by violating the intention of the Food Quality Protection Act (FQPA) to protect the nation's infants, children, and susceptible subpopulations, unless the Agency adhered to principles of scientific integrity and sound science in the pesticide tolerance reassessment it was undertaking."

Furthermore, they stated, "we urge the Agency to adhere to its principles of scientific integrity and employ the precautionary approach intended by the FQPA in assessing the cumulative and aggregate exposure and risk from the use of these neurotoxicants. This approach -- compliance with the FQPA and our principles of scientific integrity -- is the only way to remain faithful to the public trust and ensure that our children will not be exposed to pesticides that may permanently damage their brains and nervous systems."

Here is their letter:

http://www.biospotvictims.org/epaScientistsFqpa.pdf

Unfortunately, their advice went largely unheeded by the EPA, which abandoned the FQPA's 10X safety factor for many pesticides that are commonly found in pet pesticide products.

The Natural Resources Defense Council has also been highly critical of EPA's risk assessment methodology:

http://switchboard.nrdc.org/blogs/gsolomon/tell_petco_petsmart_to_take_to.html

http://switchboard.nrdc.org/blogs/jsass/whats_wrong_with_our_nations_a.html

http://switchboard.nrdc.org/blogs/mrotkinellman/epa_continues_to_lag_in_protec.html

According to Miriam Rotkin-Ellman, public health scientist at the NRDC, EPA's risk assessments are based on the ridiculous assumption that young children only put their hands in their mouth once a day while playing with a pet, and only with three fingers, which grossly underestimates the danger of pet pesticide products.

Despite the fact that EPA's risk assessments are based on unrealistic assumptions, they consistently show that pet spot-on products represent one of the most dangerous residential pesticide exposure scenarios for toddlers, with margins of exposure that approach or exceed the EPA's level of concern.

The majority of pet pesticide products on the market contain pyrethrins and pyrethroids. Recently, the EPA expressed concern over a possible connection between allergic and respiratory reactions in susceptible individuals and the use of these pesticides. The EPA is also concerned that young children may be at risk of developmental disorders from exposure to the pyrethrins and pyrethroids. As a result, the EPA issued data call-in notices for pyrethrins and pyrethroids in May 2009:

http://www.biospotvictims.org/Pyrethrin_069001.pdf

http://www.biospotvictims.org/Permethrin_109701.pdf

Recent studies have linked exposure to pyrethrins and pyrethroids with developmental disorders. Here is a study, sponsored by the National Institutes of Health and the EPA, which concluded that it may be prudent to evaluate pyrethroid exposure as a risk factor for attention-deficit hyperactivity disorder (ADHD):

http://www.biospotvictims.org/ADHD.pdf

Here is another study, conducted by researchers at Columbia University, which found that children exposed to higher levels of pyrethroids before birth scored 3.9 points lower on the Mental Developmental Index than those with lower exposures. The drop in IQ points was reported to be comparable to that observed in response to lead exposure:

http://www.mailman.columbia.edu/academic-departments/environmental-health/research-service/common-household-insecticide-linked-delay

For all the above reasons, BioSpotVictims.org urges ACE3 to consider pet pesticide products as an indoor environmental contaminant that poses significant health risks to children.

> **Response:** ACE3 contains a substantial increase in the number of indicators over the 2003 edition of ACE; addition of further indicators for this edition is not feasible. We do not believe data related to pet pesticide products are available that satisfy the criteria for ACE indicators.

EPA responses to comments submitted by Claudia Tietze, TinyTimmy.org

To Whom It May Concern:

My name is Claudia Tietze and I represent approximately 50,000 supporters who include concerned citizens, parents and pet owners. TinyTimmy.org is an ambitious effort to help educate pet owners on harmful flea and tick products and advocate for use of safer alternatives. Thank you for allowing TinyTimmy.org to respond with suggestions to ACE3.

Sadly, labels do little to educate pet owners on the true dangers of these products, brought intimately into our homes, and particularly the risks to children, especially toddlers, from these products.

This is a message I recieved on our website, which has a page that allows people to light virtual candles for those harmed by flea and tick products. *"We would like to light a candle on behalf of our daughter, Reeses Marie Meyer, who is currently struggling to overcome Sentry products. We would like to light this in hope that our family can find strength to help her fight a good fight and stay strong like mom and dad tell her every day. She is our light and a blessing. Mr & Mrs. Meyer"* Reeses Marie is not alone. There are numerous accounts of children being harmed by flea and tick products designed for use on companion animals. Most of these adverse reactions are settled privately and so little comes to public light. This should never happen. These parents should have been informed, prior to use of the Sentry companion animal product, of any and all risks to children.

I believe that ACE3 is a step in the right direction, however was incredibly saddened to see that companion animal flea and tick products were minimally addressed.

Considering that these products, in the form of collars, sprays, spot-on/drops/squeeze on, shampoos, mousse, powders and dips leave residue that is widely unmeasured in the home environment to date and due to the habits of children, particularly toddlers, the exposure to these pesticides is very intimate and has been shown to be incredibly high. For example, the NRDC has submitted a petition to the EPA requesting immediate cancellation of certain flea collars. They were incredibly concerned about the use of flea collars on companion animals, particularly those containing propuxor and tetrachlorvinphos in their active ingredients. These are both considered neurotoxins to mammals and known to be carcinogentic. These collars and their active ingredient chemicals pose risk of damaging the brain and nervous system of humans, especially toddlers, as well as the pets that they are used on.

You can read the NRDC press release from April 23, 2009
http://www.nrdc.org/media/2009/090423a.asp

Here is an excerpt (my highlights):

…tested the fur of dogs and cats wearing flea collars to measure the invisible pesticide residues left on the pets from these collars. This analysis, which was the first study of propoxur residues on pet's fur, found that propoxur levels are so high in some products that they pose a cancer risk in children that is up to 1,000 times higher than the EPA's acceptable levels, and up to 500 times higher for adults. The study also showed that after three days, 100 percent of the pets wearing collars containing propoxur and 50 percent of the pets wearing collars with TCVP posed a significant neurological risk to toddlers. Testing also revealed that unsafe levels of pesticide residue remain on a dog's or cat's fur two weeks after a collar is put on an animal. Families with multiple pets that wear flea collars have even greater exposure risks.

Many flea and tick products for companion animals contain heavily restricted pesticides or those cancelled for other household uses, yet remain in the home environment through the application on our companion animals, in our homes and in our yards. Often the carriers are more of a concern, such as the use of benzene, which is not required to be disclosed by claiming an entire formularly is CBI.

The flea and tick products regulated by the EPA do not have adequate aftermarket surveillance in place. Pet products are only required to submit fairly short term studies regarding acute toxicity and the potential for long term issues often goes disregarded by the registrants when reports are submitted to the EPA regarding adverse reactions. For example, there is no way to currently measure the increases in certain cancers or other health issues to humans, toddlers and companion animals from the use of such products. There have been no submitted tests or statistics that I am aware of submitted to the EPA from manufacturers, although there are such studies showing an increase of bladder cancers among dogs who are treated as little as once per year with such topical flea and tick products from non-industry sources.

Many of these companion animal flea and tick products contain ingredients that are known endocrine disruptors, particulatly to children whose systems are still developing and due to their habits, increase their exposure risk. TEDX - The Endocrine Disruptor Exchange, has compiled a large number of studies on permethrin, for example, and it's effects found in scientific studies. Permethrin is a very common ingredient found in many pet products as well as house sprays, foggers and similar products to fight insects in general, particularly fleas and ticks. You can find the link to download the raw data and charts here
http://www.endocrinedisruption.com/pesticides.permethrin.spreadsheets.php

It is, of course, alarming that children are exposed in schools and day care centers to potentially high levels of pesticides, however it is more alarming to me that parents, believing they are being responsible and good pet owners, bring such intimate contact to these potentially devastating pesticides into their homes. Labeling of these products does not allow a pet owner to make educated decisions as they do not include a complete list of known adverse reactions, nor the dangers that may be caused to humans and children, let alone to their companion animals. Owners mistakenly believe that if these products are available on store shelves that

they must have a high margin of safety. This is completely untrue and, again, long term testing is inadequate.

Registrants have a vested interest in not completing more thorough studies, particularly to the exposure risk that children and especially toddlers face from their products. In order for the EPA to get accurate information regarding the risks to children and toddlers, the EPA must implement other measures of acquiring such studies. I recommend that registrants pay into a pool either a small percentage of their profits, or what they would normally invest in such studies, and that the pool is governed by an independent organization with no relations to the pesticide or chemical industry. The purpose of such a pool would be to stimulate studies that are more impartial and still take the burden of the cost of studies out of the budget of the EPA.

It is naive and reckless for the EPA to continue to rely solely on industry backed studies for toxicology and environmental information. This has been shown over and over to harm the environment, human health, and wild life. I understand that the EPA must follow certain guidelines and legalities put in place since the 70's that benefit industry and protect profits. However, human life, particularly that of our legacy in the form of our children, is more precious than another million here or there. The EPA should create an incentive program for registrants to explore and market known safer alternatives in the fight of fleas and ticks (and other pests found in agriculture and in schools and daycare centers) such as diatomaceous earth. Patents could be given in the form of novel and new application methods of such safer alternatives.

It is my opinion that ACE3 is a step in the right direction, but that pet products for use on companion animals have not been given the attention they ought to have, particularly the exposure these products bring to our toddlers and children.

My recommendations are as follows and none require "re-inventing the wheel" - meaning all pertinent resources are already present:

1. The use of now available computer models that accurately predict long term toxicity in humans, children, toddlers, companion animals, wild life, the environment.
2. Clear labels on pet products that state, much as prescriptions for humans do, known health risks from both acute and chronic exposure, to companion animals, human adults, children and toddlers from active and inert/inactive ingredients and entire formularies of pet pesticide products registered by the EPA.
3. A fund, seeded by industry by either a small percentage of profits or what industry has traditionally paid for studies in one year, administered by a non-industry panel which includes concerns citizens, to allow the EPA to carry out scientific toxicology studies showing both acute and chronic exposure risks from the use of pesticide pet products used on companion animals.

4. The inclusion of data already statistically assessed of studies reviewed by TedX - The Endocrine Disruptor Exchange when evaluating exposure risks to humans, children and toddlers.
5. More thorough examination of the exposure risks to children and toddlers from the use of pesticide pet products, which includes adequate estimates of hand-to-mouth transmission as well as sleeping arrangements with treated pets and the number of pets and type treated in a household.
6. The public discloser of inert/inactive ingredients of all products containing pesticide products in the home and strict regulation and discloser of entire formularies including synergists and their mode of action in making active ingredients even more harmful to mammals, including children and toddlers.

It is my belief and that of the 50,000 supporters I represent, that not including a more thorough study of pet flea and tick product residue and risks in the home that ACE 3 will be sadly flawed an incomplete.

> **Response:** ACE3 contains a substantial increase in the number of indicators over the 2003 edition of ACE; addition of further indicators for this edition is not feasible. We do not believe data related to pet pesticide products are available that satisfy the criteria for ACE indicators.

EPA responses to comments submitted by Tom Vischi

A brief editorial comment on Measure E1: Percentage of children living in counties in which air quality standards were exceeded:

For an outsider, it is not clear whether counties "in which air quality standards were exceeded" are doing better than the standard or worse than the standard. The later context makes it clear that the standard is a maximum, which should not be exceeded. In which case exceeding the standard is a bad thing. But, at first reading, it could seem that exceeding the standard might be a good thing. Better to make it unambiguous. For example: "Percentage of children living in counties in which standards for maximum levels of air pollutants were exceeded." Something like that.

> **Response:** Title has been changed to "Percentage of children age 0 to 17 years living in counties with pollutant concentrations above the levels of the current air quality standards, 1999-2009."

EPA responses to comments submitted by Paul V Williams, MD, University of Washington School of Medicine

I have had the opportunity, in an unofficial capacity on behalf of the Section on Allergy & Immunology of the American Academy of Pediatrics, to review the Health indicators on respiratory diseases for ACE 3. I suggest that another indoor allergen/pollutant associated with asthma morbidity is mouse allergen. There have been numerous papers dating back to the original inner city asthma studies citing mouse allergen as a major trigger for asthma exacerbations and correlations with asthma control. There also does not appear to be a discussion in this section about VOCs and asthma.

> **Response:** We have added text related to rodent allergens as well as text related to VOCs.

It would be nice to develop an indicator that relates environmental factors and asthma prevalence and morbidity. For example, linking air pollution data from various cities or inner city environments and ER visits/hospitalizations. Another example would be an indicator relating to environmental tobacco smoke exposure and asthma ER visits or hospitalizations, or even prevalence since the IOM considers such exposure to be associated with causation of asthma in children.

> **Response:** Linking exposures and health outcomes is beyond the scope of ACE; please see the discussion in the report introduction.

EPA responses to August 26, 2011 comments from David P. Gosen, Perchlorate Study Group

1. Clarification of Statements

In three of the four sections in which perchlorate is discussed, there are statements that are not accurate as written or not supported by the references provided. Each section briefly describes the mechanism of action of perchlorate. None of the following statements considers the dose of perchlorate necessary to cause any of these effects.

Exposure to perchlorate has been shown to block the uptake of iodide into the thyroid gland. (Biomonitoring: Perchlorate, p. 1).

Exposure to perchlorate inhibits iodide uptake into the thyroid gland, disrupting the functions of the thyroid and potentially leading to a reduction in the production of thyroid hormone. (Environments and Contaminants: Drinking Water, p. 3).

Comment: The document would be made more accurate by adding scientific information that IUI has been demonstrated solely with doses of perchlorate greater than the NOEL (approximately 245 ppb) which is much greater than levels commonly found environmentally [Footnote: According to EPA's UCMR data, average concentrations in drinking water across the USD were less than 10 ppb. Further, even these data do not reflect measured perchlorate reductions since 2003]. Moreover, IUI is a non-adverse effect and should be stated as such, lest the reader incorrectly assume that this is an adverse effect. The use of an adverse effect as the point of departure when developing RfDs is a common approach of EPA. The NRC panel, comprising scientists with expertise in thyroid endocrinology, pediatric endocrinology, and toxicology, reported a notably conservative level (drinking approximately 2 liters every day of water with 14,000 ppb for several months) at which the sustained degree of inhibition would be required to overcome homeostasis and lead to changes in thyroid hormones.

> **Response:**
> These statements have been amended to "Exposure to high doses of perchlorate…" Discussion of reference dose derivation is beyond the scope of ACE3. EPA has determined that levels of perchlorate in drinking water and potential thyroid hormone effects warrant regulatory action.

The section on Health: Neurological Disorders states:
Perchlorate, a naturally occurring and man-made chemical that is used to manufacture fireworks, explosives, and rocket propellant, is known to disrupt thyroid hormone levels in pregnant women, which can be a risk factor for neurodevelopmental impairment. (Health: Neurodevelopmental Disorders, p. 2)

Comment: This statement is scientifically false as written. As such, it should be changed or removed. There is no study we are aware of that demonstrates that perchlorate is ..."known

to disrupt thyroid hormone levels in pregnant women..." and in fact the weight of the scientific evidence, including two separate studies in 2010 and 2011 by Pearce et al, consistently leads to the opposite conclusion.

Response:
This statement has been revised to: "Perchlorate is a naturally occurring and man-made chemical that has been found in drinking water and foods in the United States. Exposure to elevated levels of perchlorate inhibits iodide uptake into the thyroid gland, thus possibly disrupting the function of the thyroid and potentially leading to a reduction in the production of thyroid hormone. Moderate deficits in maternal thyroid hormone levels during early pregnancy have been linked to reduced childhood IQ scores and other neurodevelopmental effects."

The corresponding statement in "Environments and Contaminants: Food Contaminants" is more accurate in that it conveys the need of "high doses."

Exposure to high doses of perchlorate has been shown to inhibit iodide uptake into the thyroid gland, thus disrupting the functions of the thyroid and potentially leading to a reduction in the production of thyroid hormone. (Environments and Contaminants: Food Contaminants, p. 4).

Nonetheless, this section should explicitly acknowledge that IUI must also occur for several months without any biological compensation to cause any change in thyroid hormones. The NRC (2005) concluded that individuals with normal iodide intake would require a perchlorate dose large enough to lower thyroid iodide uptake by at least 75%, a dose estimated as being no lower than 30 mg/d (0.4 mg/kg-d for a 70-kg person or approximately 14,000 ppb assuming 2 L of water consumption per day) for several months or longer to cause thyroid hormone production to decline to the point where hypothyroidism could occur.

Response:
Discussion of these details is beyond the scope of ACE. We note that not all members of the population have normal iodide intake. There is now at least some evidence (study by Blount et al.) suggesting there may be effects on thyroid hormone levels at lower perchlorate doses.

The section “Biomonitoring: Perchlorate" notes that perchlorate can be naturally occurring in soils, but attributes groundwater contamination solely to military and industrial sources. The section states:

"Perchlorate has also been found in groundwater supplies near military and industrial facilities where perchlorate was used."

Comment: While the statement appears to consider the potential presence of naturally occurring contamination, it, nevertheless does not accurately characterize these sources in

groundwater. The document would be made more accurate by adding information regarding the other sources of perchlorate that are the result of natural deposition. This includes occurrences in groundwater. Perchlorate is naturally occurring and has been detected in groundwater from Holocene and Pleistocene ages (Jackson et al., 2010) and found in areas with no ascertainable anthropogenic source (Dasgupta et al., 2005).

Another source of perchlorate in ground water is from agricultural use of imported Chilean nitrate fertilizer. This type of fertilizer is used in organic farming and contains natural perchlorate. The amount of perchlorate in typical Chilean nitrate fertilizer is approximately 0.1% by weight (Dasgupta et al., 2005). One study estimated that over the past 60 years, the source strength from Chilean nitrate fertilizer in food was 800 tons per year and natural sources contributed approximately 150 - 700 tons per year (Dasgupta et al., 2006).

Response:
Text has been revised to indicate that perchlorate may be found naturally in groundwater: “It is found naturally in groundwater and soils throughout many regions in the United States and other arid regions of the world. Perchlorate is presumed to migrate into groundwater during the process of irrigation, and has also been found in groundwater supplies near military and industrial facilities where perchlorate was used.” A statement about Chilean fertilizer has also been added: “Perchlorate has been detected in some fertilizers produced in Chile; however, fertilizers appear to be a negligible source of perchlorate in the United States.” Additional cited sources include NRC 2005, Dasgupta et al. 2005, Dasgupta et al. 2006, TRC 1998 and Susarla et al. 1999 and 2000.

There are statements in "Biomonitoring: Perchlorate" that are not supported by the references given. For example, "Biomonitoring: Perchlorate" states:

Low levels of thyroid hormone are widespread among U.S. adult women, potentially increasing the risk for effects on fetal development from exposure to perchlorate…

Comment: The statement references Miller et al. (2009), Aoki et al. (2007), and Morreale de Escobar et al. (2000). None of these studies supports the claim that "low levels of thyroid hormone are widespread among U.S. adult women ... " Miller et al. (2009) cites Aoki et al. (2007) and states: "An estimated 7.3% of the U.S. population either have self-reported hypothyroidism or take thyroid medication, and three-quarters of these are women." Aoki et al. (2007) also report that "Hypothyroidism prevalence (Thyroid Stimulating Hormone (TSH) > 4.5 mIU/ L) in the general population was 3.1%. Among women of reproductive age (12-49 years), hypothyroidism prevalence was 3.1%." Morreale de Escobar et al. (2000) do not discuss thyroid levels in US women or women in areas where iodine intake is sufficient as in the US (Caldwell et al., 2011). These studies support that most US women have both sufficient thyroid hormone and iodine intake.

Another critical element conspicuously absent from this discussion is that the predominant cause of hypothyroidism in the US (and most other developed countries where the information can be determined) is Hashimoto's Thyroiditis, an autoimmune disease. This disease is effectively the body attacking itself. It is not known to be caused by perchlorate (Brent, 2010). Perchlorate also has not been reported to exacerbate thyroid conditions or to cause greater effects in people with thyroidal disease.

> **Response:**
> Text on population hypothyroidism prevalence has been removed, and text on iodine intake has been revised as follows: “In 2005–2008, approximately 38% of women ages 15 to 44 years in the United States had insufficient iodine intake, potentially increasing the risk for effects on fetal development from exposure to perchlorate.” This text is consistent with the NRC statement that “People who have compromised thyroid function resulting from conditions that reduce thyroid hormone production and people who are iodide-deficient also constitute potentially sensitive populations.”

Citing Blount et al. (2006), Blount et al. (2009), and Steinmaus et al. (2007), the section "Biomonitoring: Perchlorate" also states:

Increasing levels of perchlorate in the urine of females ages 12 years and older has been associated with decreased thyroid hormone levels, and tobacco smoke and perchlorate may interact to affect thyroid function at commonly occurring perchlorate levels. (Biomonitoring: Perchlorate. p. 1).

Comment: As written, the assertion is not based on the results of the papers cited and should be corrected. First, the data are from NHANES, which is a national program to gather data about a number of non-environmental and environmental data. NHANES data are best used for hypothesis generation. NHANES data only take information on an individual at one specific point in time. Iodine content (diet, serum, urinary) can vary dramatically day to day. The NHANES data obtained are very limited for understanding thyroid function. Only total thyroxine (T4) and thyroid stimulating hormone (TSH) are measured. Missing are free T4, triiodothyronine (T3), thyroid peroxidase (TPO), and others. Other criticisms have been noted by Charnley (2008) and Tarone et al. (2010). [Footnote: There are a number of examples. Neither Blount et al. (2006) nor Steinmaus et al. (2007) normalize the urinary output of iodine, perchlorate, or any other urinary measure. The ACE3 draft does choose to use this normalization (although does not state it is required) reporting "The constant excretion of creatinine in urine allows for an adjustment that partially accounts for the measurement variability due to changes in urinary output:' but does go on to caution that variations due to "... age, sex, diet, health status (specifically renal function), body-mass index, race/ethnicity, and pregnancy status ..." could "... affect comparisons between individuals or populations." Both Blount et al. (2006) and Steinmaus, et al. (2007) statistically adjust for creatinine, but this does not perform the same function and was not used to classify individuals by iodine status (Tarone et al., 2010). Lastly, the mean and 95% confidence interval for total T4 (8.27 ug/dL, confidence interval 7.97-8.58)

and TSH (1.36 mIU/L, confidence interval 1.31-1.42) presented by Blount et al. (2006), even in the subpopulation of women with urinary iodine less than 100 ug/L , were not out of normal ranges (reference ranges: TSH 0.3-3.0 mIU/L, total thyroixine (T4) 4.5- 12.5 ug/dL: Pearce et al., 2011) and clearly not "decreased."] Steinmaus et al. (2007) is based on the same dataset and conducted in a similar manner; therefore the same criticisms apply.

The citation of Blount et al. (2009) is not correct in this sentence and should be removed. The authors did not evaluate thyroid function in either mothers or their offspring. They did conclude that they "found no association between cord blood levels of these anions [perchlorate, iodine, nitrate, and thiocyanate] and newborn weight, length, and head circumference."

Furthermore, placing equal weight on these studies, without providing a balanced view of many other studies that present an alternative interpretation, may lead the reader to misinterpret the science. While we believe Blount et al. (2006) and Steinmaus et al. (2007) are interesting, they are contrary to the overwhelming weight of scientific evidence. Further research should be done to confirm or dispute the results. Others have commented on numerous scientific issues related to these studies which are not borne out in the ACE3 draft documents. The ACE3 draft documents should be revised to reference the lack of reliability or expressed concern regarding these studies.

Response:

Text regarding epidemiological findings has been expanded. A summary of the NRC 2005 findings regarding the epidemiological evidence available at that time has been inserted. The text regarding Blount et al. 2006 and Steinmaus et al. 2007 was edited to better clarify the nature of the study population and now reads: “A study of urinary perchlorate and thyroid hormone levels in more than 11,000 U.S. females ages 12 years and older in 2001–2002 found that increasing levels of perchlorate in urine were associated with decreased thyroid hormone levels. Further analysis of this data set found that tobacco smoke and perchlorate may interact to affect thyroid function at commonly occurring perchlorate levels.” This is now followed by new text on the findings of Pearce et al. 2010 and Tellez Tellez et al. 2005: “In contrast, a study of first-trimester pregnant women identified as iodine-deficient, and a long-term exposure study of women in early pregnancy and late pregnancy in Chile, found that exposure to low levels of perchlorate did not result in decreased levels of thyroid hormones.” A new paragraph on studies of perchlorate and thyroid hormone levels in newborns was added. The citation to Blount et al. 2009 was deleted.

In the section Health: Neurodevelopmental Disorders, it states:

Perchlorate, a naturally occurring and man-made chemical that is used to manufacture fireworks, explosives, and rocket propellant, is known to disrupt thyroid hormone levels in

pregnant women, which can be a risk factor for neurodevelopmental impairment. (Health: Neurodevelopmental Disorders, p. 2)

Comment: This statement cites Greer et al. (2002), Haddow et al. (1999), and Miller et al. (2009). The reference to Greer et al. (2002) should be removed as it is incorrect as used. Greer et al. (2002) was a clinical study in which healthy non-pregnant women and men were given perchlorate in drinking water for 14 days and IUI and thyroid hormones were measured. The study determined the NOEL that is the basis of the EPA RfD and the drinking water advisories in California and Massachusetts. Even at the highest dose, 0.5 mg/kg-day, equivalent to nearly 15,000 ppb of perchlorate per day, no changes in clinical chemistry parameters, thyroidal hormones, pituitary hormones, etc. were noted. [Footnote: There was a "marginally significant association of TSH with blood-draw even in the 0.5 mg/kg-d dose group" and there was a significant association between the morning blood draws and TSH in the 0.5 mg/kg-d group only. There was an overall downward trend (the opposite of what would be expected if perchlorate were having an effect) during exposure with recovery after exposures were complete (Greer et al., 2002)]. What was seen in all doses above the 0.007 mg/kg-day dose (NOEL), was IUI. At the highest dose, IUI was less than 70%. Pregnant women, their offspring, and neurodevelopmental disorders were not evaluated.

The reference to Haddow et al. (1999) should be removed as it is also incorrect as used. Haddow et al. (1999) did not evaluate the effects of perchlorate. In this study, children of women who had TSH levels greater (cause unknown) than the 99.7th percentile or TSH between the 98th and 99.6th percentile and low T4 (hypothyroid) during pregnancy were compared between age seven to nine with children of mothers who had TSH less than the 98th percentile (controls). The authors reported that the average IQ of children whose mothers had untreated hypothyroidism during pregnancy was 100 (this is the median score for modern IQ tests) compared to controls who had an average IQ of 107. The average IQ of children whose mothers were hypothyroid, but received treatment during pregnancy was 111. The average serum TSH levels for hypothyroid women and controls were 13.2 and 1.4 mIU/L, respectively. The average serum T4 levels for hypothyroid women and control were 7.4 and 10.6 µg/dL, respectively. As stated above, a pregnant woman would have to ingest at least 30 mg/d (0.4 mg/kg-d for a 70-kg person) for several months for a change in thyroid hormones to possibly occur.

Finally, the reference to Miller et al. (2009) should be removed as it is incorrect as used. Miller et al. (2009) is not an experimental study. It is a review of selected literature with the objective to:
... review the role of THs [thyroid hormones] in development and adult life, the impact of xenobiotics on thyroid status, the relationships between adverse outcomes of thyroid disruption and upstream causal biomarkers, and the societal implications of perturbations in THs by xenobiotic chemicals.

This review *hypothesizes* that perchlorate exposure could disrupt thyroid hormones in a pregnant woman which in turn could affect her fetus; however, there is no scientific reference or demonstrable evidence for a relationship between perchlorate exposure and neurodevelopmental effects in children. Rather, one study has demonstrated that when women with hyperthyroidism took therapeutic levels (approximately equivalent to the dose a person would receive if they drank 2 L/d of water with a perchlorate concentration of 400,000 to 500,000 ppb) of perchlorate during pregnancy, offspring were unaffected. The only reported effect was an enlarged thyroid gland in one infant that resolved to normal size within six weeks after birth (Crooks and Wayne, 1960). If EPA has scientific studies that provide evidence of this, then the document would benefit by the addition of these references. This is a transparent means of presenting the scientific information.

Response:

This statement has been revised to: "Perchlorate is a naturally occurring and man-made chemical that has been found in drinking water and foods in the United States. Exposure to elevated levels of perchlorate inhibits iodide uptake into the thyroid gland, thus possibly disrupting the function of the thyroid and potentially leading to a reduction in the production of thyroid hormone. [Refs: Greer et al. 2002, NRC 2005] Moderate deficits in maternal thyroid hormone levels during early pregnancy have been linked to reduced childhood IQ scores and other neurodevelopmental effects. [Refs: Haddow et al. 1999, Miller et al. 2009, Morreale de Escobar et al. 2000]"

2. PER1 Indicator Not Indicative of Health Effects

According to "Biomonitoring: Perchlorate," the purpose of the PER1 indicator is to demonstrate:

... the distribution of median perchlorate concentrations in women ages 16 to 49 years, based on concerns for effects on children from perchlorate exposure in women who are pregnant or may become pregnant.

First, based on the robust literature and exposure data (albeit old), while there might be a theoretical concern, there is no demonstrated concern. In fact, the argument is stronger for the lack of concern, as it has scientific support. The peer reviewers should be aware of this information, and the document should include it.

The results of the biomonitoring analysis should be placed into the context of what this exposure level means for health effects. The PER1 indicator and the NHANES dataset it is based on were not intended to determine health effects from perchlorate exposure and did not attempt to measure any. The median perchlorate level reported for PER1 was 2.7 ug/g creatinine for women ages 16 to 49. In comparison, Blount et al. (2007) reported the median of urinary perchlorate reported for all females was 3.59 ug/g creatinine which corresponded to a dose of 0.059 ug/ kg-d, well below the experimental results of the low dose NOEL reported by

Greer et al. (2002) and below the EPA RfD. The dose for women ages 15 to 44 was not provided, but the urinary level reported was 2.97 ug/g creatinine and lower than for all females. The study by Greer et al. (2002) which reported the lowest dose which could cause a non-adverse effect (IUI) in healthy adults was 0.007 mg/ kg-d. This dose is approximately 120 times greater than the dose estimated by Blount et al. (2007). No study has demonstrated an effect of perchlorate below the NOEL.

It would be important for the reader to understand that a mean urinary concentration of perchlorate of 2.7 ug/g creatinine means that the U.S. population of women ages 16 to 49 is unlikely to suffer any health effect from perchlorate at environmental levels.
It is also interesting that data are presented for children age six to ten and 11 to 17 with no explanation or rationale for this breakdown. The PER1 indicator..... presents median perchlorate levels for women ages 16 to 49 years for different population groups defined by race/ethnicity and family income." As the most sensitive population has been defined as the pregnant woman and her fetus, the relevance of women of reproductive age as the basis for PER1 is clear, but it is unclear why children ages six through 17 are presented.
In the "Biomonitoring: Perchlorate" document, data are also presented for children and adolescents. It reports:

The median perchlorate level among children ages 6 to 10 years was twice as high as the level found in women of childbearing age in 2001-2004, while the median perchlorate level among children ages 11 to 17 years was 11% higher than that of women. The 95th percentile level among children ages 6 to 10 years was 68% higher than that of women, while the 95th percentile level among children ages 11 to 17 years was 3% lower than that of women. (Biomonitoring: Perchlorate, p.7)

There should be some explanation of why the results of this group were presented; that children are not the most sensitive subpopulation; and that these urinary values are not associated with adverse health effects in children, despite being greater than those of women of reproductive age.

Response:
As indicated in the NRC 2005, "fetuses and preterm newborns constitute the most sensitive populations..." Therefore, data on perchlorate exposures in women of childbearing age (16-49 years) are presented in the perchlorate indicator. The initial sentence cited in this comment has been revised to: "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 perchlorate."
The statement from NRC 2005 continues with, "...although infants and developing children are also considered sensitive populations." Given this complete statement, we would be remiss in failing to report data available for children. Additional data on perchlorate exposures in children are therefore provided in data tables.

In the ACE3 review draft, data for children ages 6-10 and 11-17 years were presented separately because of differences observed in creatinine-adjusted urinary perchlorate levels by age group. However, creatinine-adjustment has been removed based on comments from peer reviewers. Because the difference in age groups is not observed in the unadjusted values, we now present the values for ages 6-17 years combined without the division into two age groups.

3. Inclusion of Perchlorate in Other Topics

In the section "Environments and Contaminants: Food Contaminants," perchlorate is discussed as being detected in water and from the manufacture of fireworks, explosives, flares, and rocket propellant. There is no science offered, or even a discussion of, how perchlorate could become a food contaminant (e.g., irrigation with contaminated water, use of Chilean nitrate fertilizers, use of hypochlorite in dairy farming).
Comment: The brief discussion of perchlorate is inappropriate as the indicator for food is based solely on organophosphate pesticides which have no relation to perchlorate or perchlorate exposure. The draft states:
Following this text, an indicator is presented for organophosphate pesticides in selected foods. Many chemicals of concern in food lack sufficient data to generate reliable, nationally representative indicators for those contaminants, particularly for children. Selected chemicals that are frequently found in foods are summarized below. (Environments and Contaminants: Food Contaminants, p. 1)

Response:
The format of ACE3 includes discussion of topics that go beyond the information captured in the indicators presented. Studies that have detected perchlorate in produce (leafy vegetables, etc.) have been identified and cited appropriately. A likely mechanism of food contamination is implied by stating that "Perchlorate is a naturally occuring and man-made chemical that has been detected in surface and ground water in the United States." More detailed discussion of perchlorate in the Food Contaminants topic is not needed; we reserve additional details for the perchlorate topic in the Biomonitoring section.

The section "Environments and Contaminants: Drinking Water Contaminants," states:
The two indicators [E6 and E7] that follow use the best data currently available to EPA to characterize the performance of water systems in meeting EPA's health-based drinking water standards and in reporting monitoring results.

Indicator E6 estimates the percentage of children served by community water systems that did not meet: all applicable health-based drinking water standards. Indicator E7 estimates the percentage of children served by systems with violations of drinking water monitoring and reporting requirements. Monitoring and reporting violations occur when a water system does not monitor, does not report monitoring results, or was late in reporting results. Such violations

in monitoring and reporting may mean that some health-based violations were not reported; this could cause the percentages shown in Indicator E6 to be underestimated. (Environments and Contaminants: Drinking Water Contaminants, p 4)

Comment: Perchlorate is not currently regulated at the federal level; therefore it is unclear how perchlorate could be used with this indicator. There is no Federal MCL to exceed; therefore. perchlorate could not factor into indicator E6. If perchlorate is included as a part of indicator E7, it could only be a violation of monitoring or reporting which is not health based.

Response:
Perchlorate is not included in either of the drinking water indicators. However, we include discussion of perchlorate in the topic text because we are trying to highlight contaminants that may be of concern, regardless of whether or not they are represented in the indicator. The topic text includes discussion of a variety of other contaminants in addition to perchlorate that are not included in the presented indicators.