

**NIPPING IRIS IN THE BUD:
SUPPRESSION OF ENVIRONMENTAL SCIENCE BY
THE BUSH ADMINISTRATION'S
OFFICE OF MANAGEMENT AND BUDGET**

A staff report by the Majority Staff of the Subcommittee on Investigations and Oversight
for Subcommittee Chairman Brad Miller
Committee on Science and Technology
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NIPPING IRIS IN THE BUD: SUPPRESSION OF ENVIRONMENTAL SCIENCE BY THE BUSH ADMINISTRATION'S OFFICE OF MANAGEMENT AND BUDGET

By the end of the Bush Administration, the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) process was broken. What began two decades ago as an initiative at EPA to establish a reliable database on what science said about the risks of particular chemicals devolved by the end of the Bush Administration into a tortured round of interagency bickering, mediated and even stimulated by the Office of Information and Regulatory Affairs (OIRA). As a result of the IRIS process breaking down, public health offices across the country and around the world, as well as concerned citizens, were left without the reliable, expanding, up-to-date database of chemical risks that they had come to rely upon.

The Bush Administration's OIRA used its position at the top of the Executive branch to force EPA to undergo a multi-year, interagency review ostensibly designed to establish a new process for creating new or updated IRIS database entries. At the same time, OIRA both supplied detailed scientific challenges to proposed IRIS entries and coordinated scientific comment from agencies across the government. OIRA's own scientific comments on proposed listings included detailed editorial comments that would have changed the import and meaning of the scientific findings in EPA's documents. All of this was done in secret, without any acknowledgement to the public or the Congress that OIRA was calling the shots.¹ IRIS was broken, not by accident, but through conscious, sustained effort from officials in OIRA.

1. The Subcommittee has carried out extensive work on OIRA's role in relationship to IRIS. In 2008, the Subcommittee held two hearings on this subject. The first of these hearings was on May 21, 2008, when the Subcommittee took testimony from Dr. George Gray, the then-Assistant Administrator for Research and Development at EPA, and Ms. Susan Dudley, the then-Administrator of the Office of Information and Regulatory Affairs (OIRA) at the Office of Management and Budget. Additionally, Mr. John Stephenson of GAO testified on findings regarding the lack of productivity in the IRIS process. In the second hearing, on June 12, 2008, the Subcommittee received testimony from Mr. Jerry Ensminger (U.S.M.C., retired), Mr. Lenny Seigel (Executive Director, Center for Public Environmental Oversight), and Dr. Linda Greer (Director of the Health Program at the Natural Resources Defense Council). On June 11, 2008 Chairman Miller sent a document request to OMB asking for all materials relating to OIRA's involvement in the proposed IRIS entry for trichloroethylene (TCE). In response, the Committee received a few boxes of materials. The great majority of those materials were either peer reviewed articles, articles done by EPA staff, or research reports done under contract to industry or polluting agencies. Subcommittee staff were obliged to visit OMB's office to review thousands of pages of documents and take notes because the office refused to provide copies. A clear picture of OIRA's almost daily involvement on TCE emerged from that review. However, OIRA refused to provide access to most documents regarding interagency communications or internal communications surrounding TCE. Because the 110th Congress was drawing to a close, it was not practical to push for a subpoena for these records. We were never shown any document that could have been construed as having Executive Privilege attached to it. OIRA's entire approach appeared to amount to little more than obstruction of the work of the Subcommittee; in a sense, OIRA did to the Subcommittee's investigation what they have perfected in terms of slow-rolling IRIS proposals.

BACKGROUND

OIRA is a small office of some 50 career staff housed inside the Office of Management and Budget (OMB). With origins in the Paperwork Reduction Act of 1980, OIRA's role has expanded well beyond simply trying to reduce the paperwork burden on citizens and businesses to being the central White House voice, some would say choke-point, on regulations of all varieties. It has been OIRA that has most passionately and persistently insisted on using cost-benefit analysis in assessing proposed regulations, even in the face of criticism that such calculations tend to understate benefits because many of them are so hard to monetize, like the value of a human life.² Historically, it has been staffed by statisticians, economists and lawyers. There are real differences between the way OIRA operated under President Bill Clinton and under President George W. Bush, but there is a consistent theme of OIRA being a watchdog on what regulatory agencies were attempting to do to comply with statutes and, on occasion, court orders.

In the 110th Congress, at the direction of Subcommittee Chairman Brad Miller (D-NC), the Subcommittee on Investigations and Oversight looked very carefully at how OIRA was interfering with the science-based work of regulatory agencies. In addition to two hearings on Executive Order 13422, which the Bush Administration put in place to empower OIRA to control regulatory agendas at agencies across the government—an order the Obama Administration has now withdrawn--the Subcommittee held two hearings on the IRIS at EPA. IRIS provided a perfect example of how OIRA was branching out into challenging the science being done at regulatory agencies.

A chemical's entry in the IRIS database is nothing more than a science-based assessment of risks associated with a particular chemical. IRIS entries are produced in the Office of Research and Development (ORD) of EPA, and those entries are not an expression of regulatory intent or advice. The entries are not even all that is required of a complete risk assessment as defined in the seminal National Academies of Science report, *Risk Assessment in the Federal Government: Managing the Process* (1983).³ And risk assessment is a long step away from a regulatory effort, which is described in the terminology of the panel as "risk management." However, the absence of IRIS entries for widely used, toxic chemicals leaves state and local regulators, first responders, and citizens without crucial information that can guide their response to an emergency or an emerging health or environmental threat.

OIRA has been involved in the IRIS process since the closing years of the Clinton

2. "Life's Value Shrinks at EPA," Matthew Madia, OMB Watch, July 22, 2008.

3. In that 1983 report, "Risk Assessment in the Federal Government: Managing the Process," the National Research Council panel identified four components of a complete risk assessment: hazard identification, dose-response evaluation, exposure assessment, and risk characterization. IRIS reflects science that addresses the first two conditions. In discussing the difference between risk assessment and risk management, the Academy panel wrote: "Risk assessment is the use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations. Risk management is the process of weighing policy alternatives and selecting the most appropriate regulatory action, integrating the results of risk assessment with engineering data and with social, economic and political concerns to reach a decision." See the discussion on page 3 of the 1983 report.

Administration. Initially OIRA was pulled into the process to facilitate interagency discussions about particular chemicals proposed for IRIS listings. Agencies that had a record of pollution with certain chemicals were concerned that new IRIS standards would trigger the long march to new regulations and the end result would be that the polluting agencies would have to change their practices and clean up legacy wastes. Those who polluted saw that disputing what scientific research had found about the risks of a particular chemical could become the first line of defense against the distant possibility of regulation.⁴ By the late 1990s, OIRA was playing a role as facilitator for interagency discussions regarding particularly contentious proposed IRIS listings.⁵

Suppressing IRIS entries essentially shuts down the flow of coherent, reliable information about what chemicals pose what kinds of risks. Testimony received by the Subcommittee at the second day of hearings on this subject emphasized the important role of IRIS as a public health and safety resource. That hearing, entitled, "Toxic Communities: How EPA's IRIS Program Fails the Public," took testimony from U.S.M.C. (retired) Master Sergeant Jerry Ensminger, the Executive Director of the Center for Public Environmental Oversight, Mr. Lenny Siegel, and Dr. Linda E. Greer, Director for Health Programs at the Natural Resources Defense Council. Mr. Ensminger was particularly compelling in making a case for why polluting agencies such as DOD should not be allowed privileged access to discussions about the science of potential pollutants.

It is a known fact that the United States Department of Defense is our nation's largest polluter. It is beyond my comprehension why an entity with that type of reputation and who has a vested interest in seeing little to no environmental oversight would be included in the scientific process. Not only are they obstructing science, they are also jeopardizing the public health for millions of people all around the world... and yet this Administration and past Congresses have allowed DOD's tentacles to infiltrate the realm of science.⁶

Mr. Ensminger was stationed at Camp LeJeune. His daughter, Janey, died of acute

4 . This effort by polluters, or those who fear regulation of whatever stripe, of pushing the struggle back to what the science says about a particular risk rather than arguing over how to structure a regulation has been described as "paralysis by analysis." Science lends itself to endless study because there is never an absolute, final answer to any question, but always another layer of research that could add to the body of accumulated knowledge. If those who want to avoid regulation can shift the terms of discussion from the risk management end of the spectrum to the science and what uncertainties remain, a regulatory struggle need never begin. For analysis of how this process has unfolded among regulated industries, see, David Michaels, Doubt Is Their Product: How Industry's Assault on Science Threatens Your Health, Oxford University Press, New York, 2008.

5 . A new report from the Center for Progressive Reform has some of this history. The Subcommittee was also able to review records from 1998 when OIRA first began to push into the interagency struggles over characterizing risks to former marines and their families from TCE and other chemicals at Camp LeJeune. At that time, OIRA's interest was more in the costs of the studies and making sure the then-proposed survey study met OIRA quality standards. OIRA reviews all survey instruments as part of its authority under the Paperwork Reduction Act of 1980.

6. "Toxic Communities: How EPA's IRIS Program Fails the Public," Hearing before the Subcommittee on Investigations and Oversight, Committee on Science and Technology, June 12, 2008, p. 132.

lymposytic leukemia. Water at the Camp was contaminated with trichloroethylene (TCE) and perchlorate (perc) and these chemicals, as well as other volatile organic compounds in the water system at the Camp, may have caused Janey's condition. DOD has been working for many years to block new IRIS standards on TCE and perc.

In the Bush Administration, OIRA's involvement changed in scope and kind. John Graham, the first director of OIRA, brought in technical specialists—including toxicologists—to tend to science-based discussions of proposed environmental regulations, guidance and IRIS entries. Graham also oversaw a complete overhaul—some might describe it as an endless evolution—of the review and approval process for IRIS proposals. This report will describe that tumultuous review process, how it impacted EPA's productivity and independence, and the true nature of OIRA's role in the interagency review process.⁷

OIRA DOES SCIENCE

Before turning to how the IRIS process was subjected to ongoing interagency negotiations, it is worth examining the day-to-day reality of working on IRIS entries. OIRA has always claimed to Congress and the public that its sole function was as a facilitator of interagency science discussions. John Graham's successor at OIRA, Susan Dudley, described OIRA's role in language that might have applied during the late-Clinton years. An exchange Ms. Dudley had with Subcommittee Chairman Miller in testimony before the Subcommittee on May 21, 2008 is worth quoting at length:

Chairman Miller. Ms. Dudley, do you think it is part of the role of OMB... to review scientific assessments prepared by other agencies of government?

Ms. Dudley. OMB serves a coordinating function. We coordinate interagency review of various things, so OMB's role I think is a legitimate role. We have scientists that engage other scientists throughout the Federal Government in reviewing IRIS assessments.

Chairman Miller. Well, I understand that there is one toxicologist that works for OIRA, is that correct?

Ms. Dudley. You know, I am not sure exactly their credentials. We have toxicologists, risk assessors, statisticians.

Chairman Miller. Well, they are remarkably productive, because they respond point by point in great detail at great length to the assessments that come up from the scientific agencies of government. Is that all done in-house or are there others who are invited to participate in OIRA's work or OMB's work?

7. Rebecca Clarren, "The EPA's Stalin Era," Salon.com, November 11, 2008. This article has a succinct discussion of how IRIS entries, or the lack of them, impacts communities facing pollution problems.

Ms. Dudley. No, it is certainly an interagency effort. So OMB doesn't provide the—we don't do the analysis, we coordinate it with other agencies. So we take advantage of the expertise throughout the Federal Government.⁸

Later in that same hearing:

Ms. Dudley. We talk to other federal scientists. Our role is coordinating the scientific dialogue between scientists within the Federal Government.⁹

George Gray, then the EPA Assistant Administrator for ORD, helpfully confirmed this version of OIRA's actions in answer to a question from Chairman Miller about what happened at the OMB interagency review step in the then-new IRIS process announced on April 10, 2008:

Dr. Gray. This is when the Office of Management and Budget would coordinate a review of the document by other federal agencies... *[in answer to a follow-on question, he continued]* It is my understanding, and I don't know how OMB does the formal process for reviewing these, but this would go out to all of the federal agencies to have an opportunity to comment.¹⁰

Dudley represented to the Subcommittee that OIRA had scientists on staff so that they could facilitate interagency science discussions of IRIS entries. Gray confirmed this image of OIRA as a simple coordinator of discussion and materials. However, the Subcommittee has ample documentation showing that OIRA's staff scientists did far more than merely coordinate and facilitate science discussions across agencies. OIRA's staff scientists directly challenged the science put forward by EPA IRIS staff in very detailed peer review-type comments.

For example, on December 22, 2005, John Vandenberg, Associate Director for Health at the National Center for Environmental Assessment, ORD, EPA sent an e-mail to Nancy Beck, an OIRA toxicologist brought on staff by John Graham. It read, in relevant part:

Attached are Toxicological Reviews for four polybrominated diphenyl ethers. This has gone through the EPA IRIS development and review process and is now ready for submittal to an external peer review panel.... We're providing this to see if you'd like to discuss, and would like to know as soon as possible since we'd like to move this toward external

8. "EPA's Restructured IRIS System: Have Polluters and Politics Overwhelmed Science?," Hearings before the Subcommittee on Investigations and Oversight, Committee on Science and Technology, May 21, 2008, p. 64. The Subcommittee was in possession of some records showing detailed peer review-style OIRA comments at the time of this hearing. Other records came to the Subcommittee in response to the June 11, 2008 document request from Mr. Miller to Ms. Dudley.

9. "EPA's Restructured IRIS System," p. 71.

10. "EPA's Restructured IRIS System," pp. 68-69.

peer review and completion in a timely manner.

Two months later, on February 15, 2006, Nancy Beck sent back an e-mail:

Hi John-

Attached are agency comments on the draft. Comments came in only from HHS.... let me know how EPA plans to respond to comments. If a conversation is easiest, we can set that up.

The characterization of comments as being only from HHS is misleading. The CDC/ATSDR provided just a paragraph of text expressing their pleasure in the approach EPA is using. NIEHS provided somewhat more commentary—several brief paragraphs, but also additional science references that EPA could consult.

But these “agency comments” were not the sum of comments to come back from Beck. Beck provided more than 11 pages of OIRA’s own, very specific editorial and substantive review comments. For example, in discussing the EPA IRIS draft on polybrominated diphenyl (BDE-209), Beck writes:

- page 4- in the Swedish studies how is EPA sure that internal dose is due to inhalation and not dermal absorption?
- page 7- in the distribution section it would be useful to discuss the age-dependent differences in distribution that are mentioned.
- page 14- says the half live is “short”(sic). What is this relative to? For some chemicals a half life of a week would be considered long.
- page 14- what species are the studies referred to in the last paragraph in the half life section? Are these data from rodents?
- page 31- “Together, these studies suggest that decaBDE has a very limited potential to activate the AhR signal transduction pathway, which **is considered to be a key** is ~~the critical~~-toxicological mechanism for many persistent aromatic hydrocarbons.” Please also add a citation for this?” *[emphasis in original]*

These comments were chosen at random from approximately 130 bulleted comments provided by Nancy Beck in the response document (see attachment A).

Of the items quoted above, the last observation in the list is very disturbing because it

represents a substantive editorial change regarding how to characterize the science. White House staff re-writing the “science” was a recurring problem during the Bush Administration’s term in office. The most famous case was probably that of Philip Cooney, chief of staff at the Council of Environmental Quality, editing out climate change science language in an annual report on climate programs to play up uncertainty regarding climate change.¹¹ In the Beck review of the EPA submission of polybrominated diphenyl there are numerous editorial comments altering language, and some appear to enhance uncertainty or reduce the profile of the effect being discussed. Beck repeatedly strikes “neurobehavioral developmental toxicity” or “neurobehavioral toxicity” to replace it with “changes in spontaneous motor behavior” or similar constructions. At one point, Beck edits a statement on accumulation differing by age in the following way (Beck’s edits in bold):

 this may imply that different activities may expose different age groups more than others, or that some PBDE congeners may accumulate differently with age, **however the sample size here is very small and firm conclusions cannot be made.**¹²

You don’t have to be a scientist to recognize that many of the comments made by Beck are exactly what one would expect from a scientific peer reviewer. But the role of providing the kind of expert feedback Beck was offering is properly for external peer reviewers; that is why an agency assembles a group of experts to provide their best advice and ask smart questions.

However, Beck took upon herself the role that should be reserved for external peer reviewers. Further, she adopted that role from one of the most powerful perches in the Executive branch: OMB. From that post, her words implicitly had the endorsement of the President and the President’s top staff. This gives a weight to her observations that no external peer reviewer—no matter how much more expert than Beck—carries. At a minimum, OIRA’s intervention added another layer of review and response that delayed moving an IRIS entry through the process. EPA was not in a position to ignore OIRA’s comments, and would end up engaging them before they could move forward to external reviews. Looking over the record of endless process reforms and direct review comments and challenges, one could conclude that the whole point of the exercise was to delay IRIS products.

The Subcommittee has records of exchanges similar to that on polybrominated diphenyl on other chemicals. The Subcommittee received an e-mail record from 2005 between

11. For the original story on this, see Andrew Revkin, “Bush Aide Softened Greenhouse Gas Links to Global Warming,” *New York Times*, June 8, 2005; “Editor of Climate Report Resigns,” *NYT*, June 10, 2005; “Ex-Bush Aide Who Edited Climate Reports to Join ExxonMobil,” *NYT*, June 15, 2005.

12. This quote and proceeding are from a chain of e-mails and interagency documents that are attachment “A”. They begin with an e-mail from John Vandenberg to Amy Mills of EPA and others, dated 02/27/2006, and titled “Re: Interagency Comments here: Fw: Draft IRIS assessments for 4 PBDE.

OMB and EPA of dibutyl phthalate review prior to submitting it for external review.¹³ As with the polybrominated diphenyl review, that OIRA/interagency review also took approximately two months between the time EPA sent language to OIRA and the time OIRA provided comments back. The Subcommittee also has two sets of comments on toluene: an OIRA response to a February 2005 EPA draft and an EPA compilation of responses to December 2003 OMB comments regarding an external review draft of a toluene toxicological review. This documentary chain suggests that toluene went through one external review in 2003, the draft revised and then reviewed by OIRA; then the toluene draft entry went through further internal EPA developments followed by another round of OIRA review and response more than a year later.¹⁴

The extent and detail of OIRA's comments vary from chemical to chemical, and they appear to become more elaborate over time. But each example is a powerful illustration that neither Susan Dudley nor George Gray was candid with the Subcommittee about the role of OIRA or the impact of its interventions on EPA's work. Subcommittee staff has been told by one person on the inside of these reviews that the documents in the possession of the Subcommittee are relatively mild compared to, for example, OIRA's efforts on perchlorate. Of course none of these communications were available to the public. There was no way to know that Dudley and Gray were not telling Congress the unvarnished truth because the entire process was veiled behind "deliberative process" claims of privilege. Transparency was anything but the watchword for what OIRA was doing to IRIS both in substance and process between 2003 and 2008.

THE PROCESS IMPROVEMENT MERRY-GO-ROUND

OIRA intervention in the work of IRIS grew throughout the Bush years. It appears to have been a constantly expanding effort that endlessly tweaked the process for reviewing and discussing IRIS entries, and expanded the scope of OIRA's direct involvement in science discussions. While we do not have OIRA documents on this evolution, the Subcommittee does have some EPA documents that shed light on how EPA IRIS staff viewed the situation.

The earliest process e-mail the Subcommittee has is from John Vandenberg, Associate Director for Health at EPA's National Center for Environmental Assessment (NCEA) to Peter Preuss, Director of the NCEA, and others dated September 13, 2004. Comments by the authors of this report appear in italicized text and brackets.

Vandenberg writes,

Nancy Beck [*OIRA toxicologist*] called me this morning and conveyed

13. This appears as attachment "B". Documents start with an e-mail from John Vandenberg to Bob Benson of EPA and others, dated 02/07/2006, titled "Interagency/OMB comments on Draft IRIS assessment of Dibutyl Phthalate."

14. Records appear as attachments "C" and "D". The first has hand-written notation, "Comments from OMB (Margo Schwab) 4-19-05." The second is dated "December 30, 2003" and is titled, "Summary of OMB comments and EPA responses".

several things: 1) John Graham wants a briefing *[from IRIS staff]* on the naphthalene assessment, focused on **process** from here (e.g. interagency review, consideration of peer review comments). We should arrange in the next couple of weeks if possible. 2) She (Nancy) considers some of the external peer review comments to be significant.” *[emphasis in original]*...

I told her we’re evaluating the draft in light of peer review comments, that we’ve heard DOD plans to comment but we have not received any comments from them and I urged her to get them to share their comments. I sketched out the IRIS process insofar as it would normally proceed, noting that a formal interagency review would change the process (and that we’d share a document that reflects our revisions following external peer review). I mentioned IRIS Track (Paul Gilman had also mentioned it, they’re interested in seeing it). I didn’t give any specific dates to her (perhaps fortunately IRIS track was offline this morning!)

We should talk through how we want interagency review to occur, including any groundrules we want to get set up front to avoid paralysis (e.g., fixed time for other agencies to provide review comments; final disposition/decisionmaking by EPA/ORD on assessment document completion; criteria or conditions calling for additional external peer review). Especially for “biggies” that have interagency review we need to stake out a process that will lead us to be successful in terms of timeliness, clarity, consistency, etc.¹⁵

By May of 2005, EPA staff were engaged in a formal IRIS process brought on by OIRA’s intervention. Vandenberg writes to Preuss and others, an e-mail entitled “IRIS process comments from OMB, next steps.” Vandenberg writes:

In brief, Nancy Beck (and, she says, Dr. Graham) were expecting more detail than provided in the flow chart and 2-pager to address the ‘details’. I pushed back, not wanting to have us wait several months to develop new SOPs [standard operating procedures], as this is premature. Nancy seemed to concur, though she is checking with Dr. Graham.

We ended up agreeing to slightly revise the 2-pager to add a bullet on next steps (i.e., public workshop to discuss process and details/issues) and to emphasize or elaborate on the improvements the process will bring.... Further I agreed that in our Federal Register notice announcing the workshop, we’ll identify some of the topics and issues for discussion... OMB wants to review this FR notice....¹⁶

15 . E-mail from Vandenberg to Preuss and others, 09/13/2004, titled, “naphthalene – OMB request for briefing.” Appears as attachment “E”.

16 . E-mail from Vandenberg to Amy Mills and others, 05/24/2005, titled, “IRIS process comments from OMB, next steps.” Appears as attachment “F”.

By February of 2006, the process was still under discussion. Preuss receives an e-mail from Shannon Cunniff of the Department of Defense's Material of Evolving Regulatory Interest Team (MERIT) that went to Nancy Beck at OIRA as well as many others in agencies across the government.

OSD, NASA and DOE Sr. staff have reviewed ORD's proposed IRIS revisions chart and detailed explanation of some of the boxes and attached are our comments and suggestions. DHS and DOT were not on our last calls due to scheduling conflicts, so I can not assert to what degree they support these comments...

What you have attached is a) the flow chart – we added numbers to all boxes but also retained your numbering of the latter 10 boxes that correspond to your detailed explanation – and b) an expanded detailed explanation of the boxes that includes, as we discussed, an [sic] proposed explanation for every step to help us all achieve clarity and eventually agreement.

These inserts and changes were drafted by a committee of federal staff and recorded by Mitretek (so you might see Mitretek identified as a “commentor”(sic). All of our insertions or changes are in color and underlined.

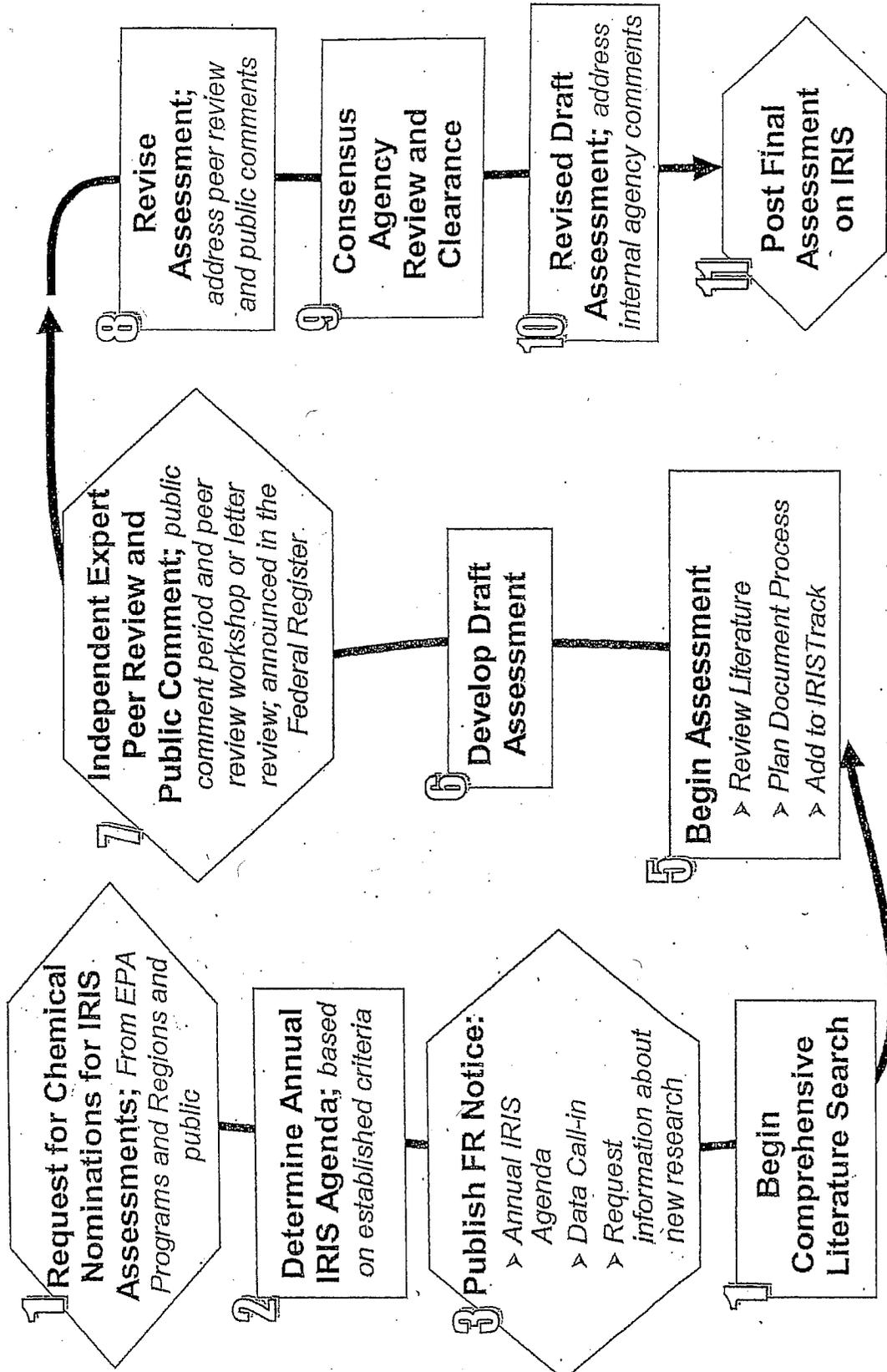
We suggest that after you look this over that we set up another multi-agency meeting to bring all the interested federal agencies together to discuss the process steps and see if together can reach consensus on the process, understand how or if this effort fits with Dr. Gray's visions for IRIS, and develop a plan for next steps.¹⁷

The Subcommittee does not have the attachments referenced in this e-mail. Nor do we have further records relating to the next steps and the final outcome.¹⁸ We do have EPA IRIS staff's own process charts designed to record this evolving process as it moved from 2004 through 2008. The next three graphics are reproductions of IRIS staff efforts at developing a flow chart that would reflect the process, as they understood it, at each moment in time.

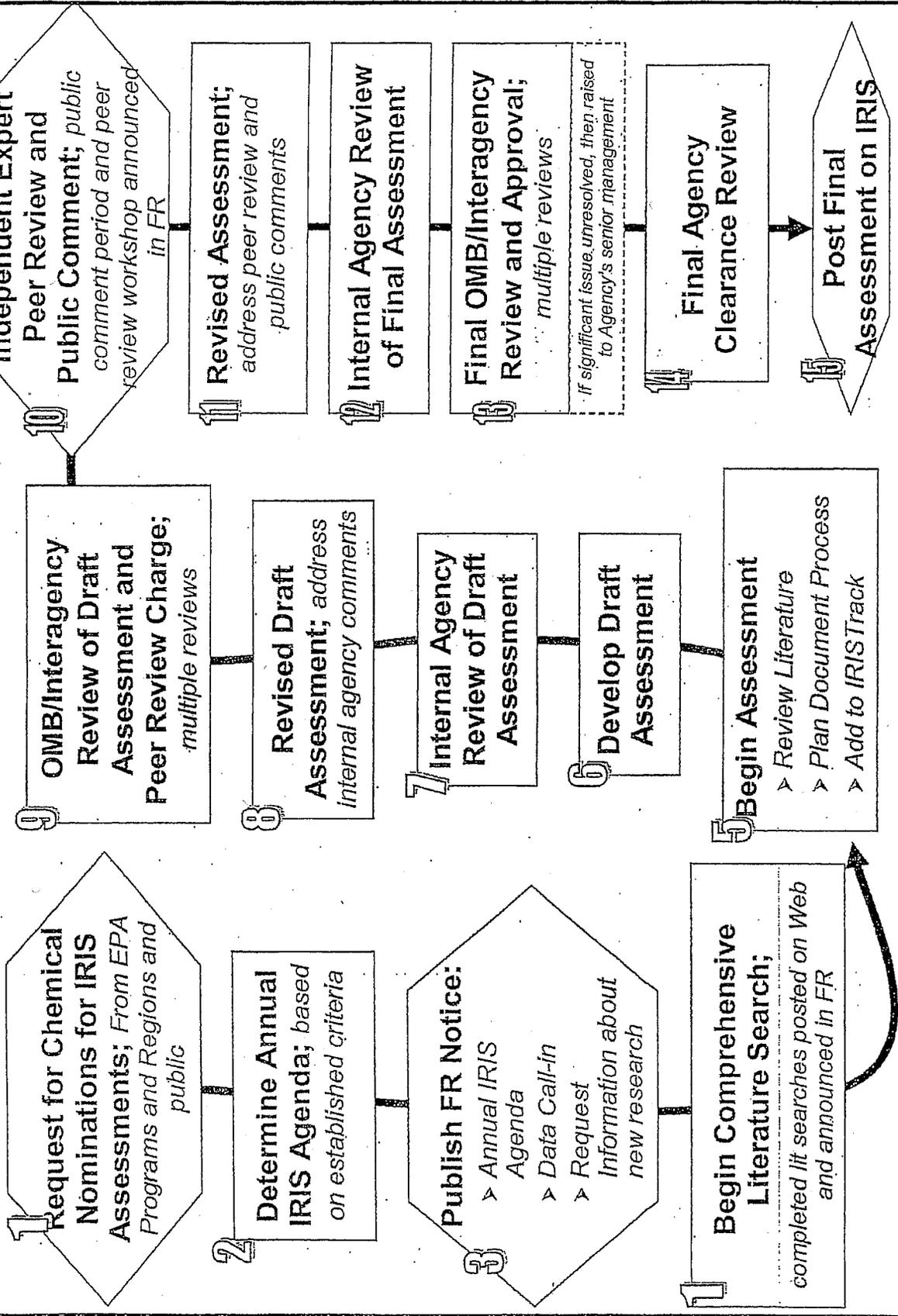
17. E-mail from Shannon Cunniff, Department of Defense, to Preuss, Beck and others, 02/02/2006, titled, “DoD, NASA, DoE comments on IRIS revisions.” Appears as attachment “g” in the report.

18. Note that GAO's report of March 2008, “Chemical Assessments: Low Productivity and New Interagency Review Process Limit the Usefulness and Credibility of EPA's Integrated Risk Information System,” shows a draft process which was under discussion in early 2008. See pages 46 and 47 of GAO-08-440.

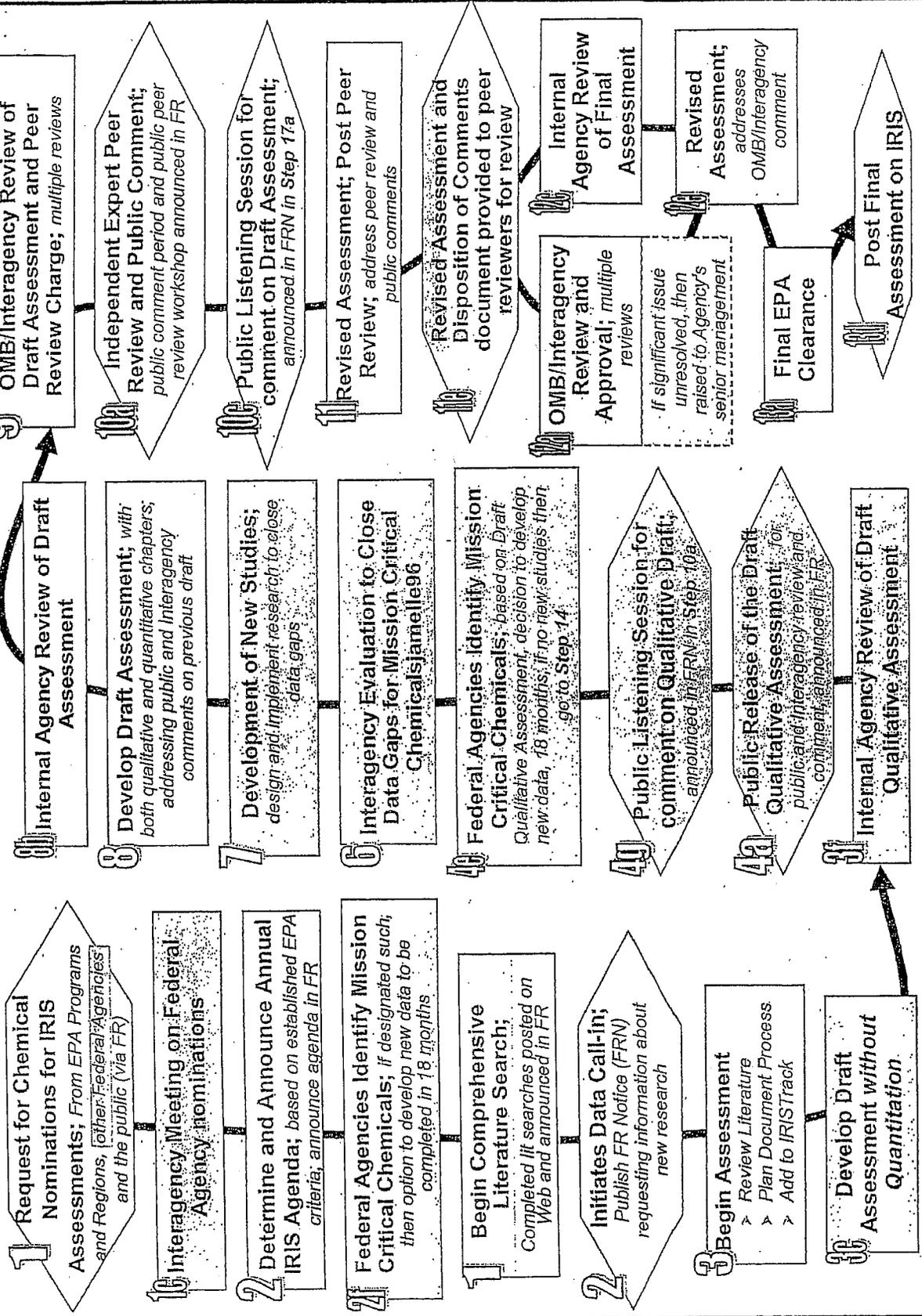
IRIS PROCESS: Pre-2004



IRIS PROCESS: 2004 to April 2008



DRAFT Revised IRIS PROCESS: Post April 10, 2008



The timeline reflected in these charts, and in the e-mails reviewed by the Subcommittee, suggests that it took three full years from the time OIRA's Graham triggered a formal effort to restructure the IRIS process until a new process had cleared all the internal hurdles. Remember that it was in February of 2006 that DOD's lead representative to interagency discussions was suggesting they should have another "multi-agency" meeting to hammer out an agreement. That agreement was not finalized until April of 2008.

Because the process continued to evolve, both before the process review began and during the formal review, IRIS staff was constantly trying to figure out what steps they needed to take to keep on track with IRIS proposals. These charts clearly reflect a process that became ever more complex and burdensome. But while the process was evolving, there was another level of chaos thrown into the IRIS mix. Uncertainties among EPA staff about how to proceed, absent a final approved process, show up in some documents in the Subcommittee's possession.

For example, in an e-mail from February 2, 2006, Vandenberg shares with IRIS staff comments that came from OIRA's Beck on dibutyl phthalates and writes,

Our approach to these interagency comments (for perc and dichlorobenzenes) has been to carefully evaluate the comments and to develop a response to comments document. I recommend you create a document that addresses each comment (include their "comment" and our "responses" as one file) and provide a point-by-point evaluation. I encourage that the tone of our "responses" be thoughtful and that we make such changes as we deem warranted. If there are some larger science-policy issues or points made where it is unclear how to respond, then flag these for discussion.

Please give me a sense of the time it may take you to respond to these comments (I'd expect a few weeks).

Vandenberg closes his note to staff with,

Thank you for all your hard work on this document, it seems we'll soon be able to move ahead!¹⁹

However, the IRIS Track currently shows the status of the dibutyl phthalate assessment start date as January 9, 2002 (four years prior to the Vandenberg e-mail quoted above) and now projects that just the draft development will be completed by the 4th quarter of 2010. Perhaps in the world of IRIS, taking eight years to move to complete the first milestone—of five—is considered as being "soon."²⁰

Later in February 2006, Amy Mills, IRIS program director, writes to Vandenberg:

19 . "Interagency/OMB comments on Draft IRIS assessment of Dibutyl Phthalate." Attachment "B."

20 . The Track IRIS database was reviewed by Subcommittee staff on Friday, June 5.

John – Are we expected to send a *revised assessment* along with the response to interagency comments to OMB? [Assuming that at least some of the comments result in some level of change to the assessment] As I recall we've done so before, but is there a pattern established? [*emphasis in original*]

Vandenberg replies,

For perc the comments didn't result in a revised assessment (changes to charge questions)... for phosgene we did send a revised assessment over. [*see attachment X*] I recommend going ahead and making revisions so we can have it ready for external peer review, and probably will send over. My view is that the disposition of comments/changes are up to us, but of course all this is evolving still.²¹

At the Subcommittee's IRIS hearing on May 21, 2008, Gray and Dudley both addressed the April 10, 2008 process. While Gray's testimony described the new process as being "announced by EPA," Dudley used language suggesting that EPA had done the revision.²²

In response to concerns both with delays in implementing IRIS assessments and lack of transparency in the IRIS process, EPA has recently revised the process to clarify the role of the public and interagency reviewers and promote greater communication and sharing of information between all interested parties and EPA.

Based on this testimony, a reasonable person would assume that the new EPA IRIS process was solely the product of EPA's work, but as a result of the documents cited above (and attached to this report), Subcommittee staff can confirm that the then-new process, and its evolution, were driven by changing demands from OIRA. Further, it is apparent that other agencies—notably agencies that have environmental pollution issues—played a substantial role in shaping that process. Again, neither Dudley nor Gray was candid with the public or the Congress in the way they portrayed this process.

CONCLUSION

The Subcommittee held two days of hearings on the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) in the last Congress. Chairman Miller was critical of the failure of IRIS to produce timely new listings of risk assessments for chemicals. The Chairman also noted that the process had devolved to the point that only two new entries were being finalized a year while approximately 700 new chemicals were entering the marketplace each year.

A key concern regarding the new IRIS process (see chart below) announced on May 20,

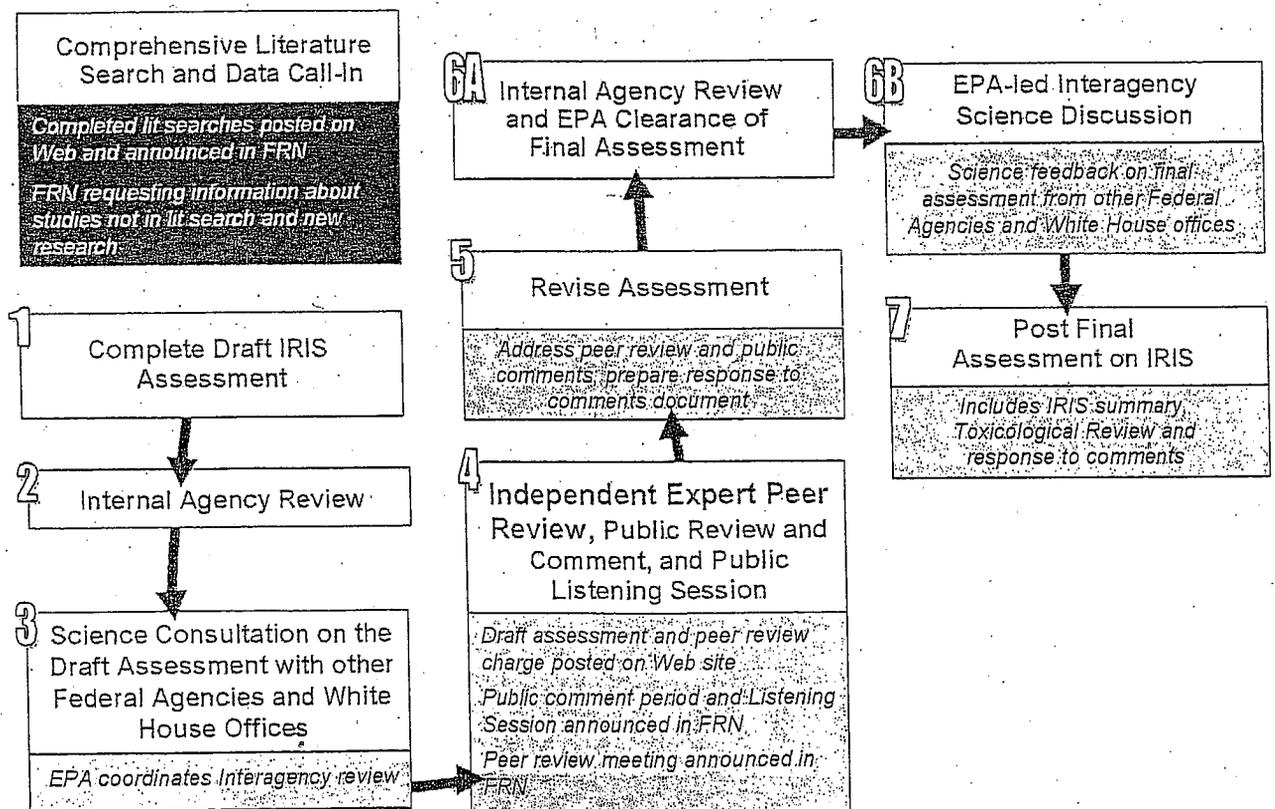
21. "Re: Interagency Comments here: Fw: Draft IRIS assessments for 4 PBDE," attachment "A".

22. "EPA's Restructured IRIS System," p. 53 for Gray and p. 58 for Dudley.

2009 is whether it will substantively empower EPA to push their entries forward. Because all interagency comments are to be solely about science, this new process could be interpreted as formally endorsing OIRA's past practice of having professional scientists on staff to discuss toxicology issues, scientist-to-scientist. Then the entire fiction of OIRA's role as merely a coordinator of an interagency process can fall away. So long as OIRA and OMB stand astride the top of the Administration as representatives for the White House in discussions with EPA or others, it is hard to see how transparency alone will limit OIRA's influence over EPA. The timelines that EPA announced with the new process may be helpful, but since there is no penalty for missing a goal, it may still come down to who has the most influence and EPA has rarely won that struggle in recent memory²³.

Given that so many of the same players who broke IRIS during the Bush years still stand in the agencies and in the White House complex, and that institutional powers and interests have not changed despite the November 2008 election results, it will take some time to determine whether EPA scientists really are calling the shots.

Assessment Development Process for New IRIS



23 . The timelines associated with the new process can be found at attachment "H" in the report.

Attachment A



John
Vandenberg/DC/USEPA/US
02/27/2006 10:02 AM

To Amy Mills/DC/USEPA/US@EPA
cc hammerstrom.karen@epa.gov, Mary
Manibusan/DC/USEPA/US@EPA
bcc
Subject Re: Interagency Comments here: Fw: Draft IRIS
assessments for 4 PBDE

For perc the comments didn't result in a revised assessment (changes to charge questions). EtO pending; for phosgene we did send a revised assessment over. I recommend going ahead and making revisions so we can have it ready for external peer review, and probably will send over. My view is that the disposition of comments/changes are up to us, but of course all this is evolving still.

John Vandenberg
Associate Director for Health
National Center for Environmental Assessment B243-01
Office of Research and Development, USEPA
Research Triangle Park, NC 27711

DC Research Triangle Park, NC
Tel: 202 564 3407 919 541 4527
Fax: 202 565 0090 919 541 5078
Amy Mills/DC/USEPA/US



Amy Mills/DC/USEPA/US
02/22/2006 10:17 AM

To John Vandenberg/DC/USEPA/US@EPA
cc Mary Manibusan/DC/USEPA/US@EPA,
hammerstrom.karen@epa.gov
Subject Re: Interagency Comments here: Fw: Draft IRIS
assessments for 4 PBDE

John - Are we expected to send a *revised assessment* along with the response to interagency comments to OMB? [Assuming that at least some of the comments result in some level of change to the assessment.] As I recall we've done so before, but is there a pattern established?

Amy Mills
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PBDES



John Vandenberg/DC/USEPA/US
02/22/2006 08:22 AM

To Mary Manibusan/DC/USEPA/US@EPA
Amy Mills/DC/USEPA/US@EPA, Karen
cc Hammerstrom/DC/USEPA/US@EPA,
preuss.peter@epa.gov, Amanda
bcc

Subject Interagency Comments here: Fw: Draft IRIS assessments
for 4 PBDE

History This message has been replied to

Mary,
Attached below are the interagency comments for PBDE, please share these with the document
co-authors.

The comments include general and detailed comments from OMB, a review by NIEHS that essentially
used the charge questions as their charge with many references cited, and a short comment by CDC.

Our approach for dealing with comments has been to create a "Comment/Response" document which
addresses each comment in turn. For many of the comments simple concurrence with the editorial
suggestions may be noted. For others, a more detailed response is likely to be necessary, particularly if
there is disagreement with the comment or if additional explanation is requested. Some comments also
raise general issues regarding EPA risk assessment approaches, these can be flagged and discussed.

Please work with the PBDE authors to evaluate the comments and gauge the effort and time necessary to
address the comments.

Thank you.
John

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--- Forwarded by John Vandenberg/DC/USEPA/US on 02/22/2006 08:07 AM ---



"Beck, Nancy"
<Nancy_Beck@omb.eop.gov
>
02/15/2006 06:05 PM

To John Vandenberg/DC/USEPA/US@EPA
cc Peter Preuss/DC/USEPA/US@EPA
Subject RE: Draft IRIS assessments for 4 PBDE

- CDC, NIEHS, ATSDR - OK with substance.

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OMB Comments on PBDE's

General Comments applicable to all 4 draft documents:

- Has WHO or the EU completed any reviews? How are their findings similar or different to EPAs?
- In all 4 drafts, a section on mechanism of action is missing. Its not clear why. Additionally, studies that look at receptor binding are in the effects section—these studies belong in a section on mechanism of action. Binding to a receptor is not an adverse effect or a typical toxicological endpoint. Its not clear why EPA has treated it as such in these drafts.
- In distribution sections:
 - Its not clear why the summary is put first? This makes reading a bit confusing, suggest moving to the end of the distribution section to be consistent with format of other sections.
 - Please clarify: “Accordingly, the data are representative of exposure to a greater extent than distribution toxicokinetics and must be regarded in that fashion.”
 - Throughout these sections for each study the sample size should be presented. Its very hard to know how representative the data are when these values are not transparently presented. In cases where EPA does not know the sample number, this should be stated. When samples are pooled, the number of samples that went into each pooled sample should be stated.
 - The tables in these sections should also provide sample number for each study and should also state the year the samples were collected as this seems very relevant and date of publication is not indicative of sample age.
 - For human data it would be useful to have a few sentences discussing how representative these data are/ are not.
- In metabolism sections:
 - These sections seem to include information on induction of metabolic enzymes (p450's, UDPGT) by BDE's, but induction of metabolic enzymes doesn't tell anything specific about how the compounds themselves are metabolized. Suggest moving this text to a section on mechanism of action in each document. It is not informative information when trying to determine how the BDE's are metabolized.
- In hazard ID sections:
 - Its not clear why studies looking at enzyme activity (PROD, EROD, etc) are discussed here. These studies should be discussed in a section on mechanism of action.
 - Its not clear why receptor interactions and receptor binding is discussed under “other studies” in this section. These studies should be discussed under mechanism of action sections in the document. Each document should have a section on mechanism/mode of action.
 - For the Viberg studies and Eriksson 2001 study it is never explained anywhere in the document what it means that there is hypoactivity and then later hyperactivity? Also

INTERAGENCY DRAFT DELIBERATIVE

developmentally how does the time change between a 2 month old and 4 month old mouse relate to age changes in humans? What is the relevance of these spontaneous motor behavior changes in humans? How important is habituation in humans?

- Section on synthesis and evaluation of effects:
 - Discussion of enzyme induction should not be included here.
 - Discussion of human exposures does not seem to belong here
- Section on possible childhood susceptibility:
 - Its not clear why discussion of levels of BDEs in humans is included here. This information relates to exposure, not susceptibility. Exposure does not mean that there is differential susceptibility.
- Section on methods of analysis:
 - Documents should explain why BMD with 1 SD is being chosen, rather than another endpoint. Why didn't EPA also present BMD10 values? Text should mention that this gives an excess risk of 10% for the proportion of individuals above the 98th percentile for normally distributed effects.
 - In some documents a BMD of 0.5SD is presented in the appendix. How did EPA choose 1SD over 0.5SD?
- Justification for creating RfDs when uncertainty is so great is not clear.

General Comments on the charge:

- Has EPA given thought to the number and type of expertise on the review panel?
- The questions should not only ask if rationale and justification is transparent and objective, but should also ask experts if they agree with the EPA determinations.

Tetra (BDE-47):

- Page 11- for the Darnerud and Risberg study it would be useful to give the levels of radioactivity (or %'s) to help understand uptake. Its not clear what is meant by 'high' and 'intermediate'. What was the % labeling in the brain?
- Page 16- 3rd full paragraph- suggest deleting 1st sentence. Edit 2nd sentence to say "to assess whether PBDE's may be detrimental to neurodevelopment, Mazdai....."
- Page 18- suggest deleting (or provide citation for) the following: "Induction of these enzymes would suggest metabolic transformation of BDE-47, and this could affect the levels of T4, as the produced metabolites may have effects on T4 homeostasis by replacing T4 at TTR binding sites."
- Page 18- what is the citation for the following sentence: "It is hypothesized that the lack of response on serum TSH levels to the reduction in T4 levels is due to BDE-47 and/or its metabolites mimicking thyroid hormones and possibly binding to thyroid hormone receptors in the pituitary, thereby blocking TSH release."

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- Page 18- Was the Eriksson study male mice only? If so this should be clearly stated. Were the “more pronounced aberrations” in behavior statistically significant (ie 2 month vs 4 month)?
 - Page 20- suggest deleting: “Based on the data from the well-studied PCBs, CDDs and CDFs, the activation of these receptor sites is associated with immunotoxicity, reproductive effects and carcinogenesis, all endpoints of interest for PBDEs (Klaassen, 2001).” This sentence is unclear. Is there a page citation for Klaassen where this is stated?
 - Page 22- please provide page citation for Klaassen, 2001 under section 4.4.1.2
 - Page 24: edits in bold: “In summary, the mechanistic studies of the ER and Ah receptor indicate that the activity of the tetraBDEs are **much** lower than the activities of dioxin and PCBs. TetraBDE-77 appears to be the most active with the Ah receptor and most PBDEs appear to be **weak** antagonists for the Ah receptor rather than agonists[**what is citation for this?**]. Receptor-site mediated activity via the ER site appears to be minimal for the tetraBDEs.”
 - Page 25- Add that although the impact on CAR receptor is similar to non-coplanar PCBs, the implications of CAR activation is not well known.
 - Page 26- since when is cell culture an endpoint in hazard ID? Suggest moving this text to sections on distribution and absorption as appropriate.
 - Page 27: “Additional research is necessary to determine the ~~full~~-mutagenic potential of BDE-47.”
 - Page 27: Alterations of behavioral parameters, namely impaired motor functions and decreased habituation capability worsening with age, have been shown to occur in adult male mice neonatally exposed to BDE-47 (Eriksson et al., 2001). ~~These behavioral disturbances raise concerns about possible developmental neurotoxicity in children.~~
- ~~———— BDE 47 has been found in human milk, maternal and cord blood, and adipose tissues. Concentrations found are high in all human biological samples in the USA, relative to other countries. Fetuses and infants are exposed to BDE 47. Whether such exposure constitute a health risk for adverse neurodevelopmental effects in these population groups is not known at this time. An association between prenatal or neonatal exposures to BDE 47 and neurobehavioral dysfunction in humans has not been established. This sentence is not about effects.~~
- Page 27- “Exposure of mice ~~and rats~~ to BDE-47 resulted in reduction of serum total and free thyroid hormone levels, **however no changes in TSH were seen** (Hallgren et al., 2001; Hallgren and Darnerud, 2002).” —the hallgren study was mice only and its not clear that any of the Hallgren and Darnerud effects were statistically significant, text does not say, thus I assume changes were not.
 - Page 28- Additional *in vitro* or *in vivo* studies are not available to determine the ~~full~~ genotoxic potential of BDE-47.”

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- Page 29-under choice of study, its not clear why effects on MFO's are discussed here.
- Page 30-
 - 1st full paragraph: please provide a citation for the discussion of critical windows.
 - Its not clear that MeHg is a great example as there is very little data on specific windows during development that may lead to effects in humans- the large epi studies included exposures that occurred throughout development and into childhood. Suggest deleting this as an example. For lead, do we know of specific developmental windows where there is an effect?
 - Please clarify the discussion of hormone change effects. How do the changes seen relate to the findings in the Eriksson study? Can EPA say anything more specific? How do we know the results are "relevant to exposure in people"? what is this based on? Hormone stores and half lives in rodents are quite different than levels in humans. How do we know that these exposure levels are relevant? What is meant by: "Taken together, the results elevate concern for environmental exposure to BDE-47 and support the use of this study as a principal study for deriving the RfD for BDE-47." How does the data elevate concern and why do they support using Eriksson as the principal study?
- Page 30/31- The description of the concerns with the Eriksson study is very good. It seems that other than the fact that the neurotox guidelines list functional neurotoxicity as an effect, and that there are PDBEs in human tissues, there is there is no support for relying on this study. The database is incredibly limited. There is one study—in one sex in one species with essentially no supporting similar studies and no information on mechanism of action. Only 2 doses were tested and the dose levels were an order of magnitude apart. This seems to be more of a range finding study than anything else. The UF EPA wants to apply is 3000 (with uncertainty in 4 different areas) and the certainty would be low. When uncertainty is so high, what is the value added of this RfD value? Is the science strong enough to support the use of this value for clean-ups conducted by program offices?
- Page 32-Choice of the database UF should not depend on whether or not cancer studies exist. Suggest deleting this reference.
- Page 32- ~~Neurobehavioral developmental toxicity~~ **Changes in spontaneous motor behavior** has been identified as the critical endpoint of concern in adult **male** mice following neonatal oral exposure to BDE-47 (Eriksson et al., 2001). ~~Since fetuses and infants are exposed to BDE 47 via maternal/cord blood and human milk, such exposure may constitute a health risk for adverse neurodevelopmental effects in these population groups.~~ Not clear why exposure is discussed here, specifically when doses are not put in a context of human body burden and actual exposure levels. Also the certainty in the RfD is so low its not clear that a risk to humans is real based on the data EPA has presented.

Penta (BDE-99):

- Page 4- in the Eriksson 2002 study were there any controls? Is it known if levels in the brain were DBE99 vs some metabolite that ended up with the radiolabel?

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- Page 5:
 - This may imply that different activities may expose different age groups more than others, or that some PBDE congeners may accumulate differently with age, **however the sample size here is very small and firm conclusions cannot be made.**
 - is Johnson-restrepo published yet?
- Page 7-
 - Please state if the strong positive relationship seen in Ohta is statistically significant.
 - Please add a citation for: "In another study in Japan, PBDEs were not detected in 8 pooled human milk samples collected in 1973."
- Page 8- "This may be explained by the fact that PBDEs are relatively new contaminants in the environment, the time period for human exposure is therefore relatively short, and different age groups (except the 0-4 years group), may thus have experienced a similar lifetime exposure (Thomsen et al., 2002)." Do you mean to say **dissimilar** lifetime exposure? also change "flame retarded" to "flame retardant".
- Page 10- Please state the dose in the Hakk 2002a study.
- Page 11- in the 2nd full paragraph, please provide the percent of uptake into each tissue. Also has Darnerud and Risberg been published yet?
- Page 13-
 - 1st full and 4th paragraph- please clarify that the Hakk conclusions are relevant to rats.
 - in the Darnerude et al 2005 study, was this with and without BDE-99? Its not clear how this relates to BDE-99.
- Page 14-1st full paragraph, is this an EPA conclusion or should there be a citation?
- Page 15-
 - 1st full paragraph under half-life: 6 days is relatively high compared to what?
 - 2nd full paragraph under half-life: why is this discussing hexa and tetra BDE? Can we say anything about sex differences with increasing degree of bromination? What were the penta half lives anyways?
- Page 16-2nd full paragraph- suggest deleting 1st sentence. Edit 2nd sentence to say "To assess whether PBDE's may be detrimental to neurodevelopment, Mazdai....."
- Page 17- please explain why comparisons to Bromkal and Aroclor are reported. In the 4th paragraph was there any BDE-99 exposure?
- Page 18-Please state whether the elevations seen in Hakk 2002a were statistically significant.

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- Page 18- its not clear how studies are ordered in section 4.3.1. Chronological might make reading easier- or by author so readers can see how things develop (eg in 2002 Viberg tested 1 dose but in 2004 did essentially the same study with multiple doses).
- Page 19-The no-observed-adverse-effect level (NOAEL) for ~~developmental neurotoxic~~ **spontaneous motor behavior** effects in this study was 0.4 mg/kg.
- Page 21-In conclusion, the behavioral disturbances observed in adult mice following neonatal exposure to BDE-99 are induced during a defined critical period of neonatal brain development, and mice at PND 10 are **more** susceptible to the neurotoxic effects of BDE-99 **than at PND 3, 10 or 19 where minimal or no effects were seen.**
- Page 21- The purpose of the PDBE exposure in the Ankarberg study is not clear.
- Page 23- A two-day delayed appearance of screen climbing response was seen in the high-dose group (30 mg/kg/day); Please state if this was statistically significant.
- Page 26-The NOAEL/LOAEL values in this study indicate that rats are equally or perhaps less sensitive than mice to the **spontaneous motor behavior** ~~developmental neurotoxic~~ effects of BDE-99.
- Page 28-
 - “In summary, treatment of rats with BDE-99 on GD 6 resulted in a dose-dependent decrease in daily sperm production, spermatid count, and relative epididymis weight in rat offsprings at 0.06 and 0.3 mg/kg.” Do you mean PND 140?
 - “The LOAEL in this study was 0.06 mg/kg based on increases in certain locomotor activity parameters on PND 36 and PND 71”. Its not clear from the text that there were effects at this dose at PND 36.
- Page 40- the discussion of gender differences should note that many studies were conducted in males only.
- Page 40- this study mentions many supporting studies to support use of Viberg 2004a- however don't most of these studies have the same study design problems? Shouldn't this be stated? Are there other better designed studies that support using Viberg and neurobehavioral effects, particularly since so little is known about mode of action? How do we know that these exposure levels are relevant? What is meant by: “Taken together, the results elevate concern for environmental exposure to BDE-99 and support the use of this study as a principal study for deriving the RfD for BDE-99.” How does the data elevate concern and why do they support using Eriksson as the principal study?
- Page 43-
 - 1st full paragraph: please provide a citation for the discussion of critical windows.
 - Its not clear that MeHg is a great example as there is very little data on specific windows during development that may lead to effects in humans- the large epi studies

INTERAGENCY DRAFT DELIBERATIVE

included exposures that occurred throughout development and into childhood. Suggest deleting this as an example. For lead, do we know of specific developmental windows where there is an effect?

- Page 44- it would be useful to present a table with all the BMD values from the different studies
- Page 45-Does it make sense to set an RfD with an UF of 3000 with low confidence? Is there anything EPA is confident of? Are there any data on mechanism of action that may help? This is an order of magnitude lower than the previous RfD, yet the certainty in the data does not appear to have increased.
- Page 47- Not clear why exposure is discussed here, specifically when doses are not put in a context of human body burden and actual exposure levels.

Hexa (BDE-153):

- Page 4: “Of the hexaBDE congeners, BDE-153 is ~~therefore~~ present at higher levels than BDE-154 in both the penta- and octaPBDE commercial products.”
- Page 5-“ This property of hexaBDE is ~~quite~~ evident from the data on distribution in humans. The human data come from monitoring of PBDEs in human populations rather than from measured dosing studies.”
- Page 5- what were the levels of hexaBDE in adipose?
- Page 6- unclear why the following is included in this section: “Concentrations of PBDEs were, on average, similar to those for PCBs. PBDE concentrations did not increase with increasing age of the subjects, whereas concentrations of PCBs increased with increasing age in males but not in females. These results suggest differences between PBDEs and PCBs in their sources or time course of exposure and disposition.”
- Page 7-
 - in liver section, suggest deleting text regarding BDE 47 and 99, is not relevant.
 - the human milk section talks of PDBE levels being higher than those in Japan or Europe. How do the Hexa BDE levels compare?
 - Focus throughout the distribution and elimination sections should be on hexa and not total or other BDEs
- Page 11-1st paragraph under 4.1: suggest deleting 1st sentence. Edit 2nd sentence to say “To assess whether PBDE’s may be detrimental to neurodevelopment, Mazdai.....”
- Page 14- “The NOAEL for BDE-153 (92.5% pure) in this study (Viberg et al., 2003) was 0.45 mg/kg, and the LOAEL 0.9 mg/kg for changes in spontaneous motor behavior, worsening with increasing age, and for effects on learning and memory ability.” What is meant by learning and memory ability? Is this relearning?

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- Page 14- suggest deleting: “Based on the data from the well-studied PCBs, CDDs and CDFs, the activation of these receptor sites is associated with immunotoxicity, reproductive effects and carcinogenesis, all endpoints of interest for PBDEs (Klaassen, 2001).” This sentence is unclear. Is there a page citation for Klaassen where this is stated? Please also provide a citation for: “Xenobiotic compounds with the strongest Ah receptor binding affinity tend to be those with the greatest toxic potency.”
- Page 16- please provide a page citation for: “Receptor induced mitogenic activity has been linked to tumor formation in the affected organs (Klaassen, 2001).”
- Page 17: “In summary, the mechanistic studies of the Ah receptor and the estrogen receptor indicate that the activity of BDE-153 and BDE-154 are significantly lower than the activities of dioxin and PCBs.” Isn't there essentially no ER activity? Why not just say this?
- Page 18- Please state what binding to the CAR receptor mean as far as effect goes.
- Page 18: “The **meaning importance** of this observation for humans has yet to be resolved.”
- Page 18: “Alterations of behavioral parameters, namely impaired spontaneous motor behavior worsening with age, and effects on learning and memory capability have been shown to occur in adult male mice neonatally exposed to BDE-153 (Viberg et al., 2003). These behavioral disturbances raise concerns about possible developmental toxicity in children.” Considering the problems with study design, is this truly a concern? How do these disturbances relate to what we may see in humans? Are the disturbances actually adverse?
- Page 20- The description of the concerns with the Viberg study is very good. It seems that other than the fact that the neurotox guidelines list functional neurotoxicity as an effect, and that there are PDBEs in human tissues, there is there is no support for relying on this study. The database is incredibly limited. There is one study—in one species (its not clear if it is males only-text seems to go back and forth with this) with essentially no supporting similar studies and no information on mechanism of action. The UF EPA wants to apply is 3000 (with uncertainty in 4 different areas) and the certainty would be low. When uncertainty is so high, what is the value added of this RfD value? Is the science strong enough to support the use of this value for clean-ups conducted by program offices?
- Page 20-
 - 1st full paragraph: please provide a citation for the discussion of critical windows.
 - Its not clear that MeHg is a great example as there is very little data on specific windows during development that may lead to effects in humans- the large epi studies included exposures that occurred throughout development and into childhood. Suggest deleting this as an example. For lead, do we know of specific developmental windows where there is an effect?
- Page 21- Does it make sense to set an RfD with an UF of 3000 with low confidence? Is there anything EPA is confident of? Are there any data on mechanism of action that may help?

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Deca (BDE-209):

- Page 4- in the Swedish studies how is EPA sure that internal dose is due to inhalation and not dermal absorption?
- Page 7- in the distribution section it would be useful to discuss the age-dependent differences in distribution that are mentioned.
- Page 14- says the half live is “short”. What is this relative to? For some chemicals a half life of a week would be considered long.
- Page 14- what species are the studies referred to in the last paragraph in the half life section? Are these data from rodents?
- Page 31-“Together, these studies suggest that decaBDE has very limited potential to activate the AhR signal transduction pathway, which is **considered to be a key** ~~is the critical~~ toxicological mechanisms for many persistent aromatic hydrocarbons.” Please also add a citation for this?
- Page 32-
 - “Results from these studies provide ~~no~~ evidence that parent decaBDE in the presence or absence of exogenous liver metabolic system **does not** react directly or indirectly with DNA to cause either gene mutations, DNA damage, or chromosomal effects.”
 - suggest deleting the 1st paragraph in 4.5. this section should not present hypotheses, particularly when the previous text does not support them. It makes things confusing.
 - much of the discussion in this section is on mechanism and does not belong here.
 - ~~“Given that the critical toxicological mechanism for many persistent aromatic hydrocarbons involves binding to the aryl hydrocarbon receptor (AhR), DNA binding, and gene expression, Several *in vivo* and *in vitro* studies.....”~~
- Page 33
 - “DecaBDE also caused thyroid gland follicular cell hyperplasia in male mice and thyroid tumors in male and female mice [**previous text says thyroid tumors were in male mice only**], effects that are indicative of thyroid toxicity (NTP, 1986). Based on these effects, decaBDE may share the general property of organohalogenated compounds in which *in vivo* exposure in rodents results in reduction of serum total and free thyroid hormone (T₄) levels (Legler and Brouwer, 2003). Its not clear why this is relevant here.
 - the doses in Zhou were up to 100mg/kg. Seems odd to say that lack of effects is due to insufficient target dose—isnt it really just a lack of effect, considering the high dose?
 - seems odd that the Norris, 1973 study is mentioned for the first time here and is not discussed earlier.
- Page 34- suggest deleting sentence beginning with “a number of studies..” as its not clear what studies these are and all the IRIS drafts find no effect. Also the text says no studies

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were found that looked at deca, however the last sentence in this paragraph discusses findings of such a study. This is confusing.

- Page 41-
 - in discussing the choice descriptor it would be useful to provide more information- e.g. the effects are seen at extremely high doses only. Is this a situation where the classification should be dependent on exceeding a certain dose?
 - What does the information on mechanisms and dosing tell us about likelihood of effects at environmental doses? Should this factor into EPA's decision to quantitate?
 - Why does EPA believe the evidence is on the strong end of the spectrum? This is not explained at all. The cancer guidelines call for a narrative discussion. This assessment could do a better job providing this information, in conjunction with the descriptor label.
 - Why is a dose response assessment deemed appropriate here? Considering the high doses tested and the lack of genotoxicity, what is EPA's rationale for doing dose response assessment? This needs to be further bolstered. It seems as though effects in each study were quite limited, particularly considering the doses.

- Page 42- "The increase in the radioactivity in the brain coupled with the behavioral disturbances on exposure to decaBDE on postnatal day 3 appear to suggest that differences may exist in the absorption and metabolism of decaBDE between neonates and slightly older ones and that the effect persisted and also worsened with age." When did the increase in radioactivity occur? It's not clear that significant differences in absorption and metabolism exist.

- Page 44
 - Does it make sense to use the Viberg study for the RfD? There is one study—in one species, in one sex, with essentially no supporting similar studies and no information on mechanism of action. Only 2 doses were tested. The UF EPA wants to apply is 300 and the certainty would be likely low. Is the science strong enough to support the use of this value for clean-ups conducted by program offices?
 - what does the following sentence mean: "In some respects the observation that effects occurred with such limited dosing argues for the importance of this study."?
 - The description of the concerns with the Viberg study is very good. It seems that other than the fact that the neurotox guidelines list functional neurotoxicity as an effect, and that there are PDBEs in human tissues, there is no support for relying on this study.

- Page 45-
 - 1st full paragraph: please provide a citation for the discussion of critical windows.
 - It's not clear that MeHg is a great example as there is very little data on specific windows during development that may lead to effects in humans- the large epi studies included exposures that occurred throughout development and into childhood. Suggest deleting this as an example. For lead, do we know of specific developmental windows where there is an effect?

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- Is 20mg/kg a reasonable dose to expect humans to receive? Is this dose level relevant to today's exposure levels?
- Does it make sense to set an RfD in this situation?? Is there anything EPA is confident of? Are there any data on mechanism of action that may help?

- Page 48

- suggest deleting: "Furthermore, a developmental neurotoxicity study in mice has been conducted (Viberg et al., 2003)." Considering all the problems with the study design, it's hard to believe that EPA believes this study fulfills all the criteria for DNT testing.
- It's not clear to me why an UF for database is not needed here. What is it that makes the Deca database so much stronger than the other BDEs?
- Is this sentence true: "When an RfD is based on systemic NOAEL of 1120 mg/kg/day from the NTP study, a database UF should be applied." Doesn't it depend on the database not the actual study that was used?

- Page 49-discussion of EPA's confidence in the proposed RfD is missing.

- Page 52-

- Just because the data can be modeled, doesn't explain why quantitation is conducted, when the weight of evidence is only suggestive and for each endpoint the strength of evidence is relatively weak. Did EPA choose to model only because it could be done? What is EPA's confidence in the values that come out of the model considering the WOE?
- why did EPA choose to use the linear multistage model? Were any other options discussed or tried? Does the fact that not mutagenicity is seen decrease EPA's confidence in doing this quantitatively?

- Page 53

- what has changed since 1987, when EPA decided not to do a quantitative cancer value?
- how does the NRC cancer slope factor derivation differ from the EPA derivation? Did they use similar methodologies and similar studies? If not, why were EPA's choices different?

- Page 54

- "DecaBDE also has been shown to induce **spontaneous motor behavior changes in one study of male mice neurobehavioral toxicity.**"
- "These data suggested that there is a critical window for the induction of behavioral disturbances, and the neurotoxic effect of neonatal decaBDE exposure was persistent and also worsened with age **in male mice.**"

- Page 55

- more narrative discussion of the cancer classification is needed.

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- "In addition, only **one study** ~~limited tests~~ on motor activity ~~was~~ ~~were~~ conducted. This paragraph certainly undermines EPA's rationale for why a database UF is not needed.
- Page 56- considering that the evidence is suggestive, EPA should discuss how reliable the slope factor value is believed to be. What is the confidence in this number? Does EPA suggest that it be broadly used? Is there a dose level above or below which it should be used?

NIEHS comments:

December 2005

CHARGE TO EXTERNAL REVIEWERS FOR THE IRIS TOXICOLOGICAL REVIEWS OF

2,2',4,4'-Tetrabromodiphenyl Ether (BDE-47) CASRN 5436-43-1

2,2',4,4',5-Pentabromodiphenyl Ether (BDE-99) CASRN 60348-60-9

2,2',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153) CASRN 68631-49-2

2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl Ether (BDE-209) CASRN 1163-19-5

The U.S. EPA is conducting a peer review of the scientific basis supporting the human health assessment of BDE-47, BDE-99, BDE-153 and BDE-209 that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). The draft documents for the external peer review contain a description of the oral database, reference dose, qualitative cancer assessment for BDE-47, BDE-99 and BDE-153, and a quantitative cancer assessment for BDE-209. Please provide detailed responses to the charge questions below.

GENERAL QUESTION

Are you aware of other published peer-reviewed toxicological studies not included in these Toxicological Reviews that could be of relevance to the health assessment of BDE-47, BDE-99, BDE-153 or BDE-209?

1. QUESTIONS RELATED TO THE DERIVATION OF THE REFERENCE DOSE FOR BDE-47, BDE-99, BDE-153 and BDE-209

1.1 Have the rationale and justification for deriving RfDs on the basis of the neurobehavioral toxicity studies been transparently and objectively described in the Toxicological Reviews of BDE-47, BDE-99, BDE-153 and BDE-209? Are there additional studies that should be considered for deriving the RfDs for any of the four PBDE congeners?

The Eriksson, Viberg et al group at the Uppsala University, Sweden have reported on various neurotoxic effects of the PBDE isomers. Generally it is appropriate to use these studies for the RfDs.

1.2 Are the Eriksson et al., 2001 (BDE-47), Viberg et al., 2004 (BDE-99), Viberg et al., 2003a (BDE-153) and the Viberg et al., 2003b (BDE-209) studies appropriate for determining the point of departure?

INTERAGENCY DRAFT DELIBERATIVE

1.3 Have the most appropriate critical effect and point of departure been selected? And has the rationale for the point of departure been transparently and objectively described?

1.4 Have the rationale and justification for each uncertainty factors (UFs) selected in the draft Toxicological Reviews of BDE-47, BDE-99, BDE-153 and BDE-209 been transparently described? If the selected UFs are not appropriate, what alternative UFs would you suggest and what are the scientific rationales for those suggested?

2. BODY BURDEN APPROACH

2.1 Are there adequate data for considering body burden as an alternative dose metric to administered doses in any of the RfD derivations?

The Birnbaum and Burka references on TK of the PBDEs need to be added and analyzed.

Sanders JM, Burka LT, Smith CS, Black W, James R, Cunningham, ML. 2005. Differential expression of *CYP1A*, *2B*, and *3A* genes in the F344 rat following exposure to a polybrominated diphenyl ether mixture or individual components. *Toxicological Sciences*, 88:127-33.

Sanders JM, Chen L-J, Lebetkin EH, Burka LT. 2006. Metabolism and disposition of 2,2',4,4'-tetrabromodiphenyl ether following administration of single or multiple doses to rats and mice. *Xenobiotica* (in press).

2.2 Do you agree with the rationale described in the Toxicological Review of BDE-99 that the data on the window of susceptibility of the cholinergic receptors to BDE-99 tend to minimize body burden concerns?

3. QUESTIONS RELATED TO THE CARCINOGENICITY ASSESSMENT OF BDE-209

3.1 Is the weight of evidence for the carcinogenicity of BDE-209 in the draft Toxicological Review appropriately described? Are there additional studies that should be included?

No – see additional comments below.

3.2 Do the available data support the descriptor *Suggestive evidence of carcinogenic potential* for BDE-209 according to the U.S. EPA. (2005) Guidelines for Carcinogen Risk Assessment? If not, what alternative descriptor would be supported by the existing data and what is the scientific rationale?

OK, but not complete.

3.3 Is the estimation of a cancer slope factor for BDE-209 in the Toxicological Review appropriate? Have the rationale and justification for the use of linear low-dose extrapolation been objectively and transparently presented?

INTERAGENCY DRAFT DELIBERATIVE

3.4 Are there alternative modeling approaches that should have been considered instead of or in addition to the low-dose extrapolation approach?

See comment on added references.

1-09-06 - EPA Review of PBDEs

The major data gap in our knowledge on the toxicity of the polybrominated diphenyl ethers, is the toxic/cancer potential after long term exposures to these chemicals. The NTP's studies of these compounds is focused on filling this datagap, particularly after in utero/postnatal/adult exposures. It will be several years before these studies are completed.

I. EPA Toxicological Review of BDE-209, BDE-47, BDD-99, and BDE-153

a. The carcinogenicity assessment of BDE-209 is primarily based on the 1986 NTP TR study of decabromodiphenyl ether. The NTP TR reference (and also the NTP web site reference) should be added to the reference list for this report. This NTP study is used for the EPA Benchmark dose modeling.

The oral RfD for BDE-209 is 7 ug/kg/day (NTP Study, 1986); Viberg 2003).

The oral RfD for BDE-47 is 0.1 ug/kg/day (Eriksson, 2001; neurobehavioral study in mice).

The oral RfD for BDE-99 is 0.1 ug/kg/day (Viberg, 2004 reference – locomotion and rearing habituation in mice).

The oral RfD for BDE-153 is 0.2 ug/kg/day (Viberg 2003 reference – spontaneous motor behavior, learning, and memory endpoints in mice).

b. Missing from the EPA Toxicologic review of decabromodiphenyl ether (BDE-209) is a complete analysis of BDE-209 to the environment and the resultant chemical exposures.. When decabromodiphenyl ether is released into the environment does the chemical break down to lower brominated diphenyl ethers? If so, the hazard from exposure may be more extensive.

Decabromodiphenyl ether - does this chemical break down to lower brominated diphenyl ethers?

1. Stapleton, H.M., R.J. Letcher, and J.E. Baker, *Debromination of polybrominated diphenyl ether congeners BDE 99 and BDE 183 in the intestinal tract of the common carp (Cyprinus carpio)*. Environmental Science & Technology, 2004. **38**(4): p. 1054-1061.
2. Eriksson, J., et al., *Photochemical decomposition of 15 polybrominated diphenyl ether congeners in methanol/water*. Environmental Science & Technology, 2004. **38**(11): p. 3119-3125.
3. Bezares-Cruz, J., C.T. Jafvert, and I. Hua, *Solar photodecomposition of decabromodiphenyl ether: Products and quantum yield*. Environmental Science & Technology, 2004. **38**(15): p. 4149-4156.

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4. Watanabe, I. and S. Sakai, *Environmental release and behavior of brominated flame retardants*. Environment International, 2003. **29**(6): p. 665-682.
5. Gouin, T. and T. Harner, *Modelling the environmental fate of the polybrominated diphenyl ethers*. Environment International, 2003. **29**(6): p. 717-724.
6. Keum and Li. *Reductive debromination of polybrominated diphenyl ethers by zerovalent iron*. Environ Sci Technol, 2005.
7. Hites, *Global assessment of polybrominated diphenyl ethers in farmed and wild salmon*. Environ Sci Technol. 38: 4945-9, 2004

c. Calculations to determine the amount of PBDEs released into the environment, and how this correlates to environmental concentrations should be calculated. An update on the CDC nhanes data for the PBDE monitoring program would be helpful.

d. The EPA reviews of PBDEs omit the ATSDR Reference for the Toxicologic Profiles for these chemical: ATSDR Profile on PBDEs

<http://www.atsdr.cdc.gov/toxprofiles/tp68.html>

d. Other References:

McDonald, T. A. Polybrominated diphenylether levels among United States residents: daily intake and risk of harm to the developing brain and reproductive organs, Integrated Environmental Assessment and Management 1: 343-354, 2005.

D'Silva et al. Brominated organic micropollutants – igniting the flame retardant issu. Critical Reviews in Environmental Science and Technology 34: 141-207, 2004.

Other References:

Kodavanti and Ward, Differential effects of commercial polybrominated diphenyl ether and polychlorinated biphenyl mixtures on intracellular signaling in rat brain in vitro Toxicologic Sciences 85: 952-962, 2005.

Stapleton et al Polybrominated diphenyl ethers in house dust and clothes dryer lint, Envi Science Technology 39: 925-931, 2005.

Brown et al. Analysis of AH receptor pathway activation by brominated flame retardants. Chemosphere 55: 1509-1518, 2004.

Weber and Kuch. Relevance of BFRs and thermal conditions of the formation pathways of brominated and brominated-chlorinated dibenzodioxins and dibenzofurans. Environmental Internation 29: 699-710, 2003.

Gallard et al Rate constants of reactions of bromine with phenols in aqueous solution. Water Research 37: 2883-2892, 2003.

INTERAGENCY DRAFT DELIBERATIVE

Talsness et al Ultrastructural changes observed in rat ovaries following in utero and lactational exposure to low doses of a polybrominated flame retardant. *Tox. Let* 157: 189-205, 2005.

Kuriyama et al. Developmental exposure to low-dose PBDE-99 effects on male fertility and neurobehavior in rat offspring. *Envi Health Persp.* 113:149-154, 2005.

Smeds and Saukko. Brominated flame retardants and phenolic endocrine disrupters in Finnish human adipose tissue. *Chemosphere* 53: 1123-1130, 2003.

Darnerud and Risberg. Tissue localization of tetra- and pentabromodiphenyl ether congeners 9BDE-47,-85-, and -99) in perinatal and adult C57Bl mice. *Chemosphere* 62; 485-93, 2006.

Jones-Otazo et al Is house dust the missing exposure pathway for PBDEs? An analysis of the urban fate and human exposure to PBDEs. *Environ Sci Technol* 39: 5121-30. 2005.

Darnerud et al. Common viral infection affects pentabrominated diphenyl ether distribution and metabolic and hormonal activities in mice *Toxicology* 210: 159-167, 2005.

Staskal et al Toxicokinetics of BDED47 in female mice; effect of dose, route of exposure, and time. *Tox Sci* 83: 215-223, 2005.

Sjodin et al Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States. *Env Health Persp* 112: 654-658, 2004.

Background Information on Chemicals with hormone action

Book I

I. General Background

1. de Wit, C.A., *An overview of brominated flame retardants in the environment.* *Chemosphere*, 2002. **46**: p. 583-624.
2. Birnbaum, L.S. and D.F. Staskal, *Brominated flame retardants: Cause for concern?* *Environmental Health Perspectives*, 2004. **112**(1): p. 9-17.
3. Darnerud, P.O., *Toxic effects of brominated flame retardants in man and in wildlife.* *Environment International*, 2003. **29**(6): p. 841-853.
4. Legler, J. and A. Brouwer, *Are brominated flame retardants endocrine disruptors?* *Environment International*, 2003. **29**(6): p. 879-885.
5. Vos, J.G., et al., *Brominated flame retardants and endocrine disruption.* *Pure and Applied Chemistry*, 2003. **75**(11-12): p. 2039-2046.
6. Alae, M., et al., *An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release.* *Environment International*, 2003. **29**(6): p. 683-689.

II. Polybrominated Diphenyl Ethers

A. PBDE Hormone action

1. Zhou, T., et al., *Effects of short-term in vivo exposure to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weanling rats*. Toxicologic Sciences, 2001. **61**: p. 76-82.
2. Zhou, T., et al., *Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption*. Toxicological Sciences, 2002. **66**: p. 105-116.
3. Stoker, T.E., et al., *Assessment of DE-71, a commercial polybrominated diphenyl ether (PBDE) mixture, in the EDSP male and female pubertal protocols*. Toxicological Sciences, 2004. **78**(1): p. 144-155.
4. Meerts, I.A.T.M., et al., *In vitro estrogenicity of polybrominated diphenyl ethers, hydroxylated PBDEs, and polybrominated bisphenol A compounds*. Environ. Health Perspect., 2001. **109**: p. 399-407.

B. PBDE General Exposure information

1. Sjodin, A., et al., *Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States*. Environmental Health Perspectives, 2004. **112**(6): p. 654-658.
2. Hites, R.A., *Polybrominated diphenyl ethers in the environment and in people: A meta-analysis of concentrations*. Environmental Science & Technology, 2004. **38**(4): p. 945-956.
3. Petreas, M., et al., *High body burdens of 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) in California women*. Environmental Health Perspectives, 2003. **111**(9): p. 1175-1179.
4. Alcock, R.E., et al., *Understanding levels and trends of BDE-47 in the UK and North America: an assessment of principal reservoirs and source inputs*. Environment International, 2003. **29**(6): p. 691-698.
5. Covaci, A., S. Voorspoels, and J. de Boer, *Determination of brominated flame retardants, with emphasis on polybrominated diphenyl ethers (PBDEs) in environmental and human samples - a review*. Environment International, 2003. **29**(6): p. 735-756.
6. Law, R.J., et al., *Levels and trends of polybrominated diphenylethers and other brominated flame retardants in wildlife*. Environment International, 2003. **29**(6): p. 757-770.
7. Hale, R.C., et al., *Polybrominated diphenyl ether flame retardants in the North American environment*. Environment International, 2003. **29**(6): p. 771-779.
8. Sjodin, A., D.G. Patterson, and A. Bergman, *A review on human exposure to brominated flame retardants - particularly polybrominated diphenyl ethers*. Environment International, 2003. **29**(6): p. 829-839.
9. Hooper, K. and J.W. She, *Lessons from the polybrominated diphenyl ethers (PBDEs): Precautionary principle, primary prevention, and the value of community-based body-burden monitoring using breast milk*. Environmental Health Perspectives, 2003. **111**(1): p. 109-114.

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Book II

C. Other PBDE biological effects

1. Helleday, T., et al., *Brominated flame retardants induce intragenic recombination in mammalian cells*. *Mutation Research*, 1999. **439**: p. 137-147.
2. Kemmlin, S., D. Herzke, and R.J. Law, *BFR - governmental testing programme*. *Environment International*, 2003. **29**(6): p. 781-792.
3. Hakk, H. and R.J. Letcher, *Metabolism in the toxicokinetics and fate of brominated flame retardants - a review*. *Environment International*, 2003. **29**(6): p. 801-828.
4. Viberg, H., A. Fredriksson, and P. Eriksson, *Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice*. *Toxicology and Applied Pharmacology*, 2003. **192**(2): p. 95-106.
5. Viberg, H., A. Fredriksson, and P. Eriksson, *Investigations of strain and/or gender differences in developmental neurotoxic effects of polybrominated diphenyl ethers in mice*. *Toxicological Sciences*, 2004. **81**(2): p. 344-353.
6. Chen, G.S. and N.J. Bunce, *Polybrominated diphenyl ethers as Ah receptor agonists and antagonists*. *Toxicological Sciences*, 2003. **76**(2): p. 310-320.
7. Branchi, I., et al., *Polybrominated diphenyl ethers: Neurobehavioral effects following developmental exposure*. *Neurotoxicology*, 2003. **24**(3): p. 449-462.

III. Tetrabromobisphenol A

1. Meerts, I.A.T.M., et al., *Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin in vitro*. *Toxicologic Sciences*, 2000. **56**: p. 95-104.
2. Kitamura, S., et al., *Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A*. *Biochemical and Biophysical Research Communications*, 2002. **293**: p. 554-559.
3. Hakk, H., et al., *Metabolism, excretion and distribution of the flame retardant tetrabromobisphenol-A in conventional and bile-duct cannulated rats*. *Xenobiotica*, 2000. **30**: p. 881-890.
4. Samuelsen, M., et al., *Estrogen-like properties of brominated analogs of bisphenol A in the MCF-7 human breast cancer cell lines*. *Cell Biology and Toxicology*, 2001. **17**: p. 139-151.
5. Brown, D.J., et al., *Analysis of Ah receptor pathway activation by brominated flame retardants*. *Chemosphere*, 2004. **55**: p. 1509-1518.
6. Hayama, T., et al., *Determination of tetrabromobisphenol A in human serum by liquid chromatography-electrospray ionization tandem mass spectrometry*. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences*, 2004. **809**(1): p. 131-136.
7. Szymanska, J.A., J.K. Iotrowski, and B. Frydrych, *Hepatotoxicity of tetrabromobisphenol-A: effects of repeated dosage in rats*. *Toxicology*, 2000. **142**: p. 87-95.

INTERAGENCY DRAFT DELIBERATIVE

8. Inouye, B., et al., *Effects of aromatic bromine compounds on the function of biological membranes*. Toxicol Appl. Pharmacol, 1979. **48**: p. 467-477.

IV. Sodium chlorate

1. Hooth, M.J., et al., *Subchronic sodium chlorate exposure in drinking water results in a concentration-dependent increase in rat thyroid follicular cell hyperplasia*. Toxicol Pathol, 2001. **29**: p. 250-259.

Book III

V. Hexachlorobenzene

1. National Toxicology Program, *Final Report on the 13-Week toxicity study of Hexachlorobenzene*. Battelle Columbus, 2001.

VI. 3,3',4,4'-Tetrachlorazobenzene

1. National Toxicology Program, *Final Report on the 13-Week toxicity study of 3,3',4,4'-tetrachloroazobenzene*. Battelle Columbus, 2001.

VII. Decabromodiphenyl ether - does this chemical break down to lower brominated diphenyl ethers?

1. Stapleton, H.M., R.J. Letcher, and J.E. Baker, *Debromination of polybrominated diphenyl ether congeners BDE 99 and BDE 183 in the intestinal tract of the common carp (Cyprinus carpio)*. Environmental Science & Technology, 2004. **38**(4): p. 1054-1061.
2. Eriksson, J., et al., *Photochemical decomposition of 15 polybrominated diphenyl ether congeners in methanol/water*. Environmental Science & Technology, 2004. **38**(11): p. 3119-3125.
3. Bezares-Cruz, J., C.T. Jafvert, and I. Hua, *Solar photodecomposition of decabromodiphenyl ether: Products and quantum yield*. Environmental Science & Technology, 2004. **38**(15): p. 4149-4156.
4. Watanabe, I. and S. Sakai, *Environmental release and behavior of brominated flame retardants*. Environment International, 2003. **29**(6): p. 665-682.
5. Gouin, T. and T. Harner, *Modelling the environmental fate of the polybrominated diphenyl ethers*. Environment International, 2003. **29**(6): p. 717-724.

CDC comments:

CDC/ATSDR General Comments:

We have very few comments concerning the approach taken for the assessment of the

INTERAGENCY DRAFT DELIBERATIVE

new RfD for BDE-47, BDE-99 and BDE-153. We are happy to see that EPA is now basing the risk assessment to a large extent on the work of Erikson and co-workers as the most sensitive endpoint of PBDE exposure, while at the same time describing in an objective manner the limitations of these studies.

Page 1, line 3 in the BDE-153 document: At this location please change BDE-99 to BDE-153.

Attachment B

DBT



John Vandenberg/DC/USEPA/US
02/07/2006 02:34 PM

To Bob Benson/P2/R8/USEPA/US@EPA, Mary Manibusan/DC/USEPA/US@EPA, Amy Mills/DC/USEPA/US@EPA, Karen preuss.peter@epa.gov, George Alapas/DC/USEPA/US@EPA
cc
bcc
Subject Interagency/OMB comments on Draft IRIS assessment of Dibutyl Phthalate

Please see below for a number of specific comments from CDC and also OMB, it is possible other comments from CPSC will be provided later. In general, I see many technical edits and corrections, with a few bigger issues as well (e.g., the comments on pages 74-85).

Our approach to these interagency comments (for perc and dichlorobenzenes) has been to carefully evaluate the comments and to develop a response to comments document. I recommend you create a document that addresses each comment (include their "comment" and our "responses" as one file) and provide a point-by-point evaluation. I encourage that the tone of our 'responses' be thoughtful and that we make such changes as we deem warranted. If there are some larger science-policy issues or points made where it is unclear how to respond, then flag these for discussion.

Please give me a sense of the time it may take you to respond to these comments (I'd expect a few weeks). Thank you for all your hard work on this document, it seems we'll soon be able to move ahead!

John

John Vandenberg
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National Center for Environmental Assessment B243-01
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--- Forwarded by John Vandenberg/DC/USEPA/US on 02/07/2006 02:21 PM ---



"Beck, Nancy"
<Nancy_Beck@omb.eop.gov>
>
02/07/2006 09:50 AM

To John Vandenberg/DC/USEPA/US@EPA
cc Peter Preuss/DC/USEPA/US@EPA
Subject RE: Draft IRIS assessment of Dibutyl Phthalate

OMB coms

- sim to OMB rags

- precursor events of adversity. Reduced testosterone. Biochem. change.
- moa rel to humans? (Ag. trad'ly assumes relevance). (Hormonal)
- (what level in rodent rel. to humans??)

--> critical link to change.

- concordance

(need epi data?)

(- precursor effects OK via cancer glines.)

- where's data coming from - rodent only?

Hi John,

Attached are agency comments on the draft. Its possible CPSC may have some comments as well, but here are some to get you started.

Please let me know if you would like to talk through EPA responses to comments or if EPA will provide a written response. I'm happy to answer and questions and facilitate any needed dialogue with CDC as well. Otherwise, we will look forward to seeing a revised draft and responses to comments.

Many thanks,
Nancy

-----Original Message-----

From: Vandenberg.John@epamail.epa.gov
[mailto:Vandenberg.John@epamail.epa.gov]
Sent: Friday, December 02, 2005 12:34 PM
To: Beck, Nancy
Cc: Boone.Amanda@epamail.epa.gov; Mills.Amy@epamail.epa.gov;
preuss.peter@epamail.epa.gov
Subject: Draft IRIS assessment of Dibutyl Phthalate

Hi Nancy,

Here is the next draft IRIS assessment for you to look at (if you want!). Attached is the draft dibutyl phthalate tox review and draft charge questions.

This has been developed within the agency and has completed intra-agency review by the IRIS reviewers. It has not been shared with other agencies and we are not aware of any particular interest by other agencies. Our plan is to announce the availability of the document in the FR and have the document externally reviewed through a panel review (organized and managed by a contractor, timed to allow public comments to be provided prior to panel meeting).

Let me know if you have any questions about the draft.

Thanks,

John

(See attached file: Charge DiBP ext peer review3.wpd) (See attached file: Tox R DiBP ext peer review2.wpd)

John Vandenberg

Associate Director for Health

National Center for Environmental Assessment B243-01 Office of Research and Development, USEPA Research Triangle Park, NC 27711

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Dibutyl PhthalateAgencycomments.doc

Interagency Draft Deliberative

February 6, 2006 (there may be more comments coming from CPSC)

CDC Comments

Page 6, 2nd paragraph, 2nd sentence: It needs to be mentioned that there are esterases in some biological matrices, including amniotic fluid, saliva, and breast milk, that could hydrolyze DBP to MBP. Therefore, MBP could be detected in some tissues as a result of contamination with DBP that it is hydrolyzed to MBP by esterases.

Page 7, section 3.2: The Silva et al., 2003 ref (2nd line of 1st paragraph) doesn't have rats data: It should be deleted.

Last sentence of paragraph: It is not that the omega and omega-1 oxidation products of MBP were not detected, but that they were not measured. The sentence should be rewritten: Monobutyl phthalate and monobutyl phthalate glucuronide have been found in human blood and urine, but the products of omega and omega-1 oxidation have not been MEASURED (Silva et al., 2003).

Page 8, Figure 1: The correct name of the structure at the bottom right of the scheme is: 3-carboxypropyl NOT 4-carboxypropyl

Page 9, 1st paragraph: The concentrations reported in the draft from the Silva et al., 2003 paper are MEDIAN, not mean (as stated). Also, indicate the number of human samples analyzed: 283.

Page 16, 2nd paragraph, line 7: As written, it appears that in the Silva et al., 2003 paper the concentration values 14.4 and 4.2 were given. However, this statement is incorrect: The value 14.4 was given in Silva et al., 2003 (Table 2 of the manuscript). The value of 4.2 was not. If this value was calculated by EPA from data provided in Silva et al., 2003, this should be clearly indicated.

Page 16, 2nd paragraph, line 4: The presence of MBP in tissues other than urine could come, at least partially, from the hydrolysis by esterases present in the tissues of the ubiquitous DBP introduced in the sample during sampling or storage. Furthermore, the concentrations of MBP in tissues/fluids other than urine in humans are relatively low when compared to urinary concentrations. For these reasons, urinary data may be more reliable than serum data for MBP: higher MBP concentrations in urine than in serum, and minimal esterase activity in urine compared to serum. Urine, however, unlike blood/serum, is a non-regulated fluid, so dilution of urine due to hydration status may complicate calculations.

Page 17, 2nd paragraph: The Calafat et al. (2005) reference (in press at the time the draft was written) has been published. The correct citation is Calafat et al. (2006):
Calafat, A.M., Brock, J.W., Silva, M.J., Gray, L.E., Reidy, J.A., Barr, D.B., Needham, L.L., 2006 Urinary and Amniotic Fluid Levels of Phthalate Monoesters in Rats after the Oral Administration of Di(2-ethylhexyl) Phthalate and Di-n-butyl Phthalate. *Toxicology* 217, 22-30. This citation can also be updated in page 90 (reference list)

Interagency Draft Deliberative

Page 19, 1st line: Colon et al. (2000) didn't measure monobutyl phthalate in serum. They measured the parent compound, dibutyl phthalate (DBP). Therefore, the reference to this study should be deleted.

Page 19, 2nd paragraph: Data from NHANES 2001-2002 are available at www.cdc.gov/exposurereport/, so Table 3-5 could be updated to also include these data.

Page 19, 2nd paragraph: In CDC's publication using the NHANES 1999-2000 data (Silva et al, 2004a), it was shown that women of reproductive age (30-39 years old) DID NOT have higher concentrations of MBP than younger or older women. This is shown in Figure 4 of the Silva et al., 2004a paper. This finding is not mentioned in this draft and it should, especially because the draft does mention the findings from the NHANES III dataset in the 1st paragraph of this page regarding pregnant women.

Page 21: The calculation of the estimated dose conducted by Kohn et al. in 2000, used the phthalates NHANES III dataset, which was NOT representative of the U.S. population. Therefore, in page 21, the 7 microg/Kg-day dose for the general U.S. population was taken from 192 individuals and the 32 microg/kg-day for U.S. women of childbearing age was taken from only 97 women. I think here it would be a good place again to indicate the estimated exposure from the NHANES 1999-2000 and NHANES 2001-2002 data.

Page 24, last line of 1st paragraph: Specify that the NHANES samples are from NHANES 1999-2000.

Page 67, 1st paragraph, 3rd line: Delete Silva et al. 2003. In this manuscript no attempt was made to measure analytes other than MBP.

Page 67, 4th paragraph: Rewrite sentence as follows: Two studies have documented an association between some adult human semen measures with exposure to dibutyl phthalate (Murature et al., 1987) and phthalate monoesters (Duty et al., 2003a).

Page 89, end of 1st paragraph: There is only one study that suggests that "the 95th percentile for the general population is approximately 7 µg/kg-day and for women of childbearing age approximately 32 µg/kg-day." Insert the Kohn et al. 2000 reference at the end of the last sentence of the paragraph: this will indicate to the reader the source of the data. I would also suggest that the dose is calculated for the U.S. general population and for women of childbearing age using the NHANES 1999-2000 data presented in Silva et al. 2004a. The phthalates NHANES 1999-2000 and 2001-2002 were representative of the general U.S. population, the NHANES III dataset was not.

OMB Comments

- Page 1 and throughout- please use original, not 2002 recommended RfD definition.
- Page 5, the Anderson 2001 study is referred to as being 'conducted with an ethically approved protocol'. Please clarify in the text what it is that this means.

Interagency Draft Deliberative

- Page 9, in discussing Silva 2003 and elimination, the text should state what the dose (exposure) was otherwise the urine value is not informative regarding elimination rates.
- Page 14 states: “*Although a completed physiologically based pharmacokinetic model for both the rat and human is not yet available, it might be possible to use other data to provide an estimate of the relative exposure of the rat and human fetus to the toxicologically active metabolite, monobutyl phthalate, during the critical window for development of the male reproductive tract. Information on relative exposure could be used to inform the selection of the interspecies uncertainty factor used to derive a reference value.*” These statements are very broad. What is meant by “other data” and in 1st sentence? In the 2nd sentence how might relative exposure information be used to inform an UF? Its not clear how UF’s take relative exposure into account-do you mean organ specific internal dose?
- Page 15, how significant is the variability of monobutyl phthalate glucuronide, as discussed in Silva 2003?
- Page 17, for monobutyl phthalate, the range of partition coefficients is 1.9-2.8. Is there a citation for this? Its not clear where the numbers come from.
- Page 18, plots from Kremer 2005a are referred to. This citation is only an abstract. Did it really contain plots?
- Page 19, please state that the 289 samples from Blount, although part of NHANES, should not be considered to be representative as it is not a full NHANES dataset.
- Page 19, table 3-5 is confusing. Its not clear what data is being referred to-is it from the Blount study or Silva or DHHS? Also it would be useful to know if the values are for males or females or both.
- Page 20/21, its not clear at all where the values of 7ug/kg for a 95th percentile and 32 ug/kg for US women comes from. Please clarify. This is very confusing. Also, is the 32ug/kg data a mean or a 95th percentile?
- Page 22, please state whether or not the decrease in mean sperm density seen in Murature was statistically significant?
- Page 22, please state the sample size for the comparison group in Duty et al.
- Page 23, in discussing Duty, 2004, it says the dose response was ‘suggestive negative’. Please clarify what this means-was it not statistically significant?
- Page 26, please state whether or not the associations with enzyme levels in Fukuoka and the decreases in Zhou were statistically significant.

Interagency Draft Deliberative

- Page 28, in discussion of Fukuoka please state whether or not changes in testicular fructose and glucose were statistically significant. Also, what may explain the fact that blood concentrations did not change? Is this to be expected?
- Page 35, why are no NOAELs and LOAELs provided for the Gray study?
- Page 43, a NTP 2002 abstract is referred to. Is there no final report to update these data?
- Page 54, refers to a weight of evidence pointing to a dec. in testosterone in leydig cells. Where is this weight of evidence coming from? Its not clear what studies are being referred to here as the 2 most recently cited studies in the text are both abstracts.
- Page 61, its not clear where or how the studies in 4.3.2 clearly show that monbutyl phthalate is responsible for the toxic effect. Please clarify the reasoning behind this.
- Page 66, states that Dibutyl phthalate is metabolized to monobutyl phthalate and n-butanol. How come n-butanol is never mentioned in section 3.2?
- Page 68, please insert the language in bold in the following 2 sentences:
There are extensive studies documenting developmental toxicity of dibutyl and monobutyl phthalate **in rodents**. A number of studies have examined gene expression for the enzymes involved in steroid biosynthesis **in rodents**.
- Page 69, discussion of MOA should be clear that this is for rodents. Also, there seems to be no discussion about the relevance of this in humans. Is it known that the pathways in humans are the same and that levels of hormones and hormone reserves are similar?
- Page 72, please clarify that this is a proposed MOA in rodents. Also in the figure suggest saying that reduced testosterone and dihydrotestosterone can result in... Also reduced Ins3 may result in... unless all these effects are proven-although the language in the text makes it sound as though causality is possible but not known with certainty. Also in the figure its not clear if the MOA is for the testis or leydig cell?
- Page 74, why is the decrease in testosterone levels throughout the document referred to as a NOAEL and LOAEL? Isn't it really an NOEL? this should be changed throughout the document (page 85 etc) Even the Lehmann paper itself talks about a NOEL and a LOEL. Page 75 is clear that this is not an adverse effect but is a precursor for all other effects. Is it clear that all adverse developmental effects stem from the decrease in testosterone? From figure 2 it seems as though Ins3 effects are independent of testosterone.
- Page 74, is there a developmental effect in humans that is predicted by retained areolas or nipples in the male fetus? Has EPA relied on this endpoint before?
- Page 75, in perchlorate there is a precedent for regulating based on an upstream precursor effect in humans. However, here EPA is using a precursor effect in rats. A discussion of how levels of testosterone in humans and rodents may be similar in levels, reserves, metabolism, or

Interagency Draft Deliberative

stores is not provided at all. In order to justify using this endpoint, EPA needs to discuss this thoroughly and there needs to be strong evidence that pathways and regulation in humans and rodents, not just for testosterone but also for dibutyl phthalate metabolism are similar.

- Page 75, its not clear how the effect could be due to a single exposure. Text cites Carruthers and Foster, which was a multiday exposure, Thompson was an abstract only which used a 2 day exposure, and its not clear what in EPA 1991 is being referred to. The Developmental guidelines are getting pretty old and the endpoint of changes in hormone levels is not even referred to in this document—the guidelines do not discuss whether or not exposure to a precursor on a single day could justify an adverse effect.
- Page 76, figure 3 and 4 should be made more clear. It would be helpful to perhaps break these into 2 arrays—one showing responses in the 0-400 range and the other showing higher levels. The resolution at the low exposures is what is important here and it is lacking most. Also please be clear about which effects are not adverse.
- Page 79, regarding the # notation, please see the comments for page 75 regarding the exposure window.
- Page 85, in table 5-4, why is BMDL 1SD shown? Its not clear why this endpoint was chosen.
- Page 85, there is discussion as to why the BMD approach was not used and this seems to depend on limitations of the study (position in litter was not considered, gender effects, etc). How do these limitations affect the confidence in the NOEL? It seems that they likely lead to an increase in variability. Also this section is the first time the biological significance of testosterone changes is mentioned. Shouldn't there be more discussion of the levels required for significance in the MOA section of the chapter?
- Page 86, see comment on page 75 regarding single exposures. Suggest deleting this sentence.
- Page 87, its not clear why there is a discussion in the database UF section that is talking about the lack of cancer bioassays and the mode of action for tumors. Suggest deleting this language.
- Page 87, its not clear that the data support an acute, short term, or subchronic RfD. Discussion is not sufficient to support this (see comment regarding page 75).
- Page 88, besides the old RfD, are there any other safety values in existence (ATSDR or CALEPA or other?). It would be useful to mention these.
- Page 89, please change NOAEL to NOEL; please clarify where 7 and 32ug/kg come from and discuss how representative they are; why is the confidence high when there are no human developmental or reproductive data—how dose data in 7 animals translate to high confidence for the RfD?
- B-1, is it normal to use a nested model? What does this imply about the data?

Interagency Draft Deliberative

- B-5, Were the data used based on the F1 litter 3 or results from all 5 litters analyzed together?

editorial comments:

Page 16- Saliva 2005 should be Silva 2005

Page 17- in discussing the boron assessment, the ref given is to the cancer guidelines, which does not seem correct

Page 19- refers to "thelarche", do you mean "menarche"?

Page 44- refers to a 10,000ppm:0ppm exposure group. Is this a common way to describe this treatment group?

Other comments:

- What expertise will EPA have on the review panel? How many reviewers in each area?
- Has EPA set an RfD before based on a precursor effect in rodents? Based on retained nipples?
- The charge should be modified to reflect that there is no discussion of an RfC or quantitative cancer assessment
- If EPA continues to rely on the NOEL, the charge will have to have some questions asking about relevance of this precursor to humans, MOA in humans, whether or not this is adverse and at what levels, whether or not this prevents all developmental effects, etc.

Attachment C

Comments on the Toxicological Review of Toluene (Feb 2005 draft)

General Comments on RfC

1. Clarity:

We suggest improving the clarity of presentation for both this document and the actual IRIS entry file. Specifically, the document reads like a hybrid of the old focus on "color vision" and the new focus on a suite of "neurological effects."

We suggest a stronger first paragraph that reviews the potential options for the critical endpoint and clearly states that you are using an array or suite of effects, considered together as the critical endpoint. The reasons EPA determined it makes sense to use a suite of endpoints should be more clearly stated here as well.

The detailed comments below provide additional comments designed to help improve the clarity of the document.

2. Description of the Methods Used:

The "Weight of Evidence" method should be clearly explained before presenting the results (although a weight of evidence approach is common for hazard ID, but not for dose-response, thus the need for an explanation). The actual criteria that are used should be described as well. See comments below for page 75.

Some confusion might be due the apparent disconnect between the usual use of "weight of evidence," which describes an approach which weighs all of the evidence, versus it use here to describe a method of classifying available studies based on adequacy. It may be better to describe the choice of the critical endpoint as based on "weight of evidence" approach rather than the choice of the principal study. That is, EPA reviewed all of the studies, and determined that as a whole they present evidence of the potential for neurological effects. However, in determining a point of departure, EPA selected a subset of the highest quality studies to determine an "average" or "typical" level of effect.

3. Transparency with Respect to the Limitations of the Methods:

We suggest adding discussions that clearly lay out the limitations/caveats/concerns and utility associated use of **both** 1) a suite of neurological endpoints as the critical effect and 2) an average or typical metric as the point of departure. Both of these discussions would provide risk managers with the information that they need to understand what she/he is protecting against when they use this RfC.

With respect to the former, the discussion could be added to the paragraph that initially introduces the use of a **suite of endpoints**. The added discussion should highlight (based in part on peer reviewers comments) that some of these neurological endpoints may not actually be "adverse" and others may exhibit fairly high baseline population variability.

With respect to the latter, use of an average **point of departure** from a group of studies that are not strong enough in and of themselves begs the question as to meaning of the relationship being described. The reader needs some guidance as to what it means to

be "above" or "below" this number since it is not a simple NOAEL or BMD. Perhaps it would be helpful to explain it as a range: "we expect the NOAEL for this suite of neurological effects to be between x and y ppbs." Then go on to explain that you are using the average as a surrogate because of the instability of each of the individual numbers (given both EPA's and the peer reviewer concerns about utility of the individual studies). Perhaps you can show how sensitive the average is to the inclusion of certain studies or the similarity of the average with the use of specific principal studies.

Specific edits re: RfC section:

pg 73, 1st paragraph, line 2: documentation of the "developmental effect in newborn children" is not provided in the prior literature review. pls add cites to the "numerous cases" or delete

pg 73, 2nd paragraph, end of second sentence add "for individual neurological effects"

pg 73, 2nd paragraph, fourth sentence: add "at least one of the following neurological effects" between "on" and "color vision, auditory evoked....."

pg 73, 2nd paragraph, last sentence: it is not clear what the connection is between the two parts of the sentence. Should the Campagna et al 2001 study be cited in with the lower exposure studies at the beginning of the paragraph? Also, isn't this the same thought that is in the second sentence of the next paragraph?

pg 73, 3rd paragraph, second line, add "have" between "or" and "inadequate" (or change it to "do not have adequate").

pg 74, paragraph beginning on prior page: rework 1st sentence on page to focus on the key point: "For example, the study that showed effects at the lowest level of exposure (i.e., color vision at 8 ppb) included individuals who had substantial exposure to compounds other than toluene (Compagna et al. 2001).

pg 74, paragraph beginning on prior page: how does this sentence relate to the theme re: confounding? are you implying that effects were not found due to confounding? If this is so, say so and present the specific ways in which these studies were confounded that the positive studies were not. The sentence, as is, however, could just be moved to the end of the prior paragraph (it would provide the balance to the positive studies listed there.)

pg 75, line 2, insert "the potential for" or "the relationship between" after the phrase "evidence indicating"

pg 75, line 3: see comment above re: term weight of evidence. Since this is the first place this concept is introduced, please clearly define the method used to review and categorize the literature here.

pg 75, 1st full paragraph: please define the basis for determining "adequacy" here - lay out the criteria that used.

pg 75, 2nd full paragraph: suggest not using the term "discounted" (either here or in the subsequent paragraphs and summary document) because a weight of evidence approach weighs ALL of the evidence. It does not "discount" studies. It does give more weight to stronger studies, but the way the term is being used in this and subsequent pages, it implies the studies were not included. A more appropriate way of explaining would be to describe why lesser weight was given to certain studies (e.g., lower quality or strength, etc).

Table 2: Suggest a more balanced presentation in which highlights both the positive and negative results from the 10 studies are presented - that is, if several endpoints were explored, it is inadequate to just present the positive results given the impact of problem of multiple comparisons on the statistical significance of findings. Some of the information appears to be in the tables, perhaps it is an issue of re-labeling the columns?

Pg 81: 1st paragraph, line 2: not sure why effects other than neurological are being discussed here within the context of the "principal study" given that principal effect has been determined (this whole paragraph seems misplaced – perhaps it belongs as part of the first paragraph on page 72?)

Pg 81: 2nd and 3rd paragraphs, and the 1st paragraph on the next page: all three of these paragraphs discuss on deficits in visual perception, but the context for that discussion is not clear – since the "critical effect" is now a suite of neurological effects, please indicate why one set of effects is discussed.

Comments on the RfD

- It is unclear why the UF of 3 for data base sufficiency is necessary, especially given peer reviewer comments to the contrary.
- If the UF is 3000, it is unclear how the confidence could be "medium"

Attachment D

December 30, 2003

**Summary of OMB comments and EPA responses -
External review draft of the Toxicological Review of Toluene (December 2003)
Prepared by Lynn Flowers, chemical manager for toluene**

OMB comment #1: There is concern about precedent being set by using color vision as a critical endpoint and a related concern that there is not sufficient reviewer expertise to address this, particularly the biological relevance. Specific comments included:

- Are there appropriate reviewers to look at this?
- Only 50% of reviewers on previous panel were ok with this and one of these reviewers did not think documentation was sufficient.
- Others asked for increased discussion on biological relevance. This still seems to be missing from the draft.
- The added reviewer with this expertise is an author whom EPA cites for having used this test for environmental relevance in the past, thus he may not be seen as an unbiased reviewer.
- The charge question 2b should directly ask "Is this effect biologically relevant"? This would mean there needs to be experts on the panel that can answer the question. Reviewers from the previous panel sounded like they could not and these same reviewers are on the panel again.

EPA response: The peer review contractor is trying to find another color vision expert and has contacted the panel members with neurotoxicity expertise to inquire about their capability to review/comment on color vision. Additional discussion on the choice of color vision as the critical effect and biological relevance of this endpoint has been added to Section 5.2.1 of the Toxicological Review. The charge question (2b) has been clarified as follows: "The critical effect is identified as impaired color vision. Is this the correct critical effect and is it adequately described? Is the biological basis for choosing this effect adequately explained?"

OMB comment #2: Appendix A is unclear in that all reviewers agreed with the RfD principal study, yet it was changed anyway. Reads as very contradictory and needs to be clarified. Uncertainty factor discussion needs to be clarified.

EPA response: The rationale for the change in the principal study for the RfD has been clarified in Appendix A to better explain that additional key studies were identified as a result of public comment. The discussion on the application of uncertainty factors to the point of departure for the RfD has been corrected.

OMB comment #3: It is unclear why kidney weight changes are used instead of liver weight changes or in addition to liver changes. This is not explained well (especially considering distribution of toluene in the body).

EPA response: The rationale for selecting kidney weight changes as the critical effect for the derivation of the RfD has been further clarified in Section 5.1.1 of the Toxicological Review.

OMB comment #4: It is unclear if discussion of immunological studies belongs in Section 1.A.2 or 1.A.4 of the IRIS summary.

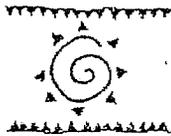
EPA response: The discussion of immunological effects from toluene exposure has been moved to Section 1.A.4 of the IRIS Summary.

OMB comment #5: Use of male rat data instead of male and female data for the RfD does not appear to be supported well, especially considering Section 4.7.2 of the Toxicological Review. If both sexes were used, how different would the value be?

EPA response: Male rat data were used for the derivation of the RfD. The response in male rats was greater than that seen in female rats as indicated in Section 4.2.1.1 of the Toxicological Review. As indicated in Section 4.7.2, male rats and mice have been shown to be more sensitive, in general, to the effects of toluene than females. Thus, the use of data from male rats is supported by the available studies.

Attachment E

John Vandenberg/DC/USEPA/US



John
Vandenberg/DC/USEPA/US
09/13/2004 10:39 AM

To Peter Preuss/DC/USEPA/US@EPA, Lynn
Flowers/DC/USEPA/US
cc George Alapas/DC/USEPA/US@EPA, Amy
Mills/DC/USEPA/US@EPA
Subject naphthalene - OMB request for briefing

Nancy Beck called me this morning and conveyed several things:

1) John Graham wants a briefing on the naphthalene assessment, focused on process from here (e.g.,

interagency review, consideration of peer review comments). We should arrange in next couple of weeks if possible.

2) She (Nancy) considers some of the external peer review comments to be significant.

3) they've heard a rumor we plan to have the document out by end of September.

I told her we're evaluating the draft in light of peer review comments, that we've heard DOD plans to comment but we have not received any comments from them and I urged her to get them to share their comments. I sketched out the IRIS process insofar as it would normally proceed, noting that a formal interagency review would change the process (and that we'd share a document that reflects our revisions following external peer review). I mentioned IRIS Track (Paul Gilman had also mentioned it, they're interested in seeing it). I didn't give any specific dates to her (perhaps fortunately IRIS track was offline this morning!)

We should talk through how we want interagency review to occur, including any groundrules we want to get set up front to avoid paralysis (e.g., fixed time for other agencies to provide review comments; final disposition/decisionmaking by EPA/ORD on assessment document completion; criteria or conditions calling for additional external peer review). Especially for "biggies" that have interagency review we need to stake out a process that will lead us to be successful in terms of timeliness, clarity, consistency, etc.

John

John Vandenberg
Associate Director for Health
National Center for Environmental Assessment B240-01
Office of Research and Development, USEPA
Research Triangle Park, NC 27711

Attachment F



John
Vandenberg/DC/USEPA/US
05/24/2005 02:52 PM

Amy Mills/DC/USEPA/US@EPA, preuss.peter@epa.gov,
To George Alapas/DC/USEPA/US@EPA, Bettyjo
Overton/DC/USEPA/US@EPA, Linda

cc

bcc

Subject IRIS process comments from OMB, next steps

In brief, Nancy Beck (and, she says, Dr. Graham) were expecting more detail than provided in the flow chart and 2-pager to address the 'details'. I pushed back, not wanting to have us wait several months to develop new SOPs, as this is premature. Nancy seemed to concur, though she is checking with Dr. Graham.

We ended up agreeing to slightly revise the 2-pager to add a bullet on next steps (i.e., public workshop to discuss process and details/issues) and to emphasize or elaborate on the improvements the process will bring. I've discussed these changes with Amy and she'll revise the 2-pager sent to OMB in preparation for Amy Farrell. Nancy will send over her comments by fax by tomorrow (to DC office, BettyJo - please keep an eye out for this and give copies to addressees here).

Further, I agreed that in our Federal Register notice announcing the workshop, we'll identify some of the topics and issues for discussion including, for example, the attribution of comments to specific reviewers, the criteria for selection of QA Check reviewers, the proposal with respect to a NAS risk assessment panel, the availability of relevant information on web sites, etc. OMB wants to review this FR notice. I emphasized the FR notice will not be exhaustive on what issues will be raised and discussed at the workshop but it will be sufficiently illustrative to inform potential participants as to the details that we will likely seek input on.

We discussed Interagency review and I informed her perc was soon to arrive for interagency review (estimate about a month from now). She clearly is concerned that OMB/OSTP have not worked out a plan for interagency review. I offered that we could help in getting materials prepared for the review process, but it is essential that the request for review come from OMB/OSTP. She asked that the bullet on interagency review refer to EOP rather than "OMB and OSTP will manage interagency review".

Next steps:

- 1) Amy will revise 2-pager and look also at Nancy's comments to see if any final changes are needed before 2-pager and flowchart are sent to Amy Farrell
- 2) I'll send a note to Amy Farrell noting that we've discussed with OMB and expect to make final draft revisions to information by end of this week and offer to brief her
- 3) George, please send (or have BettyJo send) revised 2-pager and flow chart to Amy Farrell later this week.
- 4) Linda, Amy and IRIS staff should initiate or continue FR development and workshop planning.

John

John Vandenberg
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Attachment G



OSD-A1L"
<Shannon.Cunniff@osd.mil>

02/02/2006 10:18 AM

To Peter Preuss/DC/USEPA/US@EPA

"Beck, Nancy" <Nancy_Beck@omb.eop.gov>, "Noe, Paul R." <Paul_R._Noe@omb.eop.gov>, "Beehler, Alex, Mr, OSD-ATL" <Alex.Beehler@osd.mil>, John Vandenberg/DC/USEPA/US@EPA, "Richard Wickman (richard.a.wickman@nasa.gov)" <richard.a.wickman@nasa.gov>, "Bill McGovern (bill.mcgovern@dhs.gov)" <bill.mcgovern@dhs.gov>, "Blaine Rowley (blaine.rowley@em.doe.gov)" <blaine.rowley@em.doe.gov>, Carl Ma <carl.ma@faa.gov>, "Dave Belluck (David.Belluck@fhwa.dot.gov)" <David.Belluck@fhwa.dot.gov>, "James Leatherwood (James.L Leatherwood-1@nasa.gov)" <James.L Leatherwood-1@nasa.gov>, "JLeather@hq.nasa.gov" <JLeather@hq.nasa.gov>, "Juan Reyes (juan.reyes@dhs.gov)" <juan.reyes@dhs.gov>, Keith Holman <keith.holman@sba.gov>, "Martin, Mary" <Mary.Martin@nnsa.doe.gov>, Mike Savonis <michael.savonis@dot.gov>, Paul Atelsek <patelsek@comdt.uscg.mil>, David Moses <David.Moses@hq.doe.gov>

Subject DoD, NASA, DoE comments on IRIS revisions

Peter,
OSD, NASA and DOE Sr. staff have reviewed ORD's proposed IRIS revisions chart and detailed explanation of some of the boxes and attached are our comments and suggestions. DHS and DOT were not on our last calls due to scheduling conflicts, so I can not assert to what degree they support these comments. I will get you a confirmation on that.

What you have attached is a) the flow chart - we added numbers to all the boxes but also retained your numbering of the latter 10 boxes that correspond to your detailed explanation -- and b) an expanded detailed explanation of the boxes that includes, as we discussed, an proposed explanation for every step to help us all achieve clarity and eventually agreement.

These inserts and changes were drafted by a committee of federal staff and recorded by Mitretek (so you might see Mitretek identified as a "commentor". All of our insertions or changes are in color and underlined.

We suggest that after you look this over that we set up another multi-agency meeting to bring all the interested federal agencies together to discuss the process steps and see if together can reach consensus on the process, understand how or if this effort fits with Dr. Gray's visions for IRIS, and develop a plan for next steps.

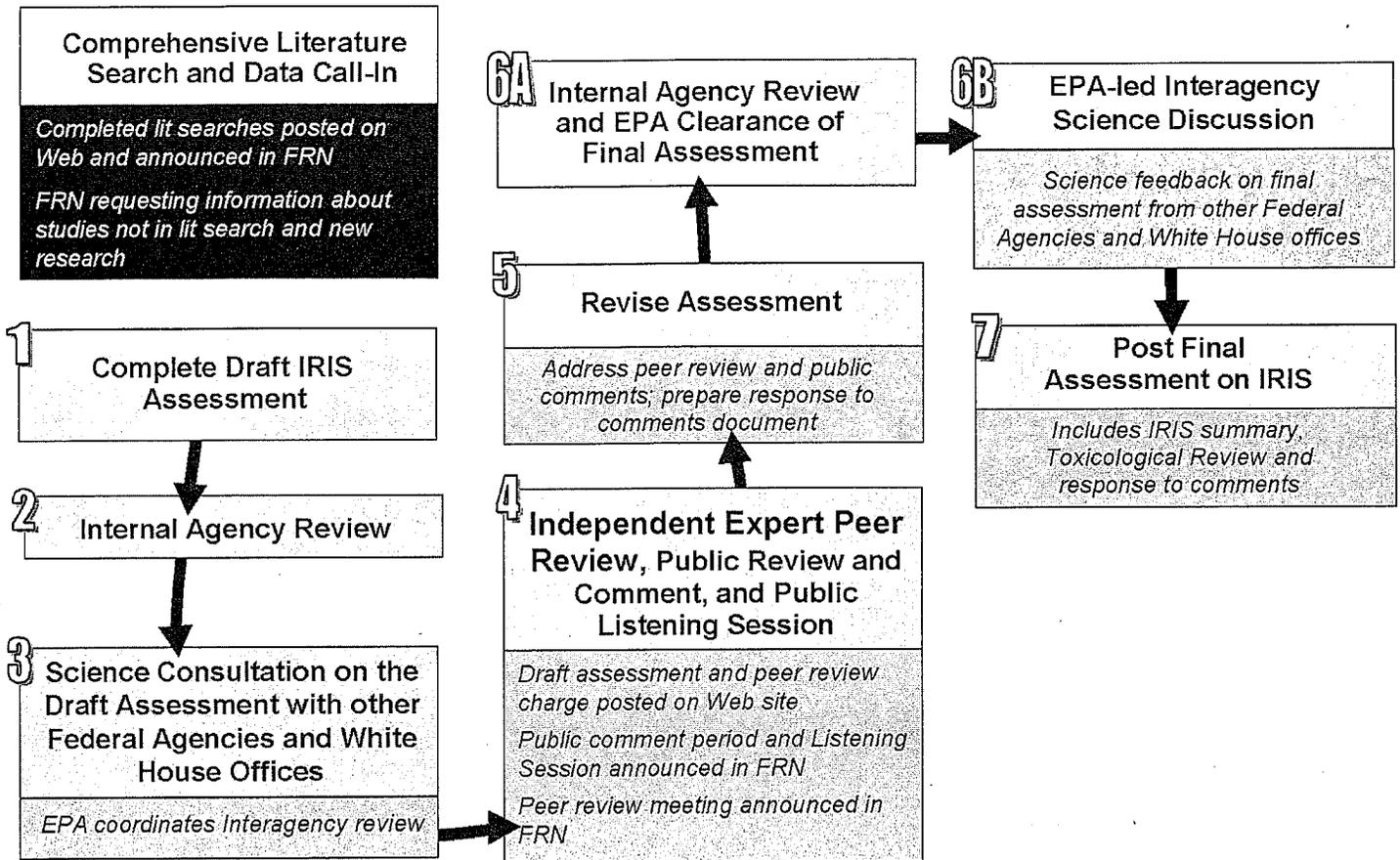
Please call me if you have any questions or comments.

Shannon E. Cunniff
Executive Lead, MERIT
Special Assistant for Emerging Contaminants



Attachment H

Assessment Development Process for New IRIS



1 **1. EPA Develops and Completes a Draft IRIS Toxicological Review (Duration**
2 **345 days)**

- 3 A. ORD assembles an IRIS assessment team.
- 4 B. ORD assesses the data in the scientific literature and any information submitted as a result of the
5 data call-in and develops a draft assessment for the chemical being assessed, including:
- 6 a. summary of potentially important health effects;
- 7 b. summary of information on potential mode(s) of action;
- 8 c. summary of information about potentially susceptible populations;
- 9 d. a quantitative assessment, including application of uncertainty factors, default approaches,
10 mode of action information, and dose-response modeling; and
- 11 e. identification of potential uncertainties that impact the qualitative and quantitative aspects of
12 the assessment.
- 13 C. ORD completes the draft IRIS Toxicological Review.
- 14

15 **2. Internal EPA Review (Duration 60 days)**

- 16 A. ORD submits the draft IRIS Toxicological Review for internal Agency review.
- 17 B. Internal Agency review includes scientists from EPA programs and regions.
- 18 C. Internal agency review identifies any scientific issues to determine the level of peer review, needed
19 panel member disciplines, and the scope of the review.
- 20

21 **3. EPA Initiates Interagency Science Consultation on Draft IRIS Toxicological**
22 **Review (Duration 45 days)**

- 23 A. EPA sends the draft IRIS Toxicological Review and draft external peer review charge to other
24 Federal agencies and White House offices for a science consultation.
- 25 B. The science consultation step is managed and coordinated by EPA
- 26 a. EPA provides a specified date for receipt of written comments.
- 27 b. EPA hosts meeting of other agencies and White House offices to discuss issues raised by
28 comments.
- 29 C. All written comments received during Interagency Science Consultation become part of the public
30 record
- 31 D. ORD revises the draft assessment documents, as appropriate.
- 32 E. If EPA considers appropriate, science questions that arise during science consultation may be
33 included as part of a charge question to the peer review panel.
- 34
- 35
- 36
- 37

1 **4. EPA Initiates Independent External Peer Review of Draft IRIS Toxicological**
2 **Review, Public Review and Comment on Draft IRIS Toxicological Review,**
3 **and Holds a Public Listening Session (Duration 105 days)**

4 A. External Peer Review

- 5 a. EPA provides the draft IRIS Toxicological Review and peer review charge questions for
6 independent external peer review.
- 7 b. EPA publishes an FRN at least 30 days prior to the peer review meeting notifying the public
8 about the time and place of the meeting.
- 9 c. Peer reviews are public meetings, generally through a face-to-face meeting of panelists,
10 though some may be held via public teleconference.
- 11 d. The report of the external peer review panel becomes part of the official public record for the
12 IRIS assessment

13 B. Public Review and Comment

- 14 a. EPA releases the draft IRIS Toxicological Review for public review and comment.
- 15 b. ORD prepares an FRN announcing a public comment period of 60 days.
- 16 i. The draft IRIS Toxicological Review is released on EPA's Web site on the day that
17 the FRN is published.
- 18 ii. The FRN includes detailed instruction for submitting public comments.
- 19 iii. The public comment period is open to all stakeholders, including other Federal
20 Agencies and White House offices.
- 21 c. Public comments are submitted to ORD
- 22 i. All comments received during the official public comment period will be submitted
23 through E-Gov (www.regulations.gov).
- 24 ii. All public comments will be part of the official public record.
- 25 iii. Public comments submitted by the close of the comment period will be provided to
26 the peer reviewers at least 10 working days prior to the peer review meeting.
- 27 iv. Only those comments received by the close of the public comment period are
28 guaranteed of being provided to the external peer review panel in advance of the peer
29 review meeting.
- 30 v. If an extension of a comment period is requested and granted, and a second FRN is
31 published, the comments submitted during the extension may not be able to be
32 provided to the peer reviewers before the meeting.

33 C. Public Listening Session

- 34 a. EPA holds a Public Listening Session after the public release of the draft assessment and
35 before the peer review meeting.
- 36 b. The Listening Session provides an opportunity for interested parties to present scientific and
37 technical comments on the draft IRIS health assessment to EPA and other interested parties.
- 38 c. An FRN announcing the Listening Session is generally published as least 30 days prior to the
39 Listening Session meeting.

- d. FRN includes all logistical information regarding the meeting.
- e. All Listening Sessions are held in the Washington, DC metropolitan area.

5. EPA Revises IRIS Toxicological Review and Develops IRIS Summary (Duration 60 days)

- A. ORD evaluates the external peer review panel report and all public comments.
- B. ORD revises the draft IRIS Toxicological Review, as appropriate, and develops the IRIS Summary.
- C. Length of revision process may depend on the complexity of the IRIS Toxicological Review and complexity and number of peer reviewer and public comments.
- D. ORD develops a disposition of peer reviewer and public comments and provides these as an appendix to the IRIS Toxicological Review.

6A. Internal EPA Review of Final IRIS Toxicological Review and IRIS Summary (Duration 45 days)

- A. ORD sends the IRIS Toxicological Review and IRIS Summary for final internal Agency review.
- B. This review is intended as a final check-in with Agency program and regions.

6B. EPA-led Interagency Science Discussion (Duration 45 days – concurrent with Step 6A.)

- A. EPA provides other agencies and White House offices with the final draft of the IRIS Summary and Toxicological Review and appendix describing disposition of peer review and public comments.
- B. Other agency and White House Office scientists have opportunity to provide written scientific feedback.
- C. EPA hosts meeting with White House offices and other agencies to discuss any scientific issues related to the final draft of the IRIS Summary and Toxicological Review and appendix.
- D. All written comments by other agencies and White House offices documented in the record.

7. EPA Completion of IRIS Toxicological Review and IRIS Summary (Duration 30 days)

- A. ORD completes the IRIS Toxicological Review and IRIS Summary.
- B. ORD prepares the final assessment for Agency's Web site posting.
- C. ORD insures 508 Compliance and EPA Web site compliance.
- D. ORD posts the assessment to the IRIS data base.
- E. ORD completes and maintains the public record.

TOTAL: 23 Months