RE: DELS-BEST-12-06: Review of EPA's draft paper State of the Science on Nonmonotonic Dose Response ("NMDR Paper"), National Research Council ("NRC"), Division on Earth and Life Sciences, Board on Environmental Studies and Toxicology

Center for Regulatory Effectiveness' ("CRE") Response to EPA's NMDR Paper and to Comments on the Paper

I. Executive Summary

Several comments on the NMDR Paper attack EPA's decision not to use specific studies in assessing and regulating NMDRs. These comments ignore the fact that EPA cannot use or rely on any NMDR data/studies unless they meet statutorily required quality standards. These Information Quality Act ("IQA") Guidelines were expounded in the recent NRC report *Assessing Risks to Endangered and Threatened Species from Pesticides*.[1]

We are surprised that no one else has brought the recent NRC report on EPA's IQA Guidelines to this committee's attention.

Reproducibility of NMDR data and studies is especially important. EPA has emphasized the need for reproducibility in its NMDR Paper and in other communications with the NRC. The need for reproducibility has also been emphasized by other federal agencies such as the National Institute of Health ("NIH").[2]

Lack of reproducibility is a major problem with reports and data published in peer-reviewed journals. Nature Magazine has acknowledged this problem and is taking steps to solve it. [3] Consequently, EPA cannot presume that peer-reviewed journal articles are reproducible.

Dr. Tyrone Hayes' comments are among those that fail to note EPA's reproducibility and other IQA Guidelines' requirements. EPA could not use Dr. Hayes' amphibian effects data because his data could not be reproduced despite extensive attempts to replicate them. These unsuccessful attempts to reproduce Dr. Hayes' data were supervised by EPA and thoroughly reviewed by

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[1] The NRC report is available online at http://thecre.com/pdf/NRCesa.pdf . EPA's IQA guidelines are available online at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf .

[2] See http://www.thecre.com/insurance/?p=1117 (reprinting article originally published in Nature Magazine).

[3] See, *e.g.*, Announcement: Reducing our irreproducibility, at http://www.nature.com/news/announcement-reducing-our-irreproducibility-1.12852 ; Challenges in Irreproducible Research, at http://www.nature.com/nature/focus/reproducibility/ ; and If a Job is worth doing, It is worth doing twice, at http://www.nature.com/news/if-a-job-is-worth-doing-it-is-worth-doing-twice-1.12727 .

EPA's Science Advisory Panel ("SAP"). The SAP is EPA's external, expert peer review mechanism for pesticides. There is no basis for Dr. Hayes' insinuations in his comments about the "questionable motives" of this testing and SAP review. Objective, expert, lengthy and expensive SAP review has already rejected Dr. Hayes' tests.

We ask that this NRC committee keep EPA's reproducibility and IQA Guidelines and any comments on studies that have not been demonstrated to be reproducible in mind when reviewing EPA's NMDR Paper.

II. The NRC has already Explained the Data Quality Standards that Govern EPA and all other Federal Agencies

In April 30, 2013, the NRC released its report *Assessing Risks to Endangered and Threatened Species from Pesticides*.[4] The NRC prepared this report at the request of EPA, the U.S. National Oceanic and Atmospheric Administration ("NOAA")/National Marine Fisheries Service ("NMFS"), the U.S. Fish and Wildlife Service ("FWS"), and the U.S. Department of Agriculture ("Ag").

CRE submitted written comments to the NRC during its review and report preparation.[5] CRE's comments briefed the NRC on the four agencies' IQA Guidelines. CRE's comments explained to the NRC that it was commenting

> "because EPA, NMFS and FWS have not adequately briefed the Committee on the Government-wide data quality protocols and standards that govern their ecological Risk assessments under FIFRA and the ESA. CRE has long been a proponent of these protocols and standards, and helped establish some of them."[6]

We were gratified to see that the NRC report acknowledges the importance of IQA Guidelines. The report explains that

> "all federal agencies are expected to comply with the Office of Management and Budget (OMB) guidelines on objectivity, utility, and integrity of disseminated information. OMB (67 Fed. Reg. 8452 [2002]) describes those attributes as follows:

[4] The NRC report is available online at http://thecre.com/pdf/NRCesa.pdf.
[5] CRE's comments to the NRC are available online at http://www.thecre.com/forum1/?p=4569 . These previous CRE comments are incorporated by reference into CRE's comments on EPA's NMDR Paper.
[6] *Id*. at page 1. CRE is widely recognized as the leading champion of the DQA. An article in Naval Law Review, http://www.thecre.com/pdf/20120301_NavalLawReview.pdf, explained that the Information (Data) Quality Act "is the result of lobby efforts by Dr. James Tozzi, Multinational Business Services and the Center for Regulatory Effectiveness (CRE)."

> 'Objectivity' focuses on the extent to which information is presented in an accurate, clear, complete and unbiased manner; and, as a matter of substance, the extent to which the information is accurate, reliable and unbiased. 'Utility' refers to the usefulness of the information to the intended users. 'Integrity' refers to security, such as the protection of information from unauthorized access or revision, to ensure the information is not compromised through corruption or falsification.'
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> The Services and EPA (EPA 2002; FWS 2007) have separately published information quality guidelines (IQGs) that follow closely the government-wide OMB guidelines. Similar basic principles for achieving a scientifically credible assessment are prescribed in the IQGs from the agencies; the agencies are committed to ensuring the quality of evaluations and the transparency of information from external sources used in their disseminated assessments and actions (EPA 2003; NMFS 2005). They also recognize that a high level of transparency and scrutiny is needed for influential information that is expected to have a substantial effect on policies and decisions (EPA 2002; NMFS 2004; FWS 2007) [citing the Agencies' DQA Guidelines]."[7]

In this previous report, the NRC discussed the application of EPA's IQA Guidelines to ecological risk assessments because they were only asked to review ecological risk assessments. However, the NRC's discussion of these quality standards also applies to human health assessments because the EPA and OMB IQA Guidelines also apply to human health assessments.

EPA is subject to challenge if they use or rely on data/studies that do not comply with EPA's IQA Guidelines.[8]

III. Reproducibility

"*Non-reproducible* single occurrences are of no significance to science."
—Karl Popper

EPA's IQA Guidelines emphasize that the Agency will ensure reproducibility of influential information like the NMDR Paper:

[7] NRC Report, page 31, at http://thecre.com/pdfNRCesa.pdf.
[8] See, *e.g.,* http://epa.gov/quality/informationguidelines/index.html for Requests for Correction of EPA information disseminations that do not IQA Guidelines requirements.

"[O]ur Guidelines now include that EPA intends to ensure reproducibility for disseminated original and supporting data according to commonly accepted scientific, financial, or statistical standards."[9]

In the NMDR Paper that EPA sent to the NRC for review, EPA also emphasizes the importance of reproducibility: *e.g.*,

"Reproducibility of NMDRs is important in establishing plausibility of a response and its potential applicability as part of the hazard characterization. Factors that influence reproducibility include:

■ Study design - dose selection, sample size, organism strain, diet, housing environment, statistical methods;

■ Robustness of physiology – physiologic compensation producing changes in slope; and

■ Competing processes– induction of metabolism, repair, or independent mechanisms."

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"There is currently no reproducible evidence that the early key events involved in the expression of NMDRs that are identified at low dose are predictive of adverse outcomes that may be seen in humans or wildlife populations for estrogen, androgen or thyroid endpoints."

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"**4.2.1.1 Specific Considerations in Reviewing the Literature on E and A**

Evaluation of the data was done to determine the robustness of the NMDR. An NMDR was considered robust if it was reproducible and biologically plausible. In some cases, even though the NMDR was not reproduced in additional studies because they had not been done, it was still considered well supported based on its biological plausibility."

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"NMDRs would be problematic only if a chemical with estrogen, androgen, or thyroid activity produced an effect *in vivo* at a dose below those used in screening, and the chemical had no effect on estrogen, androgen, or thyroid related endpoints at the higher screening dosage levels. Although, such NMDRs have been hypothesized they have not been demonstrated reproducibly, and none were found in the present evaluation."[10]

The importance of reproducibility is also being emphasized by other federal agencies and by scientific journals.

For example, CRE recently posted a Nature article on one of its websites, which explains that

[9] EPA IQA Guidelines, page 21, at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf .

[10] NMDR Paper, pages 12, 15, 13, 85, at http://epa.gov/ncct/download_files/edr/NMDR.pdf .

reproducibility problems have led the National Institutes of Health ("NIH") to consider verification rules for some experiments:

> "The growing [reproducibility] problem is threatening the reputation of the US National Institutes of Health (NIH) based in Bethesda, Maryland, which funds many of the studies in question. Senior NIH officials are now considering adding requirements to grant applications to make experimental validations routine for certain types of science, such as the foundational work that leads to costly clinical trials. As the NIH pursues such top-down changes, one company is taking a bottom-up approach, targeting scientists directly to see if they are willing to verify their experiments."[11]

This Nature article explains some of the causes for concern:

> "In biomedical science, at least one thing is apparently reproducible: a steady stream of studies that show the irreproducibility of many important experiments.
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> In a 2011 internal survey, pharmaceutical firm Bayer HealthCare of Leverkusen, Germany, was unable to validate the relevant preclinical research for almost two-thirds of 67 in-house projects. Then, in 2012, scientists at Amgen, a drug company based in Thousand Oaks, California, reported their failure to replicate 89% of the findings from 53 landmark cancer papers. And in a study published in May, more than half of the respondents to a survey at the MD Anderson Cancer Center in Houston, Texas, reported failing at least once in attempts at reproducing published data…."[12]

Nature also recognizes reproducibility problems with articles it publishes. Nature is taking steps to try to ensure reproducibility in the data it publishes.[13]

Given these significant problems and the IQA Guidelines, EPA requires that journal articles and other data sources be demonstrated to comply with the reproducibility and other IQA requirements before EPA uses or relies on the articles and other data to assess and regulate NMDRs.

IV. The Hayes and Tillitt Data are Not Reproducible

EPA's NMDR Paper explains that the Agency

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[11] http://www.thecre.com/insurance/?p=1117 (reprinting article originally published in Nature Magazine).
[12] *Id.*
[13] See, *e.g.*, Announcement: Reducing our irreproducibility, at http://www.nature.com/news/announcement-reducing-our-irreproducibility-1.12852 ; Challenges in Irreproducible Research, at http://www.nature.com/nature/focus/reproducibility/ ; and If a Job is worth doing, It is worth doing twice, at http://www.nature.com/news/if-a-job-is-worth-doing-it-is-worth-doing-twice-1.12727 .

> " restricted the scope of our review and analysis to those chemicals with adequately described mode(s) of action as they pertain to the HPG axis. For example, due to uncertainties associated with the data from atrazine exposed amphibians and fish, we did not include those in our analysis Tillitt et al. (2010); Hayes et al. (2003)."[14]

Dr. Tyrone Hayes, co-author of "Hayes et al. (2003)," filed comments with this committee criticizing EPA's exclusion of atrazine from the NMDR Paper. According to Dr. Hayes:

> "[E]very Independent scientist that has examined atrazine finds consistent effects across all vertebrate classes, and a single research group funded by the manufacturer with questionable motives finds no effects."[15]

Dr. Hayes fails to mention or cite the eight (8) EPA Science Advisory Panels that have reviewed his work and most other available work on atrazine's effects. Three of those SAP's reviewed Dr. Hayes' atrazine tests. The reports of these three SAPs are available online at

- http://www.epa.gov/scipoly/sap/meetings/2003/june/junemeetingreport.pdf ;
- http://www.epa.gov/scipoly/sap/meetings/2007/october/finalminutes.pdf ; and
- http://www.epa.gov/scipoly/sap/meetings/2010/september/091410minutes.pdf.

Dr. Hayes personally commented at 2 of these SAPs. None of them concluded that his work or any of the work he relies on in his comments is reproducible.

The atrazine manufacturer Syngenta has a website which posts other studies that have been unable to reproduce Dr. Hayes' work:
http://www.atrazine.com/Amphibians/atrazine_amphibians_research.aspx .

Dr. Hayes' "single research group funded by the manufacturer with questionable motives" is apparently the atrazine amphibian effects study that was conducted at SAP request and pursuant to EPA order. It was reviewed by both the SAP and EPA. This study could not reproduce Dr. Hayes' test results, and there is no scientific basis to challenge its findings.

Given its importance to Dr. Hayes' comments, EPA's summary of this study is set forth at some length below:

> "In June 2003, after evaluating the available literature on the potential effects of atrazine on amphibian gonadal development, EPA concluded that there was sufficient information to formulate a hypothesis that atrazine exposure can affect amphibian gonadal development; however, there was insufficient information to refute or confirm that hypothesis, mainly because of the limitations of the study designs and uncertainties in the

[14] EPA's NMDR Paper, page 57 at http://epa.gov/ncct/download_files/edr/NMDR.pdf .
[15] Hayes comments, available at http://thecre.com/pdf/nmdrhayes.pdf . Dr. Myers' comments also criticize EPA for not including atrazine, but he defers to Dr. Hayes for most details. Myers Comments, available at http://thecre.com/pdf/nmdrmyers.pdf .

data. The agency's 2003 White Paper (PDF) (8 pp, 62k…) carefully evaluated the data from 17 laboratory and field studies, discussed remaining uncertainties in evaluating the potential effects of atrazine on amphibian development, and outlined future studies that could address these uncertainties. The FIFRA SAP reviewed EPA's White Paper and concluded that the agency's review was thorough, the conclusions were valid, and the approaches and criteria for new studies were appropriate. The SAP also agreed that additional studies were warranted and that a tiered testing approach was appropriate. In response to a November 2004 Data Call-In (DCI) Notice from EPA, Syngenta, the principal atrazine registrant, developed a testing protocol for determining the effects of atrazine on amphibian gonadal development, and conducted two studies consistent with the first tier of testing described in the 2003 White Paper and the SAP review. In June 2007, Syngenta submitted to EPA its final report regarding the potential effects of atrazine on gonadal development of amphibians.

To ensure the quality and transparency of its assessment of atrazine's potential to affect amphibian gonadal development, EPA solicited advice from the SAP at a second public peer review meeting on October 9 - 11, 2007. During this meeting, EPA presented its assessment of 19 laboratory and field studies, including the registrant-submitted studies and additional studies available in the public literature since the 2003 SAP. Of the 19 studies, only the two DCI studies submitted by the registrant incorporated all of the design elements recommended by the agency and the 2003 SAP to address uncertainties identified in the 2003 White Paper.

The 2007 SAP agreed with the agency that, although both DCI studies contained some limitations, the overall design and conduct of the studies reflected a high degree of quality control that allowed them to be used to evaluate whether or not atrazine exposure affects amphibian gonadal development. The 2007 SAP also agreed with the agency that other laboratory and field studies reviewed by the agency did not fully account for experimental and environmental conditions that could influence relevant endpoints.

The SAP Panel concluded at that time that atrazine does not produce consistent, reproducible effects on the gonadal development of amphibians; however, the Panel recommended that EPA continue to be apprised of ongoing research and review any new data. The 2007 SAP's final report and recommendations are available in public docket EPA-HQ-OPP-2007-0498."[16]

Dr. Hayes' insinuations about the "motives" of this study are disturbing. He appears to be attacking the integrity of EPA's Science Advisory Panels.

The SAPs are similar to this NRC committee. They are statutorily required and consist of objective, non-agency experts who are asked by EPA to review specific scientific questions relating to EPA's regulation of pesticides. EPA's SAP website explains:

"The FIFRA SAP is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (http://www.accessreports.com/statutes/FACA.htm).

[16] http://www.epa.gov/pesticides/reregistration/atrazine/atrazine_update.htm#amphibian .

> The Panel serves as the primary scientific peer review mechanism of the United States Environmental Protection Agency (EPA), Office of Prevention, Pesticides and Toxic Substances and is structured to provide scientific advice, information and recommendations to the EPA Administrator on pesticides and pesticide-related issues as to the impact on health and the environment of regulatory actions…."
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> "FIFRA [the federal pesticides statute] requires that the Panel be composed of seven members appointed by the EPA Administrator, with nominees provided by the National Institutes of Health and National Science Foundation. SAP members serve a four-year term, utilizing a system of staggered terms of appointment."[17]

Additional ad hoc nominees are also selected for specific review projects.

SAPs play an essential role as expert external peer reviewers for EPA. There is no legitimate basis for challenging their motives or otherwise impugning their integrity.

EPA's NMDR Paper also cites data uncertainties in Tillitt 2010 as a reason for not including atrazine in the NMDR Paper. Dr. Hayes' comments also object to the exclusion of the Tillitt data.

According to the atrazine manufacturer Syngenta, the Tillitt data are not reproducible:

> "Investigations of the risk of atrazine on fish reproduction, as called for by Tillitt et al. (2010) in a USGS report, have already been conducted in multiple multi-generational tests. The results of these extensive long-term studies demonstrate the safety of atrazine to fish populations. The results reported by Tillitt are inconsistent with the results of four full life-cycle fish studies which report no effects on reproduction, two of which were for the same species (fathead minnow) of fish. These four studies were conducted using a standard protocol, reviewed and accepted by the U.S. EPA.
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> In addition, other studies conducted report no effect on fish. A U.S. EPA (2005) study was conducted using methods similar to those of Bringolf et al. (2004) and Tillitt. Results indicate that atrazine exposure to levels as high as 223 milligrams per liter (the highest concentration tested) had no effect on reproduction."[18]

VI. Conclusion

The American Chemistry Council's comments to this committee state that

> "All scientists – those from academia, government, industry and non-government organizations– should agree that decisions about the safety of chemicals in commerce

[17] http://www.epa.gov/scipoly/sap/pubs/about.htm .
[18] http://www.atrazine.com/news_releases/news.aspx?id=118147 .

must be based firmly on reproducible scientific studies and the weight of scientific evidence."[19]

We agree with this comment. We further reiterate that EPA can only use or rely on data and studies that comply with EPA's IQA Guidelines*: e.g.,* they must be demonstrated to be reproducible.

We ask that this committee keep the reproducibility and other IQA Guidelines requirements in mind during its review of EPA's NMDR Paper and the comments on it.

We thank you for the opportunity to submit these comments.

The Center for Regulatory Effectiveness
www.theCRE.com

[19] ACC comments, page 3, at http://thecre.com/pdf/nmdracc.pdf .