MICHAEL P. WALLS
VICE PRESIDENT
REGULATORY & TECHNICAL AFFAIRS

American Chemistry Council

December 5, 2012

Mr. Lek Kadeli
Acting Assistant Administrator
Office of Research and Development
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 8101R
Washington, DC 20460

Dear Assistant Administrator Kadeli:

The American Chemistry Council (ACC)* has been closely following activities and progress of the U.S. Environmental Protection Agency's (EPA) Endocrine Disruptor Screening Program (EDSP), including scientific developments relevant to standardization and validation of screens and tests and integration of screening results. With respect to the Office of Research and Development's (ORD) activities in evaluating the endocrine low-dose issue, however, we are concerned that ORD has fallen short of meeting the Administration's benchmarks of scientific integrity, transparency and public engagement.

ACC has long maintained that federal agency hazard evaluations and risk assessments can and should reflect the best science and practices, and we support actions to enhance the integration of up to date scientific knowledge, methods and practices in risk assessment programs in EPA. Clearly, ORD's research activities can play a key role in the generation of scientific information and methods for improving hazard evaluations and risk assessments throughout the Agency. Unfortunately, ORD has yet to describe its approach for conducting the scientific evaluation of the low-dose hypothesis, has not announced opportunities for public review and comment, and has not communicated its plans for obtaining independent peer review of ORD's evaluation. As

*The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $760 billion enterprise and a key element of the nation's economy. It is the largest exporting sector in the U.S., accounting for 12 percent of U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

ORD undertakes its evaluation of the low-dose hypothesis, it is critical that the Agency follow best practices of objective, comprehensive review of the scientific evidence and be more transparent.

The Agency's evaluations should build from the data underlying the 2002 EPA policy position that "[u]ntil there is an improved scientific understanding of the low-dose hypothesis, EPA believes that it would be premature to require routine testing of substances for low-dose effects in the Endocrine Disruptor Screening Program" (1). The Agency should also make use of the results of the comprehensive evaluations by the expert panel of the Center for Evaluating Risks to Human Reproduction (CERHR) (2), the Food and Drug Administration (FDA) (3) the Advisory Committee of the German Society of Toxicology (4) and the seminal research by EPA's leading endocrine research laboratory (5,6), and other publications (e.g., 7) which have shown that solid scientific evidence is still lacking for adverse effects at doses below No Observed Adverse Levels and for induction of adverse effects by non-monotonic dose responses. In addition, EPA should employ best practices for conducting systematic scientific evaluations, as discussed for example, in the recent Keystone "Research Integrity Roundtable Report (8).

Unfortunately, EPA's hazard and risk assessments have not always met the benchmarks of objectivity, transparency, and scientific accuracy needed for stakeholders to have sufficient confidence in their use for health and environmental regulatory decision making. To date, the Agency has not been transparent with respect to its plans for evaluating the low-dose hypothesis. The only information the Agency has disseminated about its plans for the low dose review are a 2-page document and a presentation made to the EPA ORD Board of Scientific Counselor's / Scientific Advisory Committee joint meeting in July, 2012(9). EPA has not described to stakeholders its processes for designing the analyses, nor has the Agency announced its plans to obtain public comment on its draft work product or for having it peer reviewed. This lack of transparency is troubling and inconsistent with President Obama's pledge to improve scientific integrity and build the public trust by establishing "a system of transparency, public participation, and collaboration" (10).

To properly serve the needs of the public, all stakeholders expect that EPA's review and analysis will be firmly based on up-to-date scientific knowledge, meet the highest standards of scientific inquiry and be evaluated in accordance with acceptable scientific approaches. With these shared expectations in mind, ACC recommends the following actions:

1. The upfront design of the assessment needs to be transparent and specify the key issues that are to be assessed, and the specific methods, assumptions, and evaluation procedures that will be utilized. The search strategy for obtaining scientific studies for review needs to be explicitly stated and documented. The Agency also needs to establish *a priori* criteria for study inclusion/exclusion, including exclusion of studies which do not meet pre-specified scientific standards of study design, conduct, data reporting, independent

review, etc. This will assure that studies that meet the scientific standards form the basis of the assessment and scientifically flawed studies are appropriately set aside. In this manner, comprehensiveness, transparency and objectivity form the foundation of the analysis. The Agency should consider soliciting review of these design phase work products by the research community and stakeholders.

2. EPA should develop and use consistent and scientifically objective data evaluation protocols to evaluate studies. In this manner, the same procedures are used irrespective of who conducted the study, where it was conducted, or who funded it. For *in vivo* studies, ACC recommends EPA ORD follow the practices of EPA's Office of Pollution Prevention and Toxics (OPPT) (11) and utilize the Klimisch approach (12) or one of its recent upgrades (e.g., 13) Guidance for data evaluation procedures for *in vitro* assays is also available (ibid). Furthermore, ORD should consider using, with modifications if necessary, the Standard Evaluation Procedures (SEPs) and Data Entry Spreadsheet Templates (DESTs) (14) that Office of Science Coordination and Policy (OSCP) developed and is applying to EDSP Tier 1 screening.

3. The analysis must be based on a clear and consistent weight of evidence framework that takes into account, and integrates, all relevant data and information and gives the greatest weight to information from the most relevant and highest quality studies. A structured evaluative framework, such as that of the World Health Organization International Programme on Chemical Safety (15,16) or the hypothesis-based weight of evidence procedure of Rhomberg and colleagues (17, 18) should be used to provide a systematic approach for assessing the overall weight of the evidence for observed effects, including null responses, and the postulated mode of action. In this manner, data from laboratory experiments, epidemiological investigations, and cutting-edge mechanistic research from all relevant studies—GLP and non-GLP—and from all investigators, regardless of affiliation or funding source, can be comprehensively reviewed, given appropriate weight, and integrated in a manner that provides a robust, biologically plausible understanding of causality with respect to the low dose questions.

4. The draft report should be released for public review and comment, prior to peer review. During the public comment period, the Agency should also request comments on the draft charge questions for the peer review. Once public comments are received, EPA should then prepare a response to comments and revise the report and peer review charge questions, as warranted. Then the full package – the revised draft report and response to comments – should be submitted for independent peer review and simultaneously released to the public. The peer review process must guarantee robust scientific exchange by the reviewers that includes adequate consideration of public comments and analyses by outside experts of the revised draft report. Furthermore, the disposition of public

comments and peer review findings and recommendations should not be left to the agency authors and the program office. An independent accountability procedure must be installed to ensure that the final report reflects best available science and the Agency has adequately addressed both public comments and the findings and recommendations of independent peer review.

For an issue as important and potentially precedent setting as the low dose hypothesis, it is imperative that stakeholders have confidence in the scientific foundation of ORD's review. If ORD implements the comprehensive review procedures recommended above, ORD's report and conclusions will be viewed with greater scientific credibility.

ACC is committed to continue working constructively with EPA to address the challenges of chemical testing and evaluation for potential endocrine activity. Please contact Dr. Richard A. Becker by email (rick_becker@americanchemistry.com) or by phone (202-249-6405) if you have any questions on ACC's recommendations or engagement in endocrine research and testing. We would appreciate an opportunity to meet with you and your staff to discuss our perspectives in greater detail.

Sincerely,

Michael P. Walls
Vice President
Regulatory & Technical Affairs

Attachment

Attachment: Citations

1. http://www.epa.gov/endo/pubs/edmvs/lowdosepolicy.pdf

2. R. Chapin et al. (2008). NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A. Birth Defects Research (Part B) 83:157–395. http://onlinelibrary.wiley.com/doi/10.1002/bdrb.20147/pdf.

3. Food and Drug Administration (2008). Draft Assessment of Bisphenol A For Use In Food Contact Applications, FDA, http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf, p 16, and subsequent scientific reviews of low-dose BPA studies available on FDA's web site.

4. G. Hengstler et al. (2011). Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A. Crit Rev Toxicol 41: 263-291. , http://informahealthcare.com/doi/pdf/10.3109/10408444.2011.558487.

5. Ryan et al. (2010). In Utero and Lactational Exposure to Bisphenol A, in contrast to Ethinyl Estradiol, Does not Alter Sexually Dimorphic Behavior, Puberty, Fertility and Anatomy of Female LE Rats. Toxicol. Sci. 114(1): 133-148. http://toxsci.oxfordjournals.org/content/114/1/133.full.

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7.. L.R. Rhomberg and J.E. Goodman (2012). Low-dose effects and nonmonotonic dose–responses of endocrine disrupting chemicals: Has the case been made? Regulatory Toxicology and Pharmacology 64: 130–133, 2012. http://www.sciencedirect.com/science/article/pii/S0273230012001262

8.. Keystone Research Integrity Roundtable (2012). Improving the Use of Science in Regulatory Decision-Making: Dealing with Conflict of Interest and Bias in Scientific Advisory Panels, and Improving Systematic Scientific Reviews. https://www.keystone.org/images/keystone-center/spp-documents/Health/Research%20Integrity%20Rountable%20Report.pdf

9. EPA Office of Research and Development (2012). ORD Science Integration: EPA's Nonmonotonic Dose Response Curve (NMDRC) Workplan. http://yosemite.epa.gov/sab/sabproduct.nsf/B90ABCD62FCABDFF85257A250052065C/$File/NMDRC+2+pager_revised+06212012.pdf

10. Memorandum for the Heads of Executive Departments and Agencies, Subject: Transparency and Open Government, http://www.whitehouse.gov/the_press_office/TransparencyandOpenGovernment and Memorandum for the Heads of Executive Departments and Agencies, Subject: Scientific Integrity http://www.whitehouse.gov/the-press-office/memorandum-heads-executive-departments-and-agencies-3-9-09.

11. EPA Office of Pollution Prevention and Toxics (1999). Determining the Adequacy of Existing Data. http://www.epa.gov/hpv/pubs/general/datadfin.htm.

12. Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology 25:1-5.

13. Schneider, K., Schwarz, M., Burkholder, I., Kopp-Schneider, A., Edler, L., Kinsner- Ovaskainen, A., Hartung, T., and Hoffmann, S. (2009). ToxRTool, a new tool to assess the reliability of toxicological data. Toxicology Letters 189:138-144.

14. EPA (2011). Standard Evaluation Procedures (SEPs) and Data Entry Spreadsheet Templates (DESTs) for EDSP Tier 1 Assays. http://www.epa.gov/endo/pubs/toresources/seps.htm

15. Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers C, et al. (2006). IPCS Framework for analyzing the relevance of a cancer mode of action for humans. Crit Rev Toxicol. 36:781–792.

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