Comments by Center for Regulatory Effectiveness ("CRE") on Registration Review, Pesticide Dockets Opened for Review and Comment, Atrazine (Case 0062) ("Atrazine Review"), http://www.gpo.gov/fdsys/pkg/FR-2013-06-26/pdf/2013-15325.pdf . Comments filed on August 26, 2013, Document ID EPA–HQ–OPP–2013–0266 at www.regulations.gov .

I. Executive Summary

EPA's Atrazine Review should document its compliance with EPA's Information Quality Act ("IQA") Guidelines. For example, EPA should document that the Atrazine Review and any atrazine consultations under the Endangered Species Act ("ESA") comply with the IQA Guidelines as expounded by the National Research Council's ("NRC") report *Assessing Risks to Endangered and Threatened Species from Pesticides*.[1] EPA should also document that the Atrazine Review and any atrazine consultations under the ESA comply with EPA's Council for Regulatory Environmental Models ("CREM") Guidance.[2]

EPA should ensure the reproducibility of any data or studies that EPA uses or relies on in the Atrazine Review. Reproducibility is required by EPA's IQA Guidelines, and EPA has emphasized the importance of reproducibility in recent communications with the NRC. The lack of reproducibility in many of its sponsored studies is prompting remedial action by the National Institute of Health ("NIH").

Lack of reproducibility is also a major problem with studies published in peer-reviewed journals like Nature. Nature has acknowledged this problem and is taking steps to solve it. EPA should not presume that peer-reviewed journal articles meet reproducibility and other IQA Guidelines requirements. EPA should require that journal articles demonstrate compliance with reproducibility and other IQA Guidelines requirements before EPA uses them in the Atrazine Review or anywhere else.

II. EPA's Atrazine Review Should Document Its Compliance with IQA Guidelines and with CREM Guidance

EPA's IQA Guidelines apply to all information disseminations related to the Atrazine Review.[3] EPA's record for the Atrazine Review should contain publicly available documentation of the

[1] The NRC report is available online at http://thecre.com/pdf/nasesa.pdf .
[2] The CREM Guidance is available online at http://www.epa.gov/crem/library/cred_guidance_0309.pdf .
[3] EPA's IQA Guidelines are available online at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf .

Review's compliance with all aspects of the IQA Guidelines, including but not limited to the Guidelines' pre-dissemination review requirements.[4]

According to EPA, "the CREM Guidance on the Development, Evaluation and Application of Environmental Models (PDF) , provides recommendations for effective use of models in environmental decision making. The draft guidance incorporates recommendations from Agency white papers, EPA's Science Advisory Board reports, and peer reviewed literature. It includes recommendations on model development, evaluation and application."[5]

EPA's record for the Atrazine Review should contain publicly available documentation of the Review's compliance with the CREM Guidance, which should be viewed as part of EPA's IQA Guidelines' requirements.

III. EPA's Atrazine Review Should Document Its Compliance with the NRC Ecological Risk Assessment Report

In April 30, 2013, the NRC released its report *Assessing Risks to Endangered and Threatened Species from Pesticides*.[6] 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.

This NRC report provides the model for all ecological risk assessments by EPA. EPA should follow it during the Atrazine Review. EPA and the Services should follow it during any ESA consultations involving atrazine.

CRE submitted written comments to the NRC during its review and report preparation.[7] CRE's comments briefed the NRC on the four agencies' IQA Guidelines. CRE's comments explained to the NRC that it was commenting on the IQA

[4] See, *e.g.*, EPA IQA Guidelines, Section 7, Administrative Mechanism for Pre-dissemination Review, available online at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf ; EPA's Data Quality Act/Information Quality Guidelines Quality Management Training Module, pages 20-22, at http://www.epa.gov/greatlakes/quality/training/guidelines/qa_guidelines.pdf ; and EPA's PRE-DISSEMINATION REVIEW GUIDELINES: Review Guidelines to Ensure That Disseminated Information Is Consistent with EPA Information Quality Guidelines, at http://www.epa.gov/region2/science/qmp/pdfs/pdr-guidelines.pdf .

[5] http://www.epa.gov/crem/model-evaluation.html .

[6] The NRC report is available online at http://thecre.com/pdf/nasesa.pdf.

[7] 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 the Atrazine Review.

> "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."

We were gratified to see that the NRC report at page 31 acknowledges the importance of IQA Guidelines:

> "[A]ll 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:
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> > '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.'
>
> 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]."

In addition to data quality, the NRC report at pages 109-110 establishes the following principles for risk characterization:

> "● Inclusion of uncertainty factors to account for lack of various data is unwarranted because there is no way to determine whether the assumptions being used substantially overestimate or underestimate the probability of adverse effect.
>
> ● RQs [risk quotients] are not appropriate for risk assessments or for any application in which it is desired to base a decision on the probabilities of the various possible outcomes.
>
> ●Scientifically defensible, statistical methods should be used to calculate risk as a probability to assist decision-makers' understanding of the potential consequences of their decisions.

● A number of existing probabilistic methods have been shown to be applicable and practical for ecological risk assessments that involve pesticides.

● The transition from concentration-ratio to probabilistic approaches should begin now, focusing on a small set of sensitive key parameters, and drawing on the considerable literature and guidance on probabilistic approaches."

With regard to sublethal effects, the NRC report concludes and recommends at page 96:

"● An adverse effect should be defined by the degree to which an organism's survival or reproduction is affected; thus, assessing the effects of a pesticide on a listed species requires quantifying the effect of the pesticide on survival and reproduction of the species in the wild. Any effect that results in a change in survival or reproduction is relevant to the assessment, and any effect that does not change either outcome is irrelevant with respect to a quantitative assessment of population effects.

● To determine whether a pesticide is 'likely to adversely affect' a listed species, a broad search should be conducted to identify information on sublethal effects of the pesticide and possible concentration-response relationships.

●To provide information to support a jeopardy determination, the Services should either (a) show how sublethal effects change survival or reproduction and incorporate such information into the population viability analysis or (b) state that such relationships are unknown but possible and include a qualitative discussion of uncertainty in the BiOp."

EPA explains on one of its websites that:

"The four agencies [EPA, NMFS, FWS and Ag] are working collaboratively and expeditiously to review the [NRC] report and identify improvements in the current scientific procedures used in evaluating the potential impacts of pesticides to endangered and threatened species. The Federal agencies will develop an implementation plan within the next 90 days to provide a timeline and approach for responding to the panel's recommendations and implementing the appropriate revisions to these procedures and approaches. The plan will be available to the public."[8]

CRE looks forward to commenting on this implementation plan before the four agencies finalize it.

[8] http://www.epa.gov/espp/nas-report.html .

IV. Reproducibility Should Be Required in the Atrazine Review

"Non-reproducible single occurrences are of no significance to science."
—Karl Popper[9]

During the Atrazine Review, EPA should only use and rely on studies or data that have been demonstrated to be reproducible. EPA's IQA Guidelines emphasize that the Agency will ensure reproducibility:

> **"**[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."[10]

EPA also emphasized the importance of reproducibility in the Non-Monotonic Dose Response ("NMDR") Paper that EPA sent to NRC for review: *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**
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> 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." [11]

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[9] Popper, K. R. 1959. The logic of scientific discovery. Hutchinson, London, United Kingdom
[10] EPA IQA Guidelines, page 21, at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf .
[11] Pages 12, 15, 85, EPA's NMDR White Paper, at http://epa.gov/ncct/download_files/edr/NMDR.pdf .

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 reproducibility problems have led 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."[12]

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…."[13]

Nature has also recognized the reproducibility problems with articles it publishes. Nature is taking steps to try to ensure reproducibility in the data it publishes.[14]

Given these problems, EPA should require that journal articles be demonstrated to comply with the reproducibility and other IQA Guidelines requirements before EPA uses or relies on the articles in the Atrazine Review.

EPA's IQA Guidelines and the sound science they represent require that EPA also ensure the reproducibility of any data or studies that EPA uses or relies on in the Atrazine Review.

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[12] http://www.thecre.com/insurance/?p=1117 (reprinting article originally published in Nature).
[13] *Id.*
[14] 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 .

We thank you for the opportunity to submit these comments, and we look forward to EPA's response to them.

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