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Via Courier

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George M. Gray, Ph.D.
Assistant Administrator for Research and Development
United States Environmental Protection Agency
Mail Code 8101 R
1201 Constitution Avenue, N.W.
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Dear Dr. Gray:

Re: IRIS Peer Review of Polybrominated Diphenyl Ethers (PBDEs)
Docket ID No. EPA-HQ-ORD 2006-0838

I am writing to convey the serious concerns of the Brominated Flame Retardant Industry Panel ("BFRIP" and "the Panel") of the American Chemistry Council (ACC)¹ regarding the ongoing toxicological assessment of PBDEs. We have particular concern with the assessments for decabromodiphenyl ether ("deca-BDE"), which is being performed by the U.S. Environmental Protection Agency ("EPA" or "the Agency") to update the Integrated Risk Information System (IRIS). BFRIP requests that you review its concerns and take steps to ensure the independence and objectivity of EPA's IRIS reassessment.

I. EXECUTIVE SUMMARY

- BFRIP is concerned about both the composition of and process for forming the Agency's external peer review panel, especially by the appearance that the peer review panel's leadership might lack the impartiality and objectivity necessary to conduct a fair and impartial review of the data.
- When recommending a revised reference dose (RfD) for deca-BDE, the external peer review panel (and EPA) appear to be ready to rely on a study that fails to meet the Agency's standards for accurate and reliable data. The study is based

¹ BFRIP is under ACC's Chemical Products and Technology Division and its members are the U.S. manufacturers and importers of brominated flame retardants: Albemarle Corporation, AmeriBrom, Inc., and Chemtura Corporation (collectively "the Panel").



upon a design that does not conform to Agency guidelines and was not performed in accordance with Good Laboratory Practices (“GLP”).

- BFRIP urges the Agency to reject any recommendations to combine the PBDEs as a group for purposes of the revised IRIS evaluation, because this is contrary to the data within the Agency’s possession and would not conform with established principles of toxicology. Each of the PBDEs and deca-BDE in particular must be evaluated on its own very robust database and the comprehensive weight of the evidence.

II. BACKGROUND AND INTRODUCTION

These concerns are of sufficient import to merit your attention. BFRIP has a long-standing tradition of working closely and cooperatively with the Agency to generate and assess data concerning the brominated flame retardants. To that end, BFRIP has submitted countless studies to the Agency (and to international bodies) and has participated in numerous Agency data-development and risk assessment programs, such as the High Volume Production (“HPV”) Challenge Program and the Voluntary Children’s Chemical Evaluation Program (“VCCEP”). Panel members also have demonstrated a strong commitment to working collaboratively with the Agency on a variety of policy and programmatic issues, including the development of a product stewardship program specifically for down-stream users of the various brominated flame retardant products BFRIP’s members produce. In addition, the manufacturers which comprise BFRIP also sponsor another stewardship program called the Voluntary Emissions Control Action Programme (“VECAP”) which was established to manage, monitor and minimize industrial emissions of brominated flame retardants through partnership with the supply chain.

Because of its close working relationship with EPA and other regulatory agencies, the Panel is compelled to formally raise its specific concerns regarding the process followed for the IRIS PBDE External Peer Review, including the reliability of the data being assessed, the integrity of the peer review process, and certain information that has come to light that could suggest the potential for bias exists on the part of the Peer Review Chairperson. In addition, the Panel has specific concerns regarding technical aspects of the Final Report of the External Peer Review published on April 4, 2007² (“Final Report”) that will be addressed in greater detail below.

The Panel members request that you personally review BFRIP’s concerns and take appropriate actions before the draft Toxicological Review is issued in final form. The importance of the IRIS Review cannot be underestimated because the IRIS data base is relied upon by various EPA offices and numerous other bodies, including federal and state regulatory agencies; thus, it is imperative that the IRIS reassessment be based upon credible information. Therefore, the Panel is willing to work with EPA in a timely

² See <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=161970>.

fashion to provide any additional comments, information, and support as needed to arrive at a final Review that meets the rigorous standards of scientific integrity and data quality that appropriately are expected of the Agency and are required by the Information Quality Act for influential government documents such as EPA's own publications and the IRIS system in particular.

III. THE PANEL'S CONCERNS REGARDING THE PEER REVIEW PROCESS

The Agency's Peer Review Handbook (3rd ed.) ("Handbook") provides a comprehensive overview of the Agency's expectations concerning the peer review process and the steps necessary to ensure transparency and accountability as required by the Office of Management and Budget's ("OMB") Final Information Quality Bulletin for Peer Review. Central to every peer review, but of particular importance here, is the Handbook's guidance on assembling and convening a peer review panel and the necessary steps that must occur before embarking on the substantive review of the underlying technical materials. Unfortunately, it is not clear that such considerations were addressed adequately by the Agency when initiating the External Peer Review for the IRIS-PBDE Toxicological Review.

A. EPA Did Not Solicit Appropriate Input As Suggested by Agency Policies

EPA's Handbook states that the

[s]election of peer reviewers should be made by identifying reviewers with the appropriate expertise and then narrowing the field of potential peer reviewers to those individuals that are independent, do not have a conflict of interest and do not appear to lack impartiality. You should also consider requesting that the public, *including scientific and professional societies*, nominate peer reviewers.

Handbook, §§3.4.1-3.4.2 at 60-61 (emphasis added); *see also* "Advisory Committee Meetings and Report Development: Process for Public Involvement" available at http://www.epa.gov/sab/pdf/sabso_04_001.pdf (stating that "[a]gency policy . . . not only allow[s] but also encourage[s] public involvement"). In the case of the PBDEs External Peer Review, the public, including well-positioned and knowledgeable scientific groups such as BFRIP, were not asked to nominate reviewers. *See* Peer Review Plan for DRAFT IRIS HEALTH ASSESSMENT OF 2,2',4,4'-TETRABROMODIPHENYL ETHER (BDE-47) CASRN 5436-43-12,2',4,4',5-PENTABROMODIPHENYL ETHER (BDE-99) CASRN 60348-60-92,2',4,4',5,5'-HEXABROMODIPHENYL ETHER (BDE-153) CASRN 68631-49-22,2',3,3',4,4',5,5',6,6'-DECABROMODIPHENYL ETHER (BDE-209) CASRN 1163-19-5. Indeed, BFRIP could have provided the drafters with valuable information and insight concerning potential peer reviewers.

Further, pursuant to government-wide and EPA directives, a Peer Review Plan for influential scientific information must be made available for public comment. *See Handbook*, §1.4.3 at 21. Without any formal comment period or published docket specific to the Peer Review Plan, BFRIP was not provided an adequate opportunity to comment on the Plan. If it had, the Panel members would have encouraged EPA to open up peer reviewer nomination process to include all relevant stakeholders.

B. The External Peer Review for PBDEs Does Not Appear to Be an “Independent, Third-Party Review”

According to EPA’s own Handbook,

[t]he goal of peer review is to obtain an independent, third-party review of the product from experts who have not substantially contributed to its development. *When experts have a material stake in the outcome of the peer review . . . or have participated substantially in the development of the product, those experts’ reviews may not qualify as unbiased, independent peer review*

Handbook, §1.2.5 at 13 (emphasis added). Thus, the selection of independent peer reviewers is critical and “EPA should always make every effort to use peer reviewers who do not have any conflict of interest or appearance of a lack of impartiality, and who are completely independent.” *Id.*, §3.4.1 at 60.

While the definition of an “appearance of a lack of impartiality” may vary somewhat depending on the status of a peer reviewer³, the basic concept is the same for all reviewers -- that is, a peer reviewer should not be or have been engaged in activities, or have an interest, that would lead a reasonable person to believe that the peer reviewer is biased or predisposed to favor one view over another. *See, e.g.*, 5.C.F.R. §2635.502(a). Indeed, EPA even recommends asking potential peer reviewers specific questions to determine whether there is an “appearance” issues, such as:

- Have you made any public statements (written or oral) on the issue?
and;
- Have you made any public statements that would indicate to an observer that you have taken a position on the issue under consideration?

Handbook, §3.4.5 at 67. Making such inquiries in context of the PBDEs Review would have revealed issues that appear not to have been addressed.

³ External peer review can be conducted by individual experts who are either Regular Government Employees (RGEs) of another agency, experts hired as EPA Special Government Employees (SGEs), or experts who are retained through a contractual process. *See Handbook*, §3.4.5. at 60. The employment status of the PBDE peer reviewers is unknown to BFRIP.

With regard to the PBDE External Peer Review, BFRIP submits that genuine “appearance” issues exist relating to independence and objectivity of the peer review panel Chairperson. Earlier this year, the Chairperson testified before the Maine legislature, on behalf of the Maine Center for Disease Control and Prevention, specifically advocating that the state mandate a phase out of deca-BDE. The proposal included a sales ban on televisions and other consumer electronics encased in plastic containing more than one-tenth of 1% of deca-BDE by January 1, 2012, as well as a sales ban on mattresses and upholstered furniture containing the same amount of deca-BDE by January 1, 2008. *See, Brominated Flame Retardants, Third Annual Report to the Maine Legislature*, January 2007.⁴ As reported in various media, the Chairperson told state lawmakers in Maine that “there is no question in her mind that deca should be eliminated because it is a persistent toxin that accumulates in the food chain.” *See Kevin Miller, DEP Urges Legislative Ban on Fire Retardant, Bangor Daily News*, February 16, 2007, at B4.⁵ Further, the Chairperson has stated that she would choose an alternative flame retardant over deca-BDE - even if equally toxic - because “[t]he reason we are in this bind is because the industry doesn’t have to collect any data about the compounds they are putting into commerce.” *Id.*

In addition, the Chairperson has authored two recent articles regarding deca-BDE. The first, entitled *Developmental Delays and Locomotor Activity in the C57BL6/J Mouse Following Neonatal Exposure to the Fully-Brominated PBDE, Decabromodiphenyl Ether (Neurotoxicology and Teratology, In Press, 2007)*⁶ suggests that deca-BDE causes adverse effects on the thyroid, however, BFRIP submits there is not reliable evidence to support that theory. Surprisingly, the Chairperson relies on this article in the Final Report to make the same claims regarding effects on the thyroid, but again offers no independent basis upon which to substantiate this claim. *See* Final Report at 24. A second article, called *Risk Assessment and Regulation of PBDEs (Neurotoxicology and Teratology, 2007)*⁷, not only appears to promote the ban of deca-BDE, but also apparently relies on the draft RfDs under review in this IRIS assessment which are by no means final nor in a form that should be circulated in the public domain.

While these are just a few examples of public statements made by the external review panel Chairperson relating to deca-BDE, there is no doubt that she has taken a very public position concerning a regulatory determination that is fundamental to the very issues presented to the panelists in the draft IRIS Toxicological Reviews. However, even more disconcerting is the fact that many of these statements and comments concerning deca-BDE were in the public domain *before* the Chairperson was selected for the IRIS External Peer Review. Thus, EPA staff had to know *or should have known* that the Chairperson has been a fervent advocate of banning deca-BDE -- the very sort of policy predisposition that has no place in an independent, objective peer review. *See, e.g., Handbook, §3.2.1 at 57* (“[T]he peer review is not for the decision or action itself, but for

⁴ A copy of this report is enclosed as Attachment 1.

⁵ A copy of this article is enclosed as Attachment 2.

⁶ A copy of the Accepted Manuscript is enclosed as Attachment 3.

⁷ A copy of the Accepted Manuscript is enclosed as Attachment 4.

the underlying scientific and/or technical work product; reviewers should not be asked to provide advice on policy”).

For these reasons, BFRIP believes that the Agency must base its final Toxicological Review on data, opinions, and conclusions other than the Chairperson’s. Otherwise, the integrity of this peer review will be further compromised -- which ultimately calls into question the overall integrity of the entire IRIS database.

IV. THE PANEL’S CONCERNS REGARDING THE DATA RELIED UPON IN THE TOXICOLOGICAL REVIEW AND PEER REVIEW

As stated in its formal written comments, BFRIP recognizes that the Agency asserts that a draft Toxicological Review is not yet a final determination made by the Agency.⁸ Nevertheless, the documents have been widely circulated and published on EPA’s web-pages for purposes of external peer review and public comment and, to the Panel’s knowledge, no effort has been made to address the current data deficiencies -- yet these deficiencies are sufficiently profound in certain cases that the draft Review (and any final version containing the same problems) would not meet EPA’s own *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated* (“Information Quality Guidelines”).

For example, the Review does not comply with the standards for “objectivity” established for data and analyses conducted by federal agencies. “Objectivity” focuses on whether such information “is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased.” Information Quality Guidelines, §5.1, at 15; *see also* 67 *Fed. Reg.* 8452, 8460 (February 22, 2002). As previously explained, there is real doubt as to whether EPA’s apparent willingness to rely on certain studies (especially the so-called “Viberg study”) when establishing a reference dose (RfD) for deca-BDE, would meet the Agency’s standards for data and information that are both accurate and reliable. At a minimum, BFRIP suggests that the Viberg study is based on a design that does not conform to Agency guidelines for developmental neurotoxicity tests, and that (minimally) the study was not performed in accordance with Good Laboratory Practices (“GLP”). Indeed, some of these same concerns have been raised by the external peer reviewers.⁹ *See, e.g.*, Final Report at 12, 13, 15. Furthermore, because (by EPA’s own interpretation) the Toxicological Review qualifies as an “influential” scientific risk assessment, the data relied upon (including the Viberg study) must meet certain standards, including:

- (A) The substance of the information is accurate, reliable and unbiased. This involves the use of:

⁸ The Panel reserves its right to file a formal Request for Correction pursuant to the procedures outlined in Section 8 of the Information Quality Guidelines.

⁹ It is noteworthy that the complete Viberg study is not believed to be in the possession of EPA, nor was it made available to the external peer reviewers.

(i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and support studies; and

(ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data).

(B) The presentation of information on human health, safety, or environmental risks, consistent with the purpose of the information, is comprehensive, informative, and understandable. In a document made available to the public, EPA specifies:

(i) each population addressed by any estimate of applicable human health risk or each risk assessment endpoint, including populations if applicable, addressed by any estimate of applicable ecological risk;

(ii) the expected risk or central estimate of human health risk for the specific populations affected . . . ;

(iii) each appropriate upper-bound and lower-bound estimate of risk;

(iv) each significant uncertainty identified in the process of the assessment of risk and studies that would assist in resolving the uncertainty; and

(v) peer-reviewed studies known to the Administrator that support, are directly relevant to, or fail to support any estimate of risk and the methodology used to reconcile inconsistencies in the scientific data.

Information Quality Guidelines, §6.4 at 21-22. As the record stands now, the draft Review fails to meet these requirements established to fulfill the Information Quality Act (and EPA's own Guidelines).

V. THE PANEL'S COMMENTS ON THE FINAL REPORT OF THE EXTERNAL PEER REVIEW

BFRIP has the following specific concerns regarding technical aspects of the External Peer Reviewer's "Toxicological Review for Polybrominated Diphenyl Ethers (PBDEs) Human Health Assessment -- FINAL REPORT" ("Final Report"), dated February 2007 and published on April 4, 2007 (<http://cfpub.epa.gov/ncea/cfm/nceawhatnew.cfm>).

The Final Report did not demonstrate that the External Reviewers conducted a balanced and reasonable review of the written and oral comments which were provided by BFRIP and other commenters well in advance of the Final Report. For example, BFRIP, ChemRisk, and The Dow Chemical Company each pointed to the critical flaws in the Viberg studies that rendered them too unreliable for IRIS use; instead, one External Reviewer, for example, has stated that there is “no alternative” but to consider Viberg. While it is recognized that one External Reviewer agreed that there were pitfalls with the Viberg studies, and one indicated that “further DNT studies are needed,” the overall recommendation of the External Reviewers appears to be that the study was sufficient for IRIS purposes.¹⁰

This conclusion regarding the Viberg data is completely contrary to the one reached by the Agency when it reviewed similar methods being used by the researcher in EPA’s June 2005 VCCEP Data Needs Decision Document (“Decision Document”).¹¹ In the Decision Document, EPA discussed the methods being used in a mouse study by Viberg as it related to some Tier 3 gaps in deca-BDE’s neurotoxicity data. It stated:

EPA notes several issues with the protocol of this study which introduces considerable uncertainty in the interpretation of the results. The issues include the mouse strain, the limited duration of exposure, and the statistical methods. In this study, multiple pups from each litter were tested and this was not controlled for in [sic] the statistical analysis. Similar issues were also raised in the peer consultation meeting. In addition, the European Union recently completed a risk assessment of [deca-BDE] and concluded the results of the Viberg et al (2003) study were not adequate for the purposes of quantitative risk assessment.

Decision Document at 15. Based on these statements, it would seem illogical for the Viberg rat study to be relied upon for the IRIS assessment since the Agency itself previously deemed such methods to be “uncertain” and also reiterated the EU’s own determination that the study was “inadequate.”¹²

Furthermore, BFRIP continues to disagree that the Viberg data should be used as a basis for IRIS, not only because of their significant limitations in design and transparency of data, and not only because a more robust guideline compliant DNT study is being undertaken, but also due to the fact that non-GLP lab work from one academic investigative lab of Viberg’s does not constitute sufficient sound scientific evidence nor

¹⁰ Surely, EPA should hold IRIS to higher standards of data quality.

¹¹ A copy of the Decision Document is enclosed as Attachment 5.

¹² At another point in the Decision Document, the Agency states that “[t]here is *substantial uncertainty* regarding the interpretation of the behavior effects noted in a recent study [Viberg et al. (2003)] of neonatal mice.” Decision Document at 1.

has it been shown that his methodologies are a reliable predictor or substitute for the OPPTS/OECD DNT guideline study. Unless or until some independent body has validated that this or other non-traditional type toxicology studies can be substituted for standardized GLP-type studies, they should only be viewed as indicative of a potential hazard, but not used quantitatively to develop RfDs.

The Final Report also demonstrates that the External Panel did not conduct an independent, balanced, and reasonably thorough review of the extensive science and toxicology database pertinent to deca-BDE, nor the overall weight of scientific evidence relating to PBDEs. For example:

- The available data do not support the conclusion that deca-BDE adversely affects the thyroid, yet the Chairperson's comments suggest that this theory is fact in the Final Report and surprisingly cites her own work from 2007 as support. A more careful review of the article referenced above and enclosed as Attachment 3, indicates that it does not, in fact, demonstrate evidence of an adverse effect.
- Based on current information, there is not adequate basis to conclude (in spite of the position taken by one External Reviewer), that PBDEs are "transgenerational pollutants". Such statements are not based on sound scientific data and represent, at best, speculation and personal opinion rather than careful consideration of the scientific evidence concerning deca-BDE and PBDEs.
- One External Reviewer stated that he is not aware of other peer-reviewed studies that would contribute to an understanding of risks associated with PBDEs. However, an article by Hays and Pyatt, (*Risk Assessment for Children Exposed to Decabromodiphenyl (Oxide) Ether (Deca) in the United States, Integrated Environmental Assessment and Management*, Vol. 2, pp 2-12, 2006) addresses this very issue and should have been identified and made available for consideration by the External Reviewers. Hays and Pyatt conclude in their peer-reviewed article that, based on comprehensive evidence, there are large margins of safety and that the current levels of exposures to deca-BDE are unlikely to represent an adverse health risk.

Furthermore, BFRIP opposes the recommendation of some of the External Reviewers to consider all of the PBDEs as a "group" for IRIS purposes. Such a recommendation lacks insight into the differences among the PBDEs and is contrary to basic scientific and toxicological principles. In fact, one reviewer incorrectly states that PBDEs "have the same toxic end points with varying degrees" and uses this as a rationale to combine the PBDEs into one IRIS document. Another reviewer uses the incorrect and unsupported argument that PBDEs are "additive" for DNT effects with other compounds such as PCBs, in order to rationalize combining the PBDEs into one IRIS document.

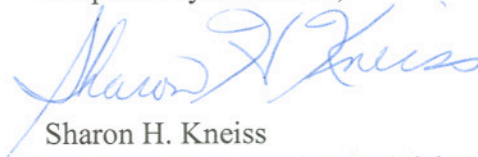
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Again, it is important to recognize that deca-BDE is a unique and specific substance (structurally, toxicologically, physically, chemically, etc.) and should be evaluated by IRIS independently based on the extensive information already available for deca-BDE. Moreover, the toxicity profile of PBDEs, for example, varies based on the degree of bromination. For the sake of comparison, not even dioxins are considered to be toxicologically equivalent among the various congeners. Thus, there are dioxin TEQs that allow for an independent evaluation of each congener's unique profile. Accordingly, BFRIP urges the Agency not to combine the PBDEs as a group, and to evaluate deca-BDE based on its relevant, substantial, and risk-based database and the comprehensive weight of the evidence.

* * *

In light of the foregoing, the Panel urges you to conclude that these concerns regarding the IRIS PBDE assessment must be addressed before any final reports are published or any republication of the preliminary documents occur. To that end, BFRIP representatives would like to meet with you and the appropriate managers and technical staff responsible for the draft Toxicological Review and the External Peer Review to discuss BFRIP's concerns. We will contact your office soon to set up that discussion. BFRIP looks forward to working with EPA in an effort to resolve these issues in a mutually agreeable manner.

Respectfully submitted,



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Enclosures

cc: Jim Gulliford, OPPTS
Charlie Auer, OPPT