

National Toxicology Program
Draft NTP Monograph on Health Effects of Low-Level Lead
Peer Review Panel Meeting

November 17-18, 2011
National Institute of Environmental Health Sciences
Research Triangle Park, NC

Summary Minutes

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I. Attendees

Peer Review Panel Members:

Deborah Cory-Slechta, University of Rochester
Pam Factor-Litvak, Columbia University
Eliseo Guallar, Johns Hopkins University
Bruce Lanphear, Simon Fraser University
Michael Pollard, The Scripps Research Institute
Joel Pounds, Pacific Northwest National Laboratory (chair)
Stephen Rothenberg, National Institute of Public Health, Mexico
Nostratola Vaziri, University of California, Irvine
Richard Peter Wedeen, Veterans Affairs New Jersey Health Care System

NTP Board of Scientific Counselors Liaison:

Judith Zelikoff, New York University Langone Medical Center

Other Federal Agency Staff:

J. Richard Bryant, Environmental Protection Agency (EPA)
Clark Carrington, Food and Drug Administration (FDA)
Gayle DeBord, National Institute for Occupational Safety and Health (NIOSH) (by telephone, day 2)
Chinara Kennedy, CDC
Ellen Kirrane, EPA
David Svendsgaard, EPA
Elizabeth Whelan, NIOSH (day 1 only)

National Institute of Environmental Health Sciences (NIEHS) Staff:

Danica Andrews	Barry McIntyre
Linda Birnbaum	Andrew Rooney
Abee Boyles	Michael Shelby
John Bucher	Robert Sills
Kembra Howdeshell	Kris Thayer
Gloria Jahnke	Nigel Walker
Annette Kirshner	Vickie Walker
Robin Mackar	Lori White
David Malarkey	Mary Wolfe
Scott Masten	

Public Attendees:

Rosalind Volpe, International Lead Zinc Research Organization
Roger Miksad, Battery Council International

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Michael Kosnett, University of Colorado (by telephone)
Gulan Sun, Texas Commission on Environmental Quality (by telephone)

II. Introductions and Welcome

The National Toxicology Program (NTP) Peer-Review Panel on the Draft NTP Monograph on Health Effects of Low-Level Lead met November 17 and 18, 2011, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. Dr. Joel Pounds served as chair. The other Peer-Review Panel members were Drs. Deborah Cory-Slechta, Pam Factor-Litvak, Eliseo Guallar, Bruce Lanphear, Michael Pollard, Stephen Rothenberg, Nostratola Vaziri, and Richard Peter Wedeen. Dr. Judith Zelikoff attended as the NTP Board of Scientific Counselors liaison. The FDA liaison was Dr. Clark Carrington and Dr. Elizabeth Whelan represented NIOSH on day 1 and Dr. Gayle DeBord on day 2.

Dr. Pounds and Dr. Birnbaum welcomed everyone to the meeting. NTP Associate Director Dr. John Bucher also welcomed attendees, and noted that it would be the first meeting to be held under the expanded scope of the former Center for the Evaluation of Risks to Human Reproduction (CERHR), which is now known as the Office of Health Assessment and Translation (OHAT). Dr. Pounds asked all present to introduce themselves for the record. Designated Federal Official Danica Andrews read the conflict of interest policy statement.

III. Public Comment

Dr. Pounds called for oral comments from public participants, beginning with commenters on the telephone.

Dr. Michael Kosnett, a medical toxicologist from the University of Colorado School of Medicine in Denver was the first speaker and noted that he was speaking on his own behalf. He applauded the effort expended on the draft, and said he concurred with much of the analysis, particularly with respect to “the well-documented adverse effect of low-level lead exposure on neurocognitive development in children.” He wished to offer a constructive suggestion regarding the draft document’s implicit analysis of the causal relationship between low-level lead exposure and some of the other endpoints.

He cited what he had interpreted as causal inferences in the monograph’s language regarding the association between blood lead levels <10 μ g/dL and cardiovascular endpoints, and the association of blood lead levels <5 μ g/dL and decrements in renal function. He felt that the current narrative in the draft was “too dismissive of the potential role of reverse causation.” Overall, he recommended more attention to the

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strengths and weaknesses of the noted effects, which would facilitate in both informing public policy and encouraging ongoing research.

Dr. Wedeen disagreed with Dr. Kosnett, particularly regarding the issue of reverse causation in renal failure, citing several references. Dr. Rothenberg had concerns regarding the extent to which causation was addressed in the document's conclusions.

Dr. Gulan Sun, a toxicologist with the Texas Commission on Environmental Quality, was the next public commenter, also by telephone. Suggesting that NTP had relied heavily on the US EPA's draft Integrated Science Assessment for lead for its conclusions, she recommended that NTP update the draft monograph to reflect updated information contained in subsequent EPA documents.

She cited several specific instances where she disagreed with NTP's conclusions in the draft monograph, including the conclusions of *sufficient* evidence of an association between blood lead levels <5 μ g/dL in children and decreased academic achievement and increased incidence of attention deficit hyperactivity disorder (ADHD). She felt that the key study cited was inadequate to support the conclusion of *sufficient* evidence of an association between blood lead levels <10 μ g/dL in children and decreased IQ. Also, she was of the opinion that concurrent blood lead levels are an inappropriate lead exposure metric for studies of chronic health effects in adults, rendering several other conclusions in the draft suspect.

She particularly noted the lack of acknowledgment in the monograph of the limitations of epidemiology studies. She felt that the role of confounders had been overlooked, especially in the case of a potential association between lead exposure and ADHD.

Dr. Factor-Litvak asked Dr. Sun whether she had considered the role of parental mental health as a confounder in ADHD, in that it would need to be associated with both exposure and outcome to be a true confounder as opposed to an effect modifier. She also asked Dr. Sun about the rise in ADHD due to increased diagnosis and/or parental acceptance of diagnosis, even in the face of a decline in ADHD associated with blood lead concentration. Dr. Sun noted that ADHD is a complex disease, and reiterated that confounders should be taken into account. Dr. Lanphear agreed that ADHD is a complex disease, a combination of environmental and genetic risk factors. He asked Dr. Sun whether the studies she had mentioned that attributed much of ADHD to genetic factors took environmental factors such as lead, tobacco, endocrine disruptors or air pollution into account. She replied that several had, and could provide Dr. Lanphear more detailed information later if requested.

Dr. Pounds called for the registered in-person commenters, none of whom were present. He acknowledged the written comments that had been received previously

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and provided to panel members. He asked whether anyone in the audience wished to make a public comment. No audience members responded.

IV. Overview of the Evaluation of Low-Level Lead

Dr. Andrew Rooney of OHAT provided an overview of the process that led to the draft NTP monograph.

He noted that lead exposure remains a significant health concern, despite policies and practices that have resulted in continued progress toward reducing exposure and lowering blood lead levels in the U.S. population. Based on that situation, NIOSH nominated lead for NTP evaluation of reproductive and developmental effects of low-level lead. NTP focused on epidemiological data for health effects at blood lead levels <10 $\mu\text{g}/\text{dL}$ because there is a relatively large database of human studies, and because human health effects are well established at higher levels (Centers for Disease Control and Prevention's (CDC) definition of elevated blood lead is currently $\geq 10\mu\text{g}/\text{dL}$ for all ages), but less so at the lower levels. NTP also expanded the scope of the evaluation to include neurological, immune, cardiovascular, and renal effects in addition to reproductive and developmental effects.

The key question addressed in the monograph is: What is the evidence that adverse health effects are associated with blood lead levels <10 $\mu\text{g}/\text{dL}$? Studies with a cut-off point of <5 $\mu\text{g}/\text{dL}$ were also considered, and that level was used in some of the conclusions as warranted by the data. Topics addressed in sub-questions included the specific health effects in the above-mentioned systems, blood lead levels associated with health effects, life stages of identified effects, and data on association with bone lead levels, with comparison to association with blood lead levels.

The monograph begins with an Executive Summary, followed by sections for methods, exposure, and the individual health effects. NTP considered four possible conclusions for specific health effects in each area:

- *sufficient evidence of an association*
 - A relationship is observed between the exposure and health outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.
- *limited evidence of an association*
 - An association is observed between the exposure and health outcome for which a causal interpretation is credible, but chance, bias, and confounding could not be ruled out with reasonable confidence.
- *inadequate evidence of an association*

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- The available studies are insufficient in quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between exposure and health outcome, or no data in humans are available.
- *evidence of no association*
 - There are several adequate studies covering the full range of levels of exposure that humans are known to encounter (in this case limited to blood lead levels <10 $\mu\text{g}/\text{dL}$), which are mutually consistent in not showing an association between exposure to the agent and any studied endpoint.

Primary literature served as the basis for the conclusions in the draft monograph, comprised of epidemiological studies with mean blood lead levels <10 $\mu\text{g}/\text{dL}$, with a careful consideration of study design. The conclusions were supported by bone lead data, laboratory animal data, and authoritative sources, including the US EPA 2006 Air Quality Criteria Document for Lead, the Agency for Toxic Substances and Disease Registry (ATSDR) 2007 Toxicological Profile for Lead, and review of internal drafts by technical advisors that are subject matter experts for the section they reviewed.

Each of the health effects sections begin with a statement of the NTP's conclusion as to whether the effect is associated with blood lead levels <10 $\mu\text{g}/\text{dL}$ or <5 $\mu\text{g}/\text{dL}$, as well as the age at which the effect is identified, and the timing of the exposure associated with the effect. Each section also includes discussion of key data and principal studies considered in developing the conclusions. Human studies from populations with low-level lead exposure were abstracted into separate appendices for each health effect. The health effects sections end with a summary of the basis for the NTP's conclusions, experimental animal data relevant to the human evidence, and discussion of consistency of the NTP conclusions with the EPA and ATSDR reports.

Dr. Rooney described in more detail the meaning of a blood lead level <10 $\mu\text{g}/\text{dL}$, noting that it reflects current exposure more closely and is the most widely available exposure metric. Bone lead, on the other hand, reflects cumulative exposure more closely, with bone storing 70-95% of total lead body burden, and data are not widely available. Thus, blood lead is the exposure metric used for the evaluation of health effects of low-level lead. Health effects in adults may have been influenced by blood lead levels <10 $\mu\text{g}/\text{dL}$ earlier in life. Multiple studies have reported significant associations between concurrent blood lead levels <10 $\mu\text{g}/\text{dL}$ and health effects in adults.

Dr. Rooney concluded by reviewing the charge to the peer review panel:

1. To determine whether the scientific information cited in the draft monograph is technically correct, clearly state, and objectively presented

2. To determine whether the scientific evidence presented in the draft monograph supports the NTP's conclusions regarding health effects of low-level lead

Dr. Carrington asked Dr. Rooney to clarify what was meant by the reference to “current period” of lead exposure. Dr. Rooney replied that that concept would be clarified in the presentation on exposure.

Dr. Lanphear identified an opportunity to clarify what was meant by the different levels of association. He said he was pleased to see the type of approach that had been utilized, because too often such assessments get “caught up in the theory of causality.” He pointed out that causality is rarely established in epidemiology, but that the upper levels of association imply that there is enough evidence to take action and establish policy. Dr. Factor-Litvak was also pleased by the levels of association, noting that they were associated with causality through strength of association, temporality, and consistency. She defined consistency in this context as the same general associations emerging from many studies in many different geographic areas using different study designs in different populations. She expressed concern that the conclusions were addressing individual studies rather than the body of literature within each topic. Dr. Thayer replied that the conclusions weren’t really affected by whether or not the term “causal” was included, since the focus had been on the human studies, without relying on some of the experimental animal studies that might have provided more causal strength to the conclusion. Dr. Factor-Litvak felt that human studies would often be sufficient to make conclusions regarding causality, which would be necessary to implement policy and recommendations for lowering the blood lead action level. Dr. Birnbaum noted that the monograph is neither a regulatory nor a policy document, but a hazard evaluation document, with the hope that it will be used by policymakers. Dr. Rothenberg approved of the fact that the monograph stressed association as defined by strength and consistency of evidence. He suggested that the inclusion of a reference to causality in the definition of *limited evidence of association* was confusing, particularly in that it was only referred to in one of the four levels, and recommended that it be removed. Dr. Thayer felt that removal was a reasonable request.

Dr. Carrington said from a regulatory perspective, causation was important, and simple association is not enough to start regulating materials. He felt that the conclusions about association would be taken to mean causation by the public. Dr. Cory-Slechta concurred with Dr. Rothenberg’s remarks, because the outcomes being described are always multi-factorial, and it would not be possible to draw direct causal conclusions as to one individual exposure leading to a particular health effect. She noted that from the CDC’s perspective, association is sufficient to influence policy. Dr. Carrington noted that when causality is proposed, then it is necessary to think about dose-response. Dr. Bucher reiterated that the draft document is designed to evaluate the strengths of

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potential associations, and should be evaluated on that basis. He appreciated the comments in the discussion, particularly since the NTP often has communications challenges associated with its documents.

Dr. Guallar pointed out that the term “health effects” in the panel’s charge implied that there should be statements about causation, versus association.

Dr. Birnbaum noted that different communities may have differing interpretations of the terminology, thanked the panel members for their comments, and said the terminology would be worked on.

Dr. Pounds went over the logistics of how each section of the report would be covered in the meeting. Dr. Guallar requested the opportunity to make a general statement about the monograph prior to the beginning of the review process.

Referring to his written submission, Dr. Guallar made several comments regarding his concerns about the methodology used in the evaluation, which he felt was not up to the state of the science. Ultimately, he felt that many of the steps that should routinely be taken in a systematic review of the literature had not been taken, leading to skepticism about the conclusions. He stated that the Methods section of the monograph needed a complete overhaul to live up to the standards of systematic review. He felt that the tables and figures used in the monograph were insufficient to convey the relevant aspects of the different studies cited, and were not effective in summarizing the information in a clear, user-friendly way. He was also of the opinion that several of the discussions in the monograph were cursory and superficial and insufficiently systematic to develop key aspects of the evaluation of low-level lead exposures. He questioned much of the terminology employed in the monograph, including what he considered to be ill-defined terms such as “supported” and “consistent.”

Dr. Bucher thanked Dr. Guallar for his detailed comments, and said the NTP is fully aware of many of the points he had raised. He added that the program is in the process of initiating an infrastructure to be able to conduct reviews such as this in the manner he was suggesting. In the absence of implementation of such a total approach, there has been heavy reliance on technical experts who are quite familiar with the aspects of the literature such as quality and bias and issues of that nature. He said also that there is much reliance on the reviewers themselves to point out any aspects of the document that have not achieved the desired precision in terms of reaching conclusions based on proper interpretation of the evidence.

V. Exposure

Dr. Abee Boyles of OHAT briefed the peer-review panel on the section of the draft monograph addressing exposure, which is designed to be background information to assist in evaluating the health effects of lead.

NTP relied on several seminal documents regarding human exposure to lead, including the EPA and ATSDR documents mentioned above, along with the CDC's 2010 Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women and its 2005 publication on Preventing Lead Poisoning in Young Children. The exposure section covers current blood lead levels as well as trends over time, other lead biomarkers, sources of environmental lead, and modifiers of lead exposure.

According to National Health and Nutrition Examination Survey (NHANES) data, U.S. blood lead levels have dropped to one-tenth of what they were in 1976-1980, to means under 2 μ g/dL in children aged 1-5, children aged 6-19, and adults 20 and older. That steep decline is likely due to bans on lead in gasoline and paint. In the 1976-1980 data and the most recent, from 2003-2008, children aged 1-5 have the highest blood lead levels compared to the other age groups, likely due to hand-to-mouth behavior and other behavioral aspects particular to young children resulting in higher exposures. It is also notable that although even the adults in the most recent data have blood lead levels under 2 μ g/dL, they are likely to have had higher blood lead levels in the past, when they were children in the 1970s.

Blood lead and bone lead are the primary biomarkers used in the epidemiological literature. Blood lead is the most widely available marker, and more closely reflects current and stored lead exposures. Bone lead is more difficult to measure, however it more accurately reflects cumulative lead exposures. The half-life of lead in blood is approximately one month, whereas in bone, it is 10-30 years. Bone lead released into the blood may account for 45-70% of blood lead. Storage and remobilization of bone lead changes with life stage; mobilization is more rapid during childhood, pregnancy, menopause, and general aging.

Sources of environmental lead include food, water, air, soil, occupational exposures, and activities that increase exposure such as hand-to-mouth behavior, home renovation, and certain hobbies such as stained glass-making.

Many of the studies examined in the monograph accounted for common modifiers of lead exposure such as age, gender, ethnicity, diet, socioeconomic status, recent immigration, and genetics.

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Dr. Boyles reviewed the general questions for the panel to consider in their evaluation of the draft monograph, and the specific charge questions for the exposure section. She noted that there are no NTP conclusions on exposure, as the goal was to clearly and concisely present issues relevant to low-level lead exposure in humans and to provide references to more detailed reviews.

Dr. Rothenberg was primary reviewer of the Exposure section. He took the opportunity to outline his general comments about all chapters of the draft monograph, as well as his comments on the Exposure chapter, with specific suggestions for changes.

He noted that there seemed to be heavy reliance on review articles, in addition to looking at studies that included original data. He said there was nothing wrong with that practice, but that although the agency reviews by EPA, ATSDR, and others were specifically identified in the monograph as they came up, the other reviews were not identified specifically as reviews in the chapters. He suggested that when reviews are introduced as supporting evidence, they should be clearly identified as reviews. He cited several examples, and said that often the review articles are referenced to support specific points rather than studies with hard data that support the points. Also, citing the example of bone lead data in children, he expressed concern about the monograph picking up investigators' suggestions in the discussion sections of their papers and using them as hard evidence. He mentioned several other examples of this practice. He questioned the statement that bone lead is superior to blood lead in assessing the effects of lead on chronic health outcomes, that although this point is averred by several investigators in the discussion sections of their papers, the superiority has not been proven by any actual evidence.

Dr. Rothenberg proceeded to refer to several specific instances in the monograph where he felt changes were needed, including an in-depth discussion of the relative merits of K-X-ray fluorescence (KXRF) and L-X-ray fluorescence (LXRF) devices for measuring bone lead levels, which are discussed in the Exposure chapter of the monograph. He suggested that a new configuration of the KXRF technology should be referenced as the most important recent advance, stressing improved precision and detection as the most important features, rather than portability of the device. He noted that "correlation" is sometimes used in the draft as being synonymous with "association," which is inaccurate.

Dr. Rothenberg said he was disappointed that there was no discussion of exposure-response relationships in the Exposure chapter. He noted that the exposure-response relationship is one of the key issues in trying to determine causality, and felt that it should have been part of every chapter in the monograph, but was only mentioned in the Neurological Effects chapter. He felt that to be able to advise regulators, who will

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determine limits to protect the population, more should be known about the exposure-response relationship.

He was also troubled by multiple, inappropriate references in the monograph to “populations” and suggested changing the term to sample when appropriate.

Overall, excepting the points he had raised, he felt that the draft described the state of the art well.

Dr. Pollard was the second reviewer of the Exposure chapter. He felt that overall the background provided in the monograph was sufficient, with certain detailed exceptions. He was concerned that the chapter included no commentary on the techniques and procedures used to measure blood lead.

Responding to Dr. Rothenberg’s comment regarding measurement of bone lead in children, Dr. Factor-Litvak referred to a study (Wasserman *et al.* 2003) that showed that bone lead level was a superior predictor of childhood intelligence compared with blood lead. Dr. Cory-Slechta referred to another article (Campbell *et al.* 2004) that found high correlations between bone lead and blood lead.

Dr. Carrington felt that section 3.4 of the Exposure chapter dealt with two issues that should have been segregated—factors influencing actual exposure, and pharmacokinetic variation.

Dr. Lanphear said the role of water-based lead exposure was diminished too much in the chapter and that if anything, it is increasingly problematic. He also felt that ethnicity as a modifier of exposure was not sufficiently emphasized, noting that in one of his studies, African-American children had 50% higher blood lead levels than their white counterparts given similar exposures. Panel members discussed that point at length, speculating about potential causes, and whether it was a result of polymorphisms.

Dr. Lanphear expressed concern about the chapter’s treatment of acute versus chronic exposures. Dr. Birnbaum wondered whether any data existed on blood lead levels in children prior to the 1970s, to provide more information on early life or *in utero* exposures, and allowing temporal comparisons. She felt that the chapter would benefit from addition of some discussion in that area. Dr. Factor-Litvak said she believed that the first such studies were done in the 1940s, but were focused on lead poisoning, not blood lead levels, and that studies incorporating blood lead levels began in the 1970s. Dr. Birnbaum noted that there should be use of reconstructive exposures, as is commonly done in environmental epidemiology looking at other exposures. Dr. Lanphear said he typically assumes that 1960 was the peak year when children were most heavily exposed to lead, and mentioned a study incorporating measurements in

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teeth that showed that lead exposures peaked in the 1960s. Dr. Birnbaum said it would be very helpful to include that information in the monograph.

Dr. Guallar felt that there was much good information in the chapter, and that some of the confounders mentioned were not incorporated later in the document. He concurred with Dr. Rothenberg's comments about generalized statements in the monograph about superiority of bone lead measurement to blood lead, noting that it is not known if that is true, particularly with regard to cardiovascular outcomes. He also wished to see more discussion of the mechanism of action of lead at low levels of exposure.

Dr. Pounds commented on the use of bone lead as a marker of exposure. He said that distribution of lead in bone is heterogeneous and subject to change related to exposure over time. Thus, he said, the release of lead from bone is a very poor marker for bone mineral mass, bone mineral turnover, or skeletal turnover. There is a gap in the understanding of bone lead metabolism, he added, which lends a caveat for its use in assessing health effects.

Dr. Boyles appreciated the panel's comments, and said many of the suggestions would be easy to adopt into the final version of the monograph.

Reviewing the panel's comments on the Exposure chapter, Dr. Pounds reiterated the perception of over-reliance on review papers, concerns about statements asserting the superiority of bone lead as a predictor of health outcomes over blood lead, over-interpretation of bone lead measurements, and a request for more exposure response summary in the chapter.

Dr. Factor-Litvak said in later chapters, less common biomarkers of lead such as in semen or follicular fluid had been introduced with little discussion, and suggested there should be more mention of those uncommon biomarkers.

VI. Immune Effects

Dr. Rooney presented the monograph's conclusions regarding immune system effects of low-level lead in humans.

The principal immune-related health effect of lead in children is increased hypersensitivity and allergic sensitization. That finding is supported by an increased level of serum immunoglobulin E (IgE) associated with blood in the data from children. There is no consistent evidence of a lead-related immune health effect in adults. The ATSDR and EPA concluded that lead alters immune parameters such as T cells and macrophages, and that lead-associated functional immune changes have not been

rigorously evaluated in humans. The ATSDR and EPA conclusions are largely based on animal data that support lead-related immunotoxicity.

Regarding the elevated serum levels of IgE in children, IgE is the primary mediator of type-1 hypersensitivity. Elevated levels are associated with allergic sensitization and can be associated with allergic disease such as asthma, but do not necessarily equate with disease.

Dr. Rooney summarized the NTP's conclusions and supporting evidence:

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 μ g/dL are associated with increased serum IgE in children.

The conclusion is based on 5 cross-sectional studies reporting such an association in children, along with other supporting studies in humans and animals.

The NTP concludes that there is *limited* evidence that blood lead levels <10 μ g/dL are associated with increased hypersensitivity responses in children.

The conclusion is based on a prospective study reporting that maternal and cord blood lead levels are associated with increased hypersensitivity diagnosed in children by skin prick testing at age 5. This conclusion is supported by studies demonstrating an association between blood lead <10 μ g/dL and increased serum IgE.

The NTP concludes that there is *inadequate* evidence of an association between blood lead levels <10 μ g/dL and eczema or asthma in children.

The conclusion is based on a lack of studies examining the association with eczema or asthma in children at any blood lead level.

The NTP concludes that there is *inadequate* evidence of an association between blood lead levels <10 μ g/dL and increased serum IgE, hypersensitivity, eczema or asthma in adults.

The conclusion is based on the existence of few studies in these areas.

The NTP concludes that there is *inadequate* evidence of an association between blood lead levels <10 μ g/dL and the other immune endpoints considered in the chapter.

There have been few studies involving these endpoints at levels <10 μ g/dL, with inconsistent results in adults and in children.

The NTP's Overall Conclusions for Immune Effects

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The NTP concludes that there is *limited* evidence that blood lead levels <10 μ g/dL are associated with adverse immune effects in children and there is *inadequate* evidence in adults.

Dr. Rooney read the specific immune charge questions that the reviewers were to consider. He also depicted the summary tables for the chapter, to help facilitate the panel's consideration and voting on the conclusions.

Dr. Pollard was the primary reviewer for the Immune Effects chapter. He said he agreed with everything stated in the document with the exception of the conclusion of *sufficient* evidence of an association with blood lead level and increased serum IgE in children. He felt the scientific evidence did not support that conclusion due to a failure to appreciate the bias of age-dependent ranges for IgE in children. Citing several studies cited in his written comments supporting his position, he recommended changing the conclusion from *sufficient* evidence to *limited* evidence, or possibly even *inadequate* evidence.

Dr. Lanphear, the second reviewer for the chapter, concurred with Dr. Pollard's findings. He felt that the serum IgE conclusion should be changed to *limited* evidence. He was particularly worried about confounding by housing. He mentioned that he was uncomfortable with what he felt were differing standards of evidence in the monograph.

Responding to the reviewers' comments, Dr. Rooney said that in some of the studies cited, the investigators had looked at housing disrepair and any potential association with increased IgE or higher blood lead level. He noted that investigators had controlled for age and increasing IgE in two of the studies cited by Dr. Pollard, who responded by saying that the age-related correction may or may not have been adequate.

Dr. Zelikoff, the NTP BSC liaison to the panel, asked for clarification in the document on use of the term "macrophages" vs. monocytes.

Dr. Pounds reiterated the reviewers' recommendations, which were to accept the chapter's conclusions as written except for the conclusion on lead-related increased serum IgE in children, which should be changed from *sufficient* evidence to *limited* evidence.

A motion was made by Dr. Vaziri and seconded by Dr. Lanphear to accept the conclusions in Table 5.4: NTP conclusions on immune effects of low-level Pb, with one modification. The Panel recommended *limited* evidence for effects of blood Pb <10 μ g/dL on increased serum IgE in children. The Panel accepted unanimously (8 yes, 0 no, 0 abstentions).

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A motion by Dr. Factor-Litvak and seconded by Dr. Rothenberg was made to accept the overall NTP conclusions for immune effects as written, there is *limited* evidence that blood Pb levels <10 $\mu\text{g}/\text{dL}$ are associated with adverse immune effects in children, and there is *inadequate* evidence in adults. The Panel accepted unanimously (8 yes, 0 no, 0 abstentions).

VII. Cardiovascular Effects

Dr. Boyles presented the monograph's conclusions regarding cardiovascular effects of low-level lead in humans.

The principle health effects of lead exposures considered by the NTP included increased blood pressure and risk of hypertension, increased risk of mortality from cardiovascular causes, and other cardiovascular effects such as heart rate variability, electrocardiogram abnormalities, and clinical cardiovascular disease. EPA and ATSDR concluded that lead increases blood pressure and deleterious cardiovascular outcomes. Also, the 2011 draft EPA Integrated Science Assessments (ISA) document concludes that there is *sufficient* evidence of a causal relationship between lead exposures and cardiovascular health effects.

Dr. Boyles reported the NTP's conclusions and supporting evidence for each of the cardiovascular outcomes addressed in the monograph.

Blood Pressure and Hypertension

The outcomes considered in the evaluation were systolic blood pressure (pumping phase), diastolic blood pressure (relaxing phase), and hypertension (systolic ≥ 140 or diastolic ≥ 90).

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with increased blood pressure and risk of hypertension.

This conclusion is based on published meta-analyses reporting blood and bone lead-associated increases in blood pressure and bone lead-associated increase in hypertension, as well as numerous studies of blood lead that support an association with increased blood pressure and risk of hypertension. There is also consistent support for an association within the bone lead literature and animal data showing that low-level lead exposures increase blood pressure. Among the studies highlighted was the 2002 meta-analysis by Nawrot *et al.* 2002, which concluded that there was a 1mmHg increase in systolic blood pressure associated with a doubling of blood lead concentration.

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Life stages were also considered in the evaluation of blood pressure and hypertension outcomes:

The NTP concludes that there is *sufficient* evidence that blood lead <10µg/dL increases the risk of hypertension in pregnant women.

This conclusion is based on consistent evidence from seven studies that identified an association of blood lead level with increased blood pressure and with gestational hypertension.

The NTP concludes that there is *inadequate* evidence for low-level lead effects on blood pressure or hypertension in children.

The conclusion is based on few studies in children with inconsistent results.

The NTP concludes that there is *inadequate* evidence for low-level lead effects on blood pressure or hypertension in menopausal women.

The conclusion is based on few studies in menopausal women with inconsistent results.

Heart Rate Variability

Decreased heart rate variability is a marker of abnormal autonomic nervous system functioning.

The NTP concludes that there is *inadequate* evidence to evaluate a potential association between lead exposure and heart rate variability.

The conclusion is based on few studies with inconsistent results.

Electrocardiogram Abnormalities

Electrocardiogram abnormalities are defined as changes in the typical pattern of electrical activity of the heart as measured by electrocardiogram (ECG).

The NTP concludes that there is *limited* evidence for lead effects on ECG abnormalities, both in adults and in children.

The Normative Aging Study supports an association in men, while the Oswego Children's Study found an association with decreased stroke volume and total peripheral resistance in children. Lack of replication of both studies led to the conclusion of *limited* evidence, although Dr. Boyles acknowledged that Dr. Rothenberg had brought to her attention that one of the Oswego study publications was in fact a replication, which she said would be noted in the monograph.

Clinical Cardiovascular Disease (General)

The outcomes considered in the evaluation were particular vascular conditions: peripheral artery disease (impaired flow to the limbs), coronary artery disease (impaired flow to the heart), cerebral vascular disease (impaired flow to the brain), myocardial infarction (damage to the heart muscle), and stroke (damage to brain tissue).

The NTP concludes that there is *limited* evidence that blood lead <10 $\mu\text{g}/\text{dL}$ and <5 $\mu\text{g}/\text{dL}$ is associated with risk of any type of clinical disease in adults, but that there was *inadequate* evidence for any of the specific clinical diagnoses.

The conclusion for *limited* evidence <5 $\mu\text{g}/\text{dL}$ was based on studies of coronary heart disease and blood lead level in men, peripheral artery disease in NHANES data in adults over 40, and measures of arterial function. This conclusion is also supported by animal data. Lack of replication for specific diseases or markers of vascular function led to the conclusion of *inadequate* evidence for specific diagnoses.

Cardiovascular Mortality

The NTP concludes that there is *sufficient* evidence that blood lead <10 $\mu\text{g}/\text{dL}$ is associated with increased mortality from cardiovascular causes in adults.

The conclusion is based on several large prospective studies with 12-14 years of follow-up, as well as biological plausibility supported by the cardiovascular effects of lead on hypertension, blood pressure, and cardiovascular disease.

The NTP's Overall Conclusions for Cardiovascular Effects

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ in adults are associated with adverse effects on cardiovascular function, and that there is *inadequate* evidence to evaluate cardiovascular effects in children.

Dr. Boyles reviewed the specific cardiovascular charge questions that the reviewers were to have considered, and depicted the summary table for the chapter.

Dr. Rothenberg pointed out that the publication by Møller of the Glostrup Population Study, which had been cited, did in fact find significant effect at a 0.05 probability value in women.

Dr. Lanphear pointed out a potential discrepancy in the conclusions, in that they state *sufficient* evidence for cardiovascular mortality, but *limited* and *inadequate* evidence for cardiovascular disease. Dr. Boyles agreed that that was a good point which bears further discussion. Dr. Bucher pointed out that the conclusions do not necessarily build upon one another. He recognized that Dr. Lanphear had pointed to a potential perceptual inconsistency, but that the stratification of the individual studies was how the

conclusions had been reached. Dr. Rooney reiterated that the subheading for clinical cardiovascular disease is actually describing *vascular* diseases, and that the evidence was in fact limited for that specific set of vascular diseases. The cardiovascular-related mortality conclusion of *sufficient* evidence, he noted, was based on the evidence supporting an association between mortality and blood lead levels as well as the evidence for all of the other cardiovascular effects.

Dr. Guallar was the primary reviewer of the chapter. He acknowledged the difficulty posed by significantly differing endpoints considered in the many cardiovascular studies. He said that other than the association of lead exposure with increases in blood pressure, which is supported by many studies, the evidence for association with cardiovascular effects is limited. He noted that in the cardiovascular field, associations are typically supported by dozens of studies that often involve thousands of patients and many years, but that there is nothing close to that for lead. He agreed that the overall evidence supports an association with blood pressure. Thus, he agreed with the NTP's conclusions in that area, although he wished to see updated data. In terms of the other cardiovascular outcomes, except mortality, he agreed with the NTP conclusions. He disagreed with the NTP conclusion of *sufficient* evidence of an association with cardiovascular mortality, and felt that it should be changed to *limited*.

Dr. Vaziri was the second reviewer of the chapter. He stated that the conclusions in the chapter were fair and acceptable, but agreed with some of the comments that had been made calling for improved documentation. He wished to clarify one point that had been made in the monograph about the lack of evidence of an association with hypertension in young children. He noted animal data that showed it took 4 months for hypertension to develop as a result of low-level lead exposure, and that it is a decade or longer in humans. Thus, he said if the age of the child is less than the incubation period, by necessity it would not yet be visible or clinically detectable.

The third reviewer, Dr. Wedeen, had no additional comments.

Dr. Rothenberg wished to reiterate the issue he had raised earlier, that many papers had been included as evidence for or against a particular health effect based on whether they had found significant results or not, without reviewing the quality of the evidence, critical examination of design, statistics, and claims made by the authors. He spoke specifically about the Chen *et al.* 2006 study, which he felt should not have been given much weight. On the other hand, he said that although he was impressed by the Park *et al.* 2009 study, he questioned the group's use of a bone lead prediction model based on blood lead. He felt that this paper should not bear any weight on conclusions in the monograph, and asked that if it was kept in the document, his comments about the techniques used should be included, to avoid the possibility that inclusion in the document without comment would essentially serve to validate its questionable

technique for predicting bone lead. Dr. Boyles said that the Park study had been included only as an example of another method of measurement and was not one of the primary sources of evidence of an association included in the cardiovascular appendix table (Appendix C). She said that clearly NTP would re-examine whether to include the study at all or to include it with Dr. Rothenberg's qualifying comments.

Dr. Lanphear questioned some of the panel's hesitation about accepting the collective evidence as being sufficient for an association between blood lead and cardiovascular mortality. He noted that the conclusion of *sufficient* evidence with respect to hypertension should be sufficient for cardiovascular mortality as well, as they are associated, and that association is well-accepted. "How much more evidence do we need to flip us that extra inch or two?" he asked. Dr. Guallar responded that although the panel all likely agreed with the issue of blood pressure, the other cardiovascular outcomes were much more in question and less clearly associated. He reiterated his position that much more evidence was needed in the other areas, and much more research was required.

Dr. Factor-Litvak said it was perplexing that there was agreement on association with hypertension, but perhaps not with clinical cardiovascular disease, but "yes" on cardiovascular mortality. She proposed thinking about a more causal pathway, seeing if some of the patients identified with hypertension in the NHANES follow-up study were those who suffered mortality later on. She also wondered about whether studies had been chosen for inclusion in the monograph based upon statistical significance. She felt that a careful examination of confidence intervals would be more reliable.

Dr. Wedeen expressed his opinion that the ongoing debate was revolving around a difference between clinical medicine and epidemiology and statistics. He said from a clinical point of view, there is no question that hypertension has an effect on cardiovascular disease. Thus, ultimately there is "no real conflict, except about studies and data management."

Dr. Rothenberg stressed the use of the term "association" to describe the relationships involved, again avoiding implications that there is proof of causality. He urged staying within the weight of the existing evidence (or lack thereof) when drawing conclusions. He said that although there may be ample evidence, for example, that hypertension leads to cardiovascular diseases, there is comparatively little to suggest that lead exposures lead to specific cardiovascular diseases—certainly not enough to say that the evidence is sufficient. Dr. Guallar added that the panel, in his opinion, was not trying to say that lead does not lead to clinical cardiovascular outcomes, but that there are linked steps that provide some level of evidence leading to the outcomes. So, although it can be seen that lead affects blood pressure and blood pressure affects mortality, clearly there are many other effects involved in addition to lead exposure. He

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said the conclusions are not about the effects of lead, but about the quality of the evidence on hand. He believed that there are in fact profound effects of lead on cardiovascular outcomes, but that much more research is needed to generate the appropriate levels of evidence to draw firm conclusions regarding potential associations. Dr. Carrington noted that associations are circumstantial evidence of causation, with the quality of the evidence varying depending on the studies, and that that is the goal of the monograph is to evaluate the overall quality of the evidence for causation.

Prior to the panel voting, Dr. Pounds reviewed the major points of the preceding discussion. He felt that in general the chapter's conclusions were agreed with, with some exceptions as noted. Lead is an important cardiovascular risk factor that is not well-recognized by the medical community. It was noted that blood pressure and other cardiovascular effects are very time-dependent, and so the absence of evidence is not the same thing as evidence of absence. NTP was also encouraged not to readily accept "exuberant conclusions" of authors regarding statistical or biological importance, but should review the data and its support for the conclusions involved. Also, the totality of the data should be evaluated, not just the individual studies.

It was moved by Dr. Vaziri and seconded by Dr. Wedeen to accept the draft monograph's table of conclusions on cardiovascular effects of low-level lead as written. Four panel members voted yes, while Dr. Factor-Litvak, Dr. Guallar, Dr. Cory-Slechta and Dr. Pollard voted no. Dr. Pounds as chair broke the tie, voting no; thus, the original draft of the table was rejected. Panelists voting no disagreed with the *sufficient* evidence conclusion for blood lead <10 μ g/dL being associated with cardiovascular mortality and felt it should be *limited* evidence.

Following the vote, Dr. Pounds reiterated the proposed change from Dr. Guallar, changing *sufficient* evidence to *limited* evidence for cardiovascular mortality associated with blood lead <10 μ g/dL. It was moved by Dr. Factor-Litvak and seconded by Dr. Guallar to accept the table with that modification. The Panel accepted (7 yes, 1 no, 0 abstentions) the conclusions in Table 6.8: Conclusions on cardiovascular effects of low-level Pb, with the recommended modification for *limited* evidence for effects of blood Pb <10 μ g/dL on cardiovascular mortality in adults. Dr. Lanphear voted no, and explained that he was comfortable that the totality of the evidence was sufficient for the original conclusion to stand and that there was *sufficient* evidence that cardiovascular mortality was associated with blood lead levels <10 μ g/dL.

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It was moved by Dr. Guallar, seconded by Dr. Lanphear, and the Panel accepted unanimously (8 yes, 0 no, 0 abstentions) the overall NTP conclusions for cardiovascular effects as written, there is *sufficient* evidence that blood Pb levels <10 μ g/dL in adults are associated with adverse effects on cardiovascular function, and there is *inadequate* evidence to evaluate cardiovascular effects in children.

VIII. Reproductive and Developmental Effects

Dr. Rooney presented the monograph's conclusions on reproductive and developmental effects of low-level lead in humans.

The principal health effects of lead in children are reduced growth and delayed puberty. In adults, effects on sperm and conception at higher blood lead levels have been noted by a number of authors. Some studies have reported association with fetal growth, pregnancy loss, and gestation length. ATSDR and EPA have concluded that there are effects on sperm and fertility at higher blood lead levels (>10 μ g/dL). Dr. Rooney reported that given that the original nomination to NTP was for reproductive and developmental effects of lead, for these health effects studies reflecting higher blood lead levels were considered. EPA and ATSDR also concluded that there was limited and mixed evidence, mixed evidence defined as some studies reporting an association of a health effect with lead and others not. Animal data support a range of reproductive and developmental toxicity of lead.

The reproductive and developmental effects considered in the NTP review were delayed puberty, postnatal growth, sperm parameters, pregnancy loss, gestation length, fetal growth, and birth defects.

Puberty

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 μ g/dL are associated with delay in puberty onset in children, *limited* evidence of an association in children with blood lead levels <5 μ g/dL, and *inadequate* evidence with prenatal exposure.

Evidence came primarily from 7 cross-sectional studies and a prospective study reporting an association between blood lead and delayed appearance of biomarkers of puberty, in children with mean blood lead levels from <1 to <10 μ g/dL. Mixed evidence was reported at mean blood lead levels <5 μ g/dL, which was the basis for the NTP conclusion of *limited* evidence at blood lead levels <5 μ g/dL. The conclusions were also supported by similar results at blood lead levels \geq 10 μ g/dL, and animal data.

Postnatal Growth

The potential effect is slower growth as indicated by height, head circumference, and other measures adjusted for the age of the child.

The NTP concludes that there is *sufficient* evidence that blood lead levels $<10\mu\text{g}/\text{dL}$ in children are associated with decreased growth, and *limited* evidence that maternal blood lead levels $<10\mu\text{g}/\text{dL}$ are associated with decreased head circumference in children up to age 4.

The conclusion of *sufficient* evidence in children is based on several prospective studies reporting an association with decreased growth and early childhood blood lead levels $<10\mu\text{g}/\text{dL}$, as well as numerous cross-sectional studies with blood lead levels $<10\mu\text{g}/\text{dL}$. The conclusion was also supported by similar effects at blood lead levels $>10\mu\text{g}/\text{dL}$ and by animal data. The *limited* evidence conclusion for prenatal exposure is based on several prospective studies reporting decreased head circumference in children associated with maternal blood lead levels $<10\mu\text{g}/\text{dL}$. No association with child height was found in these studies of maternal blood lead levels.

Sperm or Semen

These adverse effects include lead-related effects on sperm numbers, decreased motility, reduced semen volume, and increased percentage of sperm with abnormal morphology.

The NTP concludes that there is *sufficient* evidence that blood lead levels $\geq15\mu\text{g}/\text{dL}$ are associated with adverse effects on sperm or semen in adult men, and *inadequate* evidence at blood lead levels $<15\mu\text{g}/\text{dL}$.

The conclusions are based on multiple retrospective and cross-sectional studies reporting associations with blood lead levels from $15\text{-}68\mu\text{g}/\text{dL}$, including 12 occupational studies that reported adverse effects on sperm at blood lead levels from $15\text{-}50\mu\text{g}/\text{dL}$.

Fertility/Delayed Conception Time

Delayed conception time is with regard to time to pregnancy; decreased fertility relates to odds of conception over a given time.

The NTP concludes that in men there is *sufficient* evidence that paternal blood lead levels $\geq20\mu\text{g}/\text{dL}$ is associated with delayed conception time, and *limited* evidence that blood lead levels $\geq10\mu\text{g}/\text{dL}$ are associated with other measures of reduced fertility. The NTP concludes that in women there is *inadequate* evidence for an association with maternal blood lead levels $<10\mu\text{g}/\text{dL}$.

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The conclusions in men were supported by multiple retrospective and cross-sectional studies and consistency with the data supporting effects of blood lead on sperm. Three studies, however, reported no association with blood lead.

Spontaneous Abortion

Spontaneous abortion is defined as fetal loss at <20 weeks of gestation.

The NTP concludes that in women there is *limited* evidence that maternal blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with spontaneous abortion, and that in men there is *limited* evidence that paternal blood lead levels >31 $\mu\text{g}/\text{dL}$ are associated with spontaneous abortion.

The conclusion in women is based primarily on a single prospective nested case-control study, with supporting, but mixed evidence at blood lead levels from 4-16 $\mu\text{g}/\text{dL}$. The conclusion in men is based on a single retrospective nested case-control study and mixed evidence at blood lead levels from 25-60 $\mu\text{g}/\text{dL}$.

Fetal Growth/Lower Birth Weight

The effect includes several measures of reduced prenatal growth or intrauterine growth retardation, and any indication of reduced fetal growth was considered.

The NTP concludes that in women there is *sufficient* evidence that maternal blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with reduced fetal growth and lower birth weight, and that in men there is *inadequate* evidence for paternal blood lead.

The conclusion in women was based on multiple prospective, retrospective, cross-sectional studies. It was supported by association with maternal bone lead and animal data on lead-associated lower birth weight. Although one prospective and several cross-sectional studies with blood lead <10 $\mu\text{g}/\text{dL}$ found no effect, the one, very large (over 43,000 mother-infant pairs) retrospective cohort study considered (Zhu, 2010) provided enough evidence to support the conclusion of *sufficient* evidence.

Preterm Birth/Gestational Age

Preterm birth is <37 weeks of gestation. Reduced gestational age is a continuous measure of gestational length.

The NTP concludes that in women there is *limited* evidence that maternal blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with preterm birth or reduced gestational age, while in men there is *inadequate* evidence of an effect.

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The conclusion in women was based on multiple prospective and cross-sectional studies. However, there is mixed evidence and the very large (over 43,000 mother-infant pairs) Zhu 2010 retrospective cohort study did not find an association and therefore supports the NTP conclusion of *limited* evidence.

Other Reproductive Effects

The NTP concludes that there is *inadequate* evidence to evaluate the potential association between blood lead and other reproductive endpoints including stillbirth, endocrine effects, and congenital malformations.

There are few studies of these endpoints at any blood lead level, and the existing studies have yielded inconsistent results.

The NTP's Overall Conclusions for Reproductive and Developmental Effects

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 μ g/dL are associated with adverse health effects on development in children and reproduction in adult women.

Dr. Rooney reviewed the specific reproductive and developmental charge questions that the reviewers were to have considered, and depicted the summary tables for the chapter.

Dr. Factor-Litvak was the primary reviewer of the chapter. She said that this health effects chapter was confusing to review, due to the multiple outcomes considered that other experts may or may not agree are related to reproduction and development. In general, she felt that the conclusions were well thought-out, and she supported them as they stand. She said for these health effects it was difficult to discern the effects of maternal blood lead from postnatal blood lead, that is, prenatal exposure from postnatal exposure. She pointed out that there was a high degree of correlation between prenatal and postnatal blood lead levels. She suggested in this chapter that presenting a range of blood leads for each study might be more useful than simply providing the mean or median. She felt that the meanings of the measures of seminal or follicular fluid lead were not clear, particularly in terms of their pharmacokinetics. She also pointed out that the measures of postnatal growth cited were incorrect; that postnatal growth should be measured in centiles, and that studies of fertility and time to pregnancy should be measuring both partners, and that not doing so is a flaw in many of the studies. She noted that lead level studies in people who have gone to IVF or fertility clinics are useless, in that they are a very select population and not representative of the general population.

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She cited several of the above general criticisms in her summary of the individual outcomes in the chapter. With those caveats in mind, and with certain other minor criticisms in each area, she generally agreed with the specific conclusions. She felt that there should also have been a section devoted to genotoxicity studies. Citing the Zhu *et al.* 2010 study, she said that the evidence is sufficient to find an association between maternal blood lead levels <5 μ g/dL and reduced fetal growth.

Dr. Rothenberg, the second reviewer, said that he agreed with most of Dr. Factor-Litvak's remarks on the conclusions in the chapter. He reiterated several of her comments for emphasis, adding his opinions about some of the information supporting the conclusions. He also suggested several specific changes within the chapter itself. In particular he suggested taking a second look at the validity and potential effects of study design on the Staessen *et al.* 2001, Denham *et al.* 2005, and Wolff *et al.* 2008 studies. In particular, the Wolff study only had girls with a mean age of 9.5 and was, therefore, better designed to detect earlier puberty than delayed puberty. The Staessen and Denham studies had a number of different non-lead exposures that should be considered. The Yin *et al.* 2008 study should be removed or commented on because the plasma lead levels reported would have been lethal, and it is likely these numbers relate to whole blood lead levels; plasma and whole blood lead levels are repeatedly used in this and earlier studies interchangeably though they are not equivalent. The Chen *et al.* 2006 study should get less weight and the Bornschein *et al.* 1989 study should be discounted, though it does not affect the Monograph's conclusions. The Sowers *et al.* 2002 study related effects to changes in blood lead levels, but did not refer to specific ranges of blood lead levels on pregnancy outcomes, making this study not relevant for this document.

The third reviewer, Dr. Cory-Slechta, agreed with the other reviewers' conclusions and comments. She agreed with the conclusions related to endocrine effects, which mentioned *inadequate* evidence, not because of inconsistent data, but due to inadequate experimental designs. With hormones subject to much temporal fluctuation, taking a single time point measurement is insufficient.

Dr. Rooney thanked the reviewers for their specific comments and suggestions, and said they would be taken into account. He said several of the comments about the evaluation of quality of studies were already incorporated, but that NTP staff would ensure that those caveats were made clear in the text. He noted that the data on seminal fluid and follicular fluid lead levels had not been influential, as it was considered inadequate.

Dr. Rooney discussed panel members' reservations about the Wolff *et al.* 2008 and Denham *et al.* 2005 papers and asked if the panel would suggest a change to the conclusion of *limited* evidence of delayed puberty at blood lead levels <5 μ g/dL. Drs.

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Factor-Litvak and Rothenberg felt that the conclusion should remain as stated, even given reservations about the utility of those studies.

Dr. Pounds summarized the panel's comments. The difficulty of disentangling fetal blood lead, maternal blood lead and paternal blood lead was acknowledged. He felt that the discussion had been good, but he had not discerned the bottom-line recommendations. He noted remarks that it was important to consider blood lead levels in both the father and mother when looking at time to pregnancy and fertility data. Also, supporting studies often had limitations in terms of small sample size and area comparisons. There was further recommendation about examining individual study designs and not simply relying on the authors' conclusions. He asked for discussion about editing the chapter's conclusions table, to be followed by voting on proposed modifications.

The panel discussed changing the conclusion for the health effect, fertility/delayed conception time within the “population or exposure window” listing for “men - time to conception”, from *sufficient* evidence at blood lead levels $\geq 20\mu\text{g}/\text{dL}$ to “*limited* evidence.” After considerable discussion, Dr. Pounds called for a vote on that modification. Dr. Rothenberg moved for the change, but the motion was not seconded, and the proposed change was not adopted.

There was discussion of changing the blood lead level cited in the conclusion for women on spontaneous abortion from $<10\mu\text{g}/\text{dL}$ to “ $<10\mu\text{g}/\text{dL}$ and $<20\mu\text{g}/\text{dL}$.” Ultimately, Dr. Rooney said the point that had been raised by Dr. Factor-Litvak would be clarified in the text.

The panel discussed changing the blood lead level cited in the conclusion for women on reduced fetal growth and lower birth weight from $<10\mu\text{g}/\text{dL}$ to “ $<5\mu\text{g}/\text{dL}$,” based particularly on the Zhu *et al.* paper. There was consensus on the panel for the change.

Dr. Pounds called for a motion to vote on the conclusions table. It was moved by Dr. Cory-Slechta and seconded by Dr. Factor-Litvak to accept the conclusions table as edited. The vote was unanimous (8 yes, 0 no, 0 abstentions) in favor of accepting the conclusions in Table 8.6: NTP conclusions on reproductive and developmental effects of low-level Pb, with one modification. The panel recommended the blood Pb level for *sufficient* evidence in women for Reduced Fetal Growth and Lower Birth Weight be $<5\mu\text{g}/\text{dL}$.

Dr. Pounds then called for a motion to vote on the NTP's overall conclusion in the chapter. Noting that the prior change impacted the overall conclusion, additional language was added to the overall conclusion. There was a motion by Dr. Cory-Slechta and seconded by Dr. Factor-Litvak to approve the overall conclusion with that addition. The Panel accepted unanimously (8 yes, 0 no, 0 abstentions) the overall NTP

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conclusions for reproductive and developmental effects as written, there is *sufficient* evidence that blood Pb levels <10 $\mu\text{g}/\text{dL}$ are associated with adverse health effects on development in children and reproduction in adult women. In addition, the panel recommended that there is *sufficient* evidence that blood Pb levels <5 $\mu\text{g}/\text{dL}$ in women are associated with reduced fetal growth and lower birth weight.

Dr. Bucher assured the panel that their comments during the meeting would be reviewed thoroughly by NTP staff, and that there would be extensive revisions to the monograph as a result. He stressed that the outcome of this peer review is a published NTP Monograph, which would be communicated to NIOSH, the nominating agency.

Dr. Whelan from NIOSH, representing the nominating agency, briefed the panel on the background of the nomination, which stemmed from a perceived disconnect between occupational lead exposure limits and emerging literature about reproductive effects from lead exposures at far lower levels. She said there was evaluation underway at NIOSH whether to reduce the recommended occupational lead exposure limit (which is currently 40 $\mu\text{g}/\text{dL}$), and that the monograph would aid in that process. She supported the NTP's decision to broaden the evaluation to include more than just the reproductive outcomes.

IX. Renal Effects

Commencing the second day of proceedings, Designated Federal Official Danica Andrews read the conflict of interest policy statement.

OHAT Director Dr. Kristina Thayer presented the monograph's conclusions on renal effects of low-level lead in humans.

The principal health effect of low-level lead exposure on kidneys is reduced glomerular filtration rate (GFR). The EPA and ATSDR have concluded that lead can cause clinically relevant kidney effects. EPA concluded that this can occur at levels of exposure in the general population when other risk factors are present, and that it was not possible to identify a threshold for that association. In the draft 2011 EPA ISA document, the agency concludes that there is a causal relationship between lead exposures and renal health effects.

The NTP concludes that there is *sufficient* evidence in adults and *limited* evidence in children age 12 or older that blood lead levels <10 $\mu\text{g}/\text{dL}$ (and <5 $\mu\text{g}/\text{dL}$) are associated with decreased kidney function. The NTP also concludes that there is *inadequate* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with kidney effects in children under 12 years of age.

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The outcomes considered related to GFR were serum creatinine, creatinine clearance, estimated GFR, and chronic kidney disease. The conclusions as to kidney effects in adults and adolescents were supported by consistency in findings from approximately 15 publications, which were mostly cross-sectional studies, with several prospective studies also. Four studies supported association at <5 μ g/dL. Associations were stronger in certain patient populations, such as diabetics, and were supported by animal data.

The issue of reverse causality was considered, but NTP agreed with EPA's assessment that reverse causality was not sufficient to account for associations.

The conclusion of *inadequate* evidence for kidney effects in children under 12 was based on the fact that studies reported "early biological effect markers" of limited prognostic value. The findings were inconsistent, also.

The NTP's Overall Conclusions on Renal Effects

The NTP concludes that there is *sufficient* evidence in adults and *limited* evidence in children age 12 or older that blood lead levels <5 μ g/dL are associated with adverse effects on kidney function and that there is *inadequate* evidence to evaluate kidney effects in children under 12 years of age.

Dr. Thayer reviewed the specific kidney charge questions that the reviewers were to have considered, and depicted the summary table for the chapter.

Dr. Vaziri was the primary reviewer of the chapter. He stated that he fully agreed with the conclusions included in the chapter. He mentioned that lead at low levels acts as a co-factor, multiplying the injurious effects of other conditions, such as diabetes, obesity, and hypertension. Regarding kidney effects in children, he noted that lead exposure at an early age would result in a dormancy period, masking the ongoing injurious effect. Further, the onset of diabetes and other amplifying factors would not have completely expressed themselves in young children. Thus, the effect in young children should not be dismissed, although he did not disagree with the chapter's conclusion of *inadequate* evidence.

Dr. Wedeen was the second reviewer of the chapter. He agreed with Dr. Vaziri's comments. He added that hypertension and kidney disease are interrelated, and that hypertension is evidence of kidney disease. He felt that the concept of reverse causality is "greatly overused"—that there is no evidence for it, and good evidence against it. He disagreed with the conclusion in the monograph that "urinary secretion of lead should decrease as kidney function declines" and recommended that the statement be deleted. He said there is no evidence that renal failure changes the balance of lead in the body, per se. He felt that that concept was of great importance related to the idea

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of causality, in that reverse causality is not supported. He said that reverse causality is only a theory, and could be mentioned as such in the monograph in that light, but should not be referred to as factual. Dr. Bucher asked Dr. Wedeen if he felt that the monograph should be changed to reflect his comments about hypertension and kidney disease, and Dr. Wedeen agreed that there should be reference to that interrelationship.

Dr. Guallar was the third reviewer of the chapter. He agreed with the comments from the other reviewers.

Dr. Factor-Litvak also agreed with the reviewers' comments, but noted that increases in serum creatinine and declines in GFR are end stages of kidney disease. Dr. Wedeen disagreed with that assessment, noting that "end stage" implies loss of up to 90% of kidney function. Dr. Factor-Litvak said she had used the term incorrectly, and that she wanted to discuss some of the functions of the kidney that had not been addressed in the chapter. She said some of her research had shown that high levels of lead were associated with decreased production of erythropoietin, especially in anemic patients, although the effect was not seen in children. She described the hypothesis that early renal damage is associated with later problems with the hematopoietic system. She said the process is chronic, with children exposed to lead over a longer period of time rather than an acute exposure.

Dr. Carrington expressed concern that the discussion was mixing clinical effects of exposures during childhood with childhood exposures contributing to adult outcomes. He said there was evidence of reverse causality with high doses of cadmium. Dr. Wedeen reiterated that he was unaware of any evidence of reverse causality in lead, even at high doses. He said that balance is maintained – "what comes in, goes out," and the blood lead levels are the same among people with or without renal failure.

Dr. Pounds asked for and received a motion by Dr. Vaziri and seconded by Dr. Wedeen that the chapter's conclusions be accepted as written. The panel accepted unanimously (8 yes, 0 no, 0 abstentions) the conclusions as written in Table 7.5: NTP conclusions on kidney effects of low-level Pb. Dr. Pounds then asked for and received a motion by Dr. Vaziri and seconded by Dr. Wedeen to accept the chapter's overall conclusion as written. The panel accepted unanimously (8 yes, 0 no, 0 abstentions) the overall NTP conclusions as written.

X. Neurological Effects

Dr. Rooney presented the monograph's conclusions on neurological effects of low-level lead in humans.

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The principle neurological effects of lead in children are neurocognitive and neurobehavioral effects. Findings in this area have been driving the increasing recognition of the potential role of low-level lead exposures for many years, including recent studies on ADHD and delinquent behavior. That database includes some prospective studies with evidence for health effects in children of prenatal lead exposures. The adult database includes some evidence of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and essential tremor, along with decreased cognitive performance. EPA and ATSDR have concluded that lead has negative effects on neurocognitive ability and neurobehavioral outcomes in children. Animal data also support lead neurotoxicity.

In the monograph, the NTP divided the major neurological effects considered into four categories: cognitive function, behavior, neurodegeneration, and sensory organ function.

Cognitive Function: Decreased Academic Achievement

Academic achievement is a broad-based measure of cognitive function in children. Cognitive function is measured with numerous tests, and is also determined by class rank or end-of-grade testing.

The NTP concludes that there is *sufficient* evidence that childhood blood lead levels $<10\mu\text{g}/\text{dL}$ and $<5\mu\text{g}/\text{dL}$ are associated with decreased academic achievement, and that there is *inadequate* evidence for an association with prenatal blood lead levels $<10\mu\text{g}/\text{dL}$.

The conclusions are based on multiple prospective and cross-sectional studies reporting associations with blood lead levels $<10\mu\text{g}/\text{dL}$ and $<5\mu\text{g}/\text{dL}$, with a consistency of effects on several measures of academic achievement. The evidence is supported by an association with teeth dentin bone lead levels, similar effects seen in children with higher blood lead levels ($>10\mu\text{g}/\text{dL}$), and animal data. There is a lack of studies with prenatal exposure data for this outcome, leading to the conclusion of *inadequate* evidence in that area.

Cognitive Function: Decreased IQ

IQ is another broad-based measure of cognitive function. Lead-associated IQ data is considered only in children aged 4-13 in this context. It is measured with numerous tests.

The NTP concludes that there is *sufficient* evidence that blood lead levels $<10\mu\text{g}/\text{dL}$ are associated with decreased IQ in children, *limited* evidence of an

association with child blood lead <5 $\mu\text{g}/\text{dL}$, and *limited* evidence of an association with prenatal blood lead <10 $\mu\text{g}/\text{dL}$.

The conclusions are based on multiple prospective and cross-sectional studies reporting association with blood lead levels <10 $\mu\text{g}/\text{dL}$ in children, with consistency of effects in several measures of IQ. Effects were observed <5 $\mu\text{g}/\text{dL}$ in one cross-sectional study, leading to the conclusion of *limited* evidence at that level. The evidence is supported by the fact that similar effects have been seen in children at higher blood lead levels, associations seen with bone lead from the tibia and teeth, and animal data. There is mixed evidence of an association with maternal or cord blood <10 $\mu\text{g}/\text{dL}$, leading to the conclusion of *limited* evidence for prenatal blood lead <10 $\mu\text{g}/\text{dL}$.

Cognitive Function: Other General or Specific Measures

The NTP considered a third category under cognitive function: decreases in other general or specific measures of cognitive function. They are measured with numerous tests, which include broad-based tests and tests for specific cognitive domains. Tests are designed for both children and adults.

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ and <5 $\mu\text{g}/\text{dL}$ are associated with decreased cognitive function in children, *limited* evidence for prenatal blood lead <10 $\mu\text{g}/\text{dL}$ and <5 $\mu\text{g}/\text{dL}$, and *limited* evidence in older adults at blood lead levels <10 $\mu\text{g}/\text{dL}$.

The conclusions for children (aged 3 months-16 years) are based on multiple prospective and cross-sectional studies reporting associations with blood lead levels <5 $\mu\text{g}/\text{dL}$, with consistency of effects seen on multiple cognitive measures. They are supported by data showing an association with bone lead, data for similar effects in children at blood lead levels >10 $\mu\text{g}/\text{dL}$, and animal data. There was mixed evidence of an association with maternal blood lead <5 $\mu\text{g}/\text{dL}$, so the conclusion was for *limited* evidence for prenatal blood lead levels <10 $\mu\text{g}/\text{dL}$ and <5 $\mu\text{g}/\text{dL}$. The conclusion of *limited* evidence for older adults is based on studies reporting decreased cognitive function reported in older adults at blood lead levels <10 $\mu\text{g}/\text{dL}$. Other studies support association with bone lead and change in cognition over time in older adults.

Behavior: ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is a behavioral diagnosis that can be determined by diagnostic interview, and/or by use of stimulant medication.

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ and <5 $\mu\text{g}/\text{dL}$ are associated with ADHD in children, that there is *limited*

evidence for an association with prenatal blood lead <10 $\mu\text{g}/\text{dL}$, and that there is *inadequate* evidence in adults for an association at blood lead <10 $\mu\text{g}/\text{dL}$.

The conclusions in children (aged 3-18) are based on multiple prospective and cross-sectional studies, with consistent associations with blood lead levels <5 $\mu\text{g}/\text{dL}$. They are supported by studies reporting association with bone lead, and animal data. The conclusion of *limited* evidence for prenatal blood lead levels <10 $\mu\text{g}/\text{dL}$ was supported by mixed evidence of an association with maternal blood lead <10 $\mu\text{g}/\text{dL}$. The conclusion of *inadequate* evidence for adults is based on a lack of studies.

Behavior: Increased Delinquent, Criminal or Antisocial Behaviors

These problem behaviors are measured with numerous tests, and can be determined via criminal records.

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ and <5 $\mu\text{g}/\text{dL}$ are associated with antisocial behaviors including delinquent or criminal behavior in children, *limited* evidence for prenatal blood lead <10 $\mu\text{g}/\text{dL}$, and *inadequate* evidence in adults at blood lead <10 $\mu\text{g}/\text{dL}$.

The conclusions in children (aged 6-15) are based on multiple prospective and cross-sectional studies reporting associations with blood lead levels <10 $\mu\text{g}/\text{dL}$, consistency between behavioral tests and criminal arrest records, and a large cross-sectional study reporting an association at a blood lead level <1 $\mu\text{g}/\text{dL}$. They are supported by consistent associations reported with bone lead, similar effects seen in children at higher blood lead levels, and animal data. There was mixed evidence of association with maternal or cord blood lead <10 $\mu\text{g}/\text{dL}$, *limited* evidence for prenatal blood lead <10 $\mu\text{g}/\text{dL}$, and no studies with adult blood lead levels.

Psychological effects: Including Anxiety and Depression

The NTP concludes that there is *inadequate* evidence for prenatal, *inadequate* evidence for children with blood lead <10 $\mu\text{g}/\text{dL}$, and *limited* evidence in adults that blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with psychiatric outcomes.

The conclusion in adults is based on several cross-sectional studies reporting associations. It is supported by association with bone lead data, and by animal data. There have been few studies of this area in children with blood lead levels <10 $\mu\text{g}/\text{dL}$ and no studies with prenatal blood lead <10 $\mu\text{g}/\text{dL}$.

NeuroDegeneration: ALS

The NTP concludes that there is *limited* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with ALS in adults.

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The conclusion is based on several case-control studies with blood lead levels <10 $\mu\text{g}/\text{dL}$, and is supported by effects of lead seen in a mouse model of severe ALS. The issue of potential reverse causality is present in this case, in that reduced activity associated with ALS may cause greater bone lead mobilization, along with increased survival time among ALS patients, which causes a greater likelihood of individuals with higher blood lead levels being in a study. Those factors may combine to appear to support a relationship with ALS and higher lead levels. The Fang *et al.* 2010 study addressed some of the issues of reverse causality by controlling for factors associated with bone turnover and support the NTP conclusion of *limited* evidence.

Neurodegeneration: Essential Tremor

The NTP concludes that there is *limited* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with essential tremor in adults.

The conclusion is based on several case-control studies with blood lead levels <5 $\mu\text{g}/\text{dL}$, and animal data.

Neurodegeneration: Alzheimer's and Parkinson's Disease

The NTP concludes that there is *inadequate* evidence that blood lead levels <10 $\mu\text{g}/\text{dL}$ are associated with Alzheimer's or Parkinson's disease in adults.

The conclusion is based on the fact that there are no studies available with blood lead levels <10 $\mu\text{g}/\text{dL}$, and few examining a potential association with lead in this area.

Sensory Organ Function: Auditory Acuity

The NTP concludes that there is *sufficient* evidence that blood lead <10 $\mu\text{g}/\text{dL}$ is associated with decreased auditory acuity in children, *limited* evidence for prenatal blood lead <10 $\mu\text{g}/\text{dL}$, and *limited* evidence in adults for blood lead <10 $\mu\text{g}/\text{dL}$.

The conclusion for children is based on several large cross-sectional studies with blood lead <10 $\mu\text{g}/\text{dL}$, as well as a study in Polish children of increased latency of brainstem auditory evoked potentials, a marker of hearing loss. This conclusion is supported by similar effects reported in children and adults at blood lead levels >10 $\mu\text{g}/\text{dL}$, and by animal data. Few studies have been conducted in this area with maternal blood lead levels <10 $\mu\text{g}/\text{dL}$, therefore the conclusion of *limited* prenatal evidence.

Sensory Organ Function: Visual Effects

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The NTP concludes that there is *inadequate* evidence that blood lead levels <10 μ g/dL are associated with effects on vision with prenatal exposure or in children or in adults.

The conclusions are based on the availability of few studies at blood lead levels <10 μ g/dL.

The NTP's Overall Conclusions for Neurological Effects

The NTP concludes that there is *sufficient* evidence that blood lead levels <10 μ g/dL are associated with adverse neurological effects in children and *limited* evidence in adults.

Dr. Rooney reviewed the specific neurological charge questions that the reviewers were to have considered, and depicted the summary tables for the chapter.

Dr. Pounds noted that Dr. Gayle DeBord of NIOSH was joining the meeting by phone.

Dr. Lanphear was the primary reviewer of the chapter. He concurred with “the vast majority” of the section on neurological effects. In terms of the overall conclusions, he agreed with the conclusion of *sufficient* evidence in children, but wished to revisit the conclusion of *limited* evidence in adults. He felt that the different health endpoints had been dealt with inconsistently, in that some were treated more stringently than others. He said that from a population level, it seemed to him that the data were quite convincing in suggesting that chronic, low-level exposures should be considered. He felt that when looking at outcomes such as ADHD, IQ, or academic abilities, for example, chronic low-level exposure measures are likely to be more informative than peak blood lead measures of acute exposures.

Citing “amazingly consistent” evidence in “study after study,” he felt that the conclusion of *limited* evidence of IQ decrements at blood lead levels <5 μ g/dL was not correct.

Dr. Cory-Slechta was the second reviewer. She agreed with the document’s approach of not discussing the supra-linear relationship at blood lead levels <10 μ g/dL, in that it has been “a bit of a distraction” and does not characterize all of the CNS effects. She was concerned about the use of “ADHD” in a diagnostic capacity—that many things were being lumped together, such as parental reports and other elements that may not necessarily be clinical ADHD diagnoses. She suggested that the term “attention-related behaviors” would be more appropriate.

She noted that researchers using the LeadCare® method of measuring blood lead are limited to a detection level of 3 μ g/dL, and that after adding at least 2 μ g/dL or more for margin of error, it is proving difficult to be confident about measurement of low levels of blood lead. She said some of the studies should be examined to see if they were done

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with LeadCare® or confirmed by other methods. She also mentioned that animal studies are not looking for low-level thresholds.

Dr. Factor-Litvak was the third reviewer of the chapter. She agreed with the other reviewers' comments, but wished to note that in most of the studies, prenatal and early childhood blood lead concentrations track "pretty strongly," so the mother should be taken into account when assessing childhood blood lead levels. She also noted that concurrent blood lead levels mean exposures from the *in utero* period onward, and that that metric should be utilized in that context. Regarding the adult studies of essential tremor, she felt that the evidence for an association between low-level lead and essential tremor is convincing. Responding to Dr. Rooney's request for clarification, she said she would support changing the conclusion for essential tremor in adults from *limited* to *sufficient*.

Dr. Rothenberg added several points to the debate on the use of ADHD, concurring with the assertion made by Dr. Cory-Slechta. He recommended giving more credence to studies of components of current ADHD diagnoses than to the ADHD diagnosis itself. He felt that studies using stimulant prescriptions as a metric of ADHD should not be relied upon. Based on several animal studies and their correspondence with the few human studies on record, he suggested changing the conclusion on Visual Effects, prenatal, from *inadequate* to *limited*. Dr. Rooney noted that there was an error in the table of conclusions under Visual Effects, and that it would be fixed. The text cites the one study of prenatal lead exposure and potential effects on vision. The conclusions table says "no studies located" but should indicate this one study by saying "Yes, <10ug/dl", however Dr. Rooney still supported the original NTP conclusion of *inadequate* evidence.

Dr. Lanphear agreed with Dr. Cory-Slechta's assertion that LeadCare® is of more clinical value than research value. Regarding Dr. Rothenberg's point about not relying on ADHD medication prescriptions as a metric, Dr. Lanphear noted that it had been added due to discomfort with relying on parental reports alone. He felt also that from a public health and medical perspective there is value in looking at the composite of ADHD, rather than simply the components. He said researchers should not be "hog-tied" from looking at the relationships between environmental neurotoxicants and various types of behavior problems, including psychopathology. He recommended that population fractioning could be useful if employed carefully, citing an estimate of 1 in 5 children with ADHD resulting from lead exposure, using NHANES data. He stressed that that was in fact simply an estimate, but was nonetheless valuable from a public health perspective. He said that "we are the worst at taking our own research and dismissing it." He said by dismissing the research, a void is being created to the detriment of public health. He said that there is much value in the research on the

association between lead and attentional behaviors, and that there would be a lot of missed opportunities if it cannot be translated into language that the public or pediatricians understand.

Dr. Cory-Slechta said she felt that there are credibility issues trying to tie low-level lead exposures with ADHD, since a compelling case cannot be made for the clinical diagnosis. Dr. Factor-Litvak noted that ADHD is probably at the extreme of problems with attention that can be measured, and that these problems are probably more of a public health issue, because they affect a lot more kids. Thus, she felt that saying that lead is associated with attentional problems probably has more of a “public health bang” than saying it is associated with ADHD. Dr. Lanphear felt that both were important, and are intertwined from a population effect.

Dr. Rothenberg pointed out that it is important for the monograph to be clear about shortcomings of the existing research, one of which is the “sliding” nature of the ADHD diagnosis. He was concerned that the ADHD issue might be interpreted publicly as a weak link in the monograph that could be used to delay action. He felt that the malleable diagnosis of ADHD should be acknowledged in the text of the document to forestall such criticism.

Dr. Factor-Litvak likened the current discussion to those held years ago regarding a 4-point decrement in childhood IQ attributable to lead exposure, in that that decrement was meaningless when applied to any individual child, but when applied on a population level revealed a severe effect of lead exposure on childhood cognition. She felt that the same principle applies to attention problems.

Dr. Carrington noted that given sharply declining lead levels, associating lead exposure with sharply rising rates of ADHD would require some explanation. Dr. Cory-Slechta replied that a condition such as ADHD is highly multi-factorial, and that arguments such as the one Dr. Carrington was anticipating are easily dismissible. Dr. Factor-Litvak added that in a complex disease such as ADHD, it is not a fair argument to attempt to relate one exposure to one outcome.

Dr. Pounds began discussion of potential changes to the conclusions in the chapter. He reiterated the suggested changes, and asked their main proponents to summarize their reasoning.

The first was a possible change in the Cognitive Function: IQ section; that *limited* in children <5 μ g/dL should be changed to *sufficient* and no longer limited to one study, which would eliminate that line and change the *sufficient* line above by changing <10 μ g/dL to <5 μ g/dL. Dr. Lanphear repeated his thoughts.

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Dr. Pounds turned to the question of whether the effect should be called “ADHD” or “attention-related behaviors,” as proposed by Dr. Cory-Slechta and Dr. Factor-Litvak. Dr. Lanphear felt that some caveats needed to be added regarding ADHD diagnosis. Dr. Rooney asked the panel to construct an additional sentence in the overall conclusions to help clarify the point. Dr. Bucher noted that the addition would help with communication efforts related to the monograph’s findings, but it would not be included as part of the panel’s recommendations.

Dr. Pounds reiterated the suggestion that the conclusion for essential tremor <10 $\mu\text{g}/\text{dL}$ be changed from *limited* to *sufficient*, and said he had heard no dissent from that recommendation. Dr. Factor-Litvak suggested adding a designation of *limited* evidence <5 $\mu\text{g}/\text{dL}$, necessitating the addition of another line.

Dr. Pounds said a change had been proposed under Visual Effects to change prenatal from *inadequate* to *limited*. Dr. Rothenberg initially pointed out that the next column in the table might be changed to “Yes, <10 $\mu\text{g}/\text{dL}$ ” as pointed out previously there was one study and this could support a conclusion of *limited* evidence. There was considerable discussion as to the applicability and impact on those conclusions of the results reported in Rothenberg *et al.* 2002. Dr. Rothenberg reviewed the paper in question and noted that the lowest detectable effect level was 10.5 $\mu\text{g}/\text{dL}$; therefore there were no studies located with effects below 10 $\mu\text{g}/\text{dL}$ and no change was recommended for the conclusion of *inadequate* evidence.

Dr. Pounds requested and received a motion by Dr. Cory-Slechta and seconded by Dr. Factor-Litvak to accept the Neurological Effects table as edited. The panel voted unanimously in favor (8 yes, 0 no, 0 abstentions) of accepting the conclusions in Table 4.3: NTP conclusions on neurological effects of low-level Pb, with several modifications. The panel recommended *sufficient* evidence for effects of blood Pb levels <5 $\mu\text{g}/\text{dL}$ on Cognitive Function; IQ in children. The panel recommended *sufficient* evidence for effects of blood Pb levels <10 $\mu\text{g}/\text{dL}$ and *limited* evidence for effects of blood Pb levels <5 $\mu\text{g}/\text{dL}$ for Neurodegeneration: Essential Tremor in adults. The panel pointed out that one study was available to support the NTP’s conclusion of *inadequate* evidence for prenatal effects on Sensory Function: Visual. The panel recommended the term “Behavior: ADHD” be changed to “Attention-related Behaviors”.

The panel then considered the overall conclusions for Neurological Effects. Dr. Lanphear felt that the conclusion regarding children should be <5 $\mu\text{g}/\text{dL}$, while retaining <10 $\mu\text{g}/\text{dL}$ for adults. It was moved by Dr. Lanphear and seconded by Dr. Cory-Slechta to accept the overall conclusions with that change. The panel voted unanimously (8 yes, 0 no, 0 abstentions) to accept the recommended overall NTP conclusions, there is *sufficient* evidence that blood Pb levels <5 $\mu\text{g}/\text{dL}$ are associated with adverse

neurological effects in children and there is *limited* evidence in adults for blood Pb levels <10 μ g/dL.

Dr. Rooney asked the group to craft an additional sentence to the overall conclusions in order to add clarity to the message on attention-related problems. Dr. Factor-Litvak initially proposed that the addition read, “There is *sufficient* evidence that blood lead levels <5 μ g/dL are associated with increases in attention behavior problems in children; high levels of attention behavior problems in children are often associated with diagnoses of ADD or ADHD.” The panel discussed the potential added sentence at length. Dr. Cory-Slechta suggested: “There is *sufficient* evidence that blood lead levels <5 μ g/dL are associated with increases in impairments in attention-related behaviors; high levels of attention behavior problems in children are often associated with diagnoses of ADD or ADHD.” NTP staff noted that the phrase “high levels” might be problematic. Dr. Cory-Slechta suggested substituting “increases in more extreme attention-related behaviors” in place of “high levels of attention behavior problems.”

The final statement agreed upon by the panel read, “There is *sufficient* evidence that blood lead levels <5 μ g/dL are associated with increases in impairments in attention-related behaviors; increases in more extreme attention-related behaviors in children are often associated with diagnoses of ADD or ADHD.” Dr. Bucher pointed out that no vote would be needed for this additional sentence, and that it would be used by NTP staff to gain a sense of the panel’s position on the ADHD issue.

XI. Concluding Remarks

Dr. Pounds opened the floor for the panel members to make concluding remarks prior to adjournment of the meeting.

Dr. Rothenberg suggested future directions for research in the area. He said it was clear that the most pressing need was for large-scale, very long-term, prospective studies to be started as early as possible in pregnancy. He said the National Children’s Study might be a vehicle, but was cautious given that project’s funding problems. He also felt that substantial funding should be provided for improving methods of measuring accumulated lead. He recommended focusing more on multiple toxicant exposures, and paying more attention to exposure/response relationships, which can provide keys for mechanistic studies.

Dr. Cory-Slechta felt that concentrating on lead in isolation was inappropriate, in that people are typically exposed to multiple chemicals and multiple stressors. This observation implies that agents such as lead have much bigger effects, perhaps at much lower levels, and they are not picked up because the studies are not done in the real world, in the human context. She hoped to see epidemiological studies that look at

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interactions, through the development of new methods that allow examination of interactions without the need for huge sample sizes.

Dr. Factor-Litvak noted that there are new statistical methods being developed to help look at mixtures of environmental toxicants. She also felt that it was important to look at whether or not good behaviors and good nutrition might mitigate some of the adverse chemical effects. She thanked the NTP for producing a very high-quality document.

Dr. Lanphear agreed that it was a very well-done document, and added that it is “extraordinarily important.” He said that given all that is known, if epidemiology cannot make conclusions about lead, “we’re really in trouble.” He felt that it would be important in the future to not necessarily concentrate on linking exposures to clinical disease, but to make use of opportunities such as this one to convince people about the importance of population effects. He also recommended not getting so caught up in the semantics involved. He said that concentrating on associations forces too much attention on the medical model, and takes away from prevention efforts, with public health suffering as a result.

Dr. Vaziri complimented NTP on the document and thanked the staff for excellent coordination of the meeting. He felt that further animal and cell-culture studies of the mechanisms at work would help provide irrefutable evidence in the future.

Dr. Carrington said that from a policymaking point of view it would be useful to spend more time on dose/response relationships, in that the size of the effect would help determine what interventions might be necessary.

Dr. Wedeen said the monograph represented a culmination of 40 years of work on his part, and “takes us to a whole new magnitude of lead, and it’s very gratifying to see it as a consensus.”

Dr. Guallar reiterated his opinion that NTP should employ a more systematic approach to its review. He said it was obvious that lead has a very high impact on health, and that there is a need for more population-level and basic scientific research. He felt that the case had still not been made to the medical community regarding the health effects of lead. He noted that “the lower we go, we still find effects of lead...so this is not an area where we’re done yet.”

Dr. Pollard echoed the other panel members’ comments about the quality of the monograph.

Dr. Pounds agreed that it was a very lucid document. He said there remains a research need to better understand lead exposure kinetics. He also wanted to see more studies

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regarding multiple toxicants, and on genetic background and how it affects lead toxicity and susceptibility.

Dr. Thayer praised the panel's preparation and work, and said that everything the group had said would be incorporated into the document.

Dr. Birnbaum mentioned that it appears to be very difficult to distinguish prenatal exposure from childhood exposure, but that there appears to be very little attention in the medical community to measuring blood lead levels in women of reproductive age. She likened the situation to that of mercury, where warnings are issued to women of reproductive age not to eat fish high in mercury, due to concerns about prenatal exposures. She also read the panel a statement that had been made by the Advisory Committee on Childhood Lead Poisoning Prevention, which had met at CDC the previous week, which questioned the value of attempting to establish any low threshold for blood lead, underscoring the critical importance of primary prevention. She predicted the final CDC document, due in January 2012, would have an impact on public health recommendations in the future.

Dr. Bucher thanked Dr. Pounds for chairing the panel, the NTP staff for their able contributions, and the panel members for their extraordinary preparation.

Dr. Pounds adjourned the meeting at 11:55am, November 18, 2011.

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These summary minutes have been read and approved by the Chair of the November 17-18, 2011, National Toxicology Program Draft NTP Monograph on Health Effects of Low-Level Lead Peer Review Panel Meeting.

[Redacted]

Dr. Joel Pounds
Chair, NTP Monograph Peer Review Panel Meeting

Date: March 16, 2012