

The Center for Regulatory Effectiveness

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Re: Request for Joint Development of Standard Operating Procedures If Epidemiological Data is used in Pesticide Assessment and Registration

Dr. Kunickis and Ms. Vaught:

The U.S. Environmental Protection Agency has rarely used epidemiological data to assess and register pesticides under FIFRA. The Department of Agriculture correctly explained to the EPA that, “if epidemiological studies are to form the basis of the FQPA factor, a new standard operating procedure is needed.”¹ These new procedures should not be limited to pesticide safety factors because Standard Operating Procedures are necessary for any use of epidemiological data during pesticide assessment and registration.

The aforementioned procedures should be developed through public notice and comment procedures. Furthermore, they should be externally peer reviewed and developed in close cooperation with the USDA.

¹Page 2 of 18, at <http://www.thecre.com/forum1/wp-content/uploads/2016/04/usda-april-2016-SAP-comments-1.pdf>

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This is the best and perhaps only way to ensure that pesticide epidemiological data comply with the Data (Information) Quality Act (“DQA”) and with related EPA quality requirements. Prudent use of the DQA is a proven way to produce scientifically sound conclusions.

This joint, open and informed development of Standard Operating Procedures is the only way to use epidemiological data that is consistent with the EPA’s previous statements on this topic. In particular the 2010 Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment illustrates this point:

“Consistent with Administrator Lisa Jackson’s commitment to transparency and scientific integrity, OPP’s goal is to use such [epi] information in the most scientifically robust and transparent way. To accomplish this, OPP is proposing a framework to describe the scientific considerations that EPA will weigh in evaluating how such studies and scientific information can be integrated into risk assessments of pesticide chemicals. This draft framework along with the draft case studies (Attachments A-C) will be reviewed by the FIFRA Scientific Advisory Panel (SAP) and will receive public comment in February, 2010. Subsequently, OPP will evaluate the comments from the Panel and public and make the appropriate revisions to the framework.”²

Ms. Jackson is no longer the EPA Administrator, but it is safe to conclude that Administrator McCarthy is also committed “to transparency and scientific integrity.” In the case of epidemiological data the EPA correctly concluded that this commitment requires Standard Operating Procedures, or in their terms: “a framework.”

The USDA has developed substantial expertise and knowledge in this area. The Department is an active proponent of epidemiological Standard Operating Procedures and it has already offered to assist the EPA in the development of epidemiological procedures. A collaboration with the USDA would take some of the burden off the EPA by greatly enhancing the process and ensuring a diversity of views.

Several SAPs have already provided excellent recommendations about what epidemiological Standard Operating Procedures should include.³ For example, they should require:

- Public availability of raw data;

² Page 6, at <http://www.thecre.com/forum8/wp-content/uploads/2016/05/EPA-Framework.pdf> (footnote omitted).

³ See <https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0274-0064> (2008 Final Report; <https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0851-0059> (2010 SAP Minutes); <https://www.epa.gov/sites/production/files/2015-06/documents/041012minutes.pdf> (2012 SAP minutes); and https://www.epa.gov/sites/production/files/2016-05/documents/fifra_sap_04_19_16_to_04_21_16_final_transcript.pdf (2016 SAP meeting transcript).

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- Validation of all methods;
- Replication/reproducibility of results;
- Biological plausibility;
- Consistency with animal data;
- Adequate statistical power;
- Ability to generate a dose response; and
- No reliance on only one study.

These quality standards are required by

- the 2008, 2010, 2012 and 2016 SAPs; ⁴
- the Data Quality Act and EPA's related quality requirements;⁵
- OMB Circular A-110 data/property standards; ⁶
- EPA's CREM modeling guidance;⁷ and
- Public comment, including the USDA's very critical comments on EPA's ad hoc approach to the Chlorpyrifos epi data.⁸

Until Standard Operating Procedures are developed through a joint, open and informed manner, EPA should not use epidemiological data during pesticide assessment and registration. Should the EPA use such data, they must certify in the administrative record that they have complied with the quality standards required by the DQA and SAP Reports discussed in this letter. This certification should identify evidence of compliance in the administrative record.

Development of Standard Operating Procedures in this manner is an efficient and comprehensive approach to the issue. This is in contrast to using epidemiological data on

⁴ See *Id.*

⁵ See EPA's quality site, at <https://www.epa.gov/quality>

⁶ Subpart C, Post-Award Requirements, Property Standards, Intangible Property, 36 (c), (d), at https://www.whitehouse.gov/omb/circulars_a110/

⁷ https://www.epa.gov/sites/production/files/2015-04/documents/cred_guidance_0309.pdf

⁸ <http://www.thecre.com/forum1/wp-content/uploads/2016/04/usda-april-2016-SAP-comments-1.pdf>

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a case-by-case basis without any prior guidance, as the EPA tried with Chlorpyrifos, an approach that was rejected by Science Advisory Panels (“SAP”).

The aforementioned points are discussed in detail below.

EPA’S SCIENTIFIC ADVISORY PANELS HAVE REJECTED EPA’S CURRENT AD HOC AND UNPRINCIPLED APPROACH

The transcript for the 2016 SAP includes many criticisms of EPA’s attempt to use the Chlorpyrifos cord blood data.⁹ Some of them follow:

Dr. Sheryl Kunickis (USDA, pages 413, 415)

“This is a major shift in pesticide regulation and there are major potential impacts: the cost to our food supply, to our economy, to taxpayers and to low-income Americans.

We at USDA stand ready to have further dialog and assist in the technical details of this issue. In particular, we believe further interagency discussions regarding the capabilities and limitations that the Columbia study -- of the epi study and of epi studies, in general, would be a useful dialog.”

“As I stated in the beginning, the implications for the outcome of these questions you’re answering are profound with potential costs to our food supply, to our economy, to taxpayers, to low-income Americans. We’d like to work with you to further ensure that the very best science-based policy is the outcome.”

Dr. Sarah Starks (commenter, pages 332-33):

“So why is this an important issue for us? Well, as was alluded to earlier, the EPA’s use of human epi data in the absence of toxicological data for quantitative risk assessment is precedent-setting.

The EPA has relied on the Columbia study which is a single, unreplicated epidemiology study that is not designed for quantitative risk assessment.

⁹ The 2016 SAP transcript is available at https://www.epa.gov/sites/production/files/2016-05/documents/fifra_sap_04_19_16_to_04_21_16_final_transcript.pdf

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The EPA has excluded a very robust animal toxicological database of studies that have been conducted following accepted test guidelines that have been the historic foundation for pesticide risk assessment. And furthermore, there is a lack of plausible mode of action for the hypothesized association of exposure and neurobehavioral outcomes.

Also, I think it's important to remind the Advisory Panel that the conclusions from this panel and how you address the charge questions may very well likely support establishment of policy for future human health risk assessment approaches which will greatly impact regulatory decision-making."

Dr. James McManaman (SAP member, page 762-63)

"I think that this panels heard a variety of data both from the agency and from public commenter's that lead us to believe that there is a lot of uncertainty in terms of using the neurodevelopmental data as a point of departure as proposed...[T]he panel from 2012 additionally notes that studies evaluating neurodevelopmental effects entailed experimental designs that do not permit an efficient means of determining a point of departure for chlorpyrifos."

Dr. Marion Ehrich (SAP member, page 766)

"Just a general comment. In order for a registrant to put a new pesticide on the market or to re-register a pesticide the data has to be very rigorous. Now we're looking at something the opposite."

"So if we're basing this on one study where it's not been reproduced, you can't get the actual hard data, there's lots and lots of points below levels of detection, one has to give that really serious thought."

Dr. Sonya Sobrian (SAP member, page 767)

"I think if you want to use epidemiological data I think there should be some scheme for systematic evaluation of the

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strength of the different studies so people can see how you chose to use study one versus study three.”

Dr. Alvin Terry (SAP member, page 769)

“...I don’t believe epidemiology alone should drive the decision of such magnitude like this.”

The 2012 SAP also criticized the Chlorpyrifos epidemiological data for not meeting basic quality standards. The report explains that:

“[S]ome panel members expressed concern about associating the observed deficits in neurodevelopmental outcomes in children with a single chemical. This is because the studies entail a multi-chemical exposure spanning a multi-year period that encompasses an important period of sequential developmental processes necessary for brain maturation. Thus, panel members caution that it is very difficult to attribute the independent physiological effects to a single chemical in this type of multi-chemical exposure scenario. An additional concern raised by the Panel is the modest sample sizes of the studies. They deem inadequate sample size as one of the most important limitations of these studies.”¹⁰

In 2010, the EPA held a SAP devoted in part to “Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment.” The entire SAP report is a valuable guide to the quality standards that govern the use of epi data for pesticides.¹¹

DEVELOPMENT OF STANDARD PROCEDURES SHOULD BE OPEN, TRANSPARENT AND RECORDED

The EPA’s epidemiological Standard Operating Procedures should be developed publicly through a fully transparent process rather than through closed invitation-only workshops with no public record. The difference between both processes can be found by examining two papers published in the scholarly journal, *Environmental Health Perspectives*.

The 2016 EHP article, “Informing 21st-Century Risk Assessments with 21st-Century Science”¹² is based on an invitation-only meeting that took place July 15–16, 2015, in Research Triangle Park, North Carolina. We have been unable to find any online record

¹⁰ Pages 17-18, at <https://www.epa.gov/sites/production/files/2015-06/documents/041012minutes.pdf>

¹¹ See, e.g., 2010 SAP Minutes, pages 8-11, at <https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0851-0059>

¹² <http://ehp.niehs.nih.gov/15-11135/>

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of the presentations at this meeting as well as any public invitation, agenda, or list of attendees.

On the other hand, the 2014 EHP article, “Evaluating Uncertainty to Strengthen Epidemiologic Data for Use in Human Health Risk Assessments,” is based on a transparent process. This article states that it “derives from a workshop held in Research Triangle Park, North Carolina, in October 2012 to discuss the utility of using epidemiologic data in risk assessments, including the use of advanced analytic methods to address sources of uncertainty.”¹³ Unlike the 2016 *EHP* article, the 2014 *EHP* article includes authors from the public and it is not limited to select government officials.

The aforementioned *EHP* articles are inconsistent. The 2014 article emphasizes the uncertainties and data quality concerns that must always be addressed when considering the use of epidemiological data.

By contrast, the 2016 *EHP* article paints a much rosier picture of the use of epidemiological data in risk assessments. It does not even mention the 2014 *EHP* article or the 2010 Draft Framework. Were the 2016 authors aware of these two important documents on this issue? Did they deliberately ignore them in order to avoid any obstacles to the use of epidemiological data?

EHP includes the following disclaimer on its website:

“Publication of articles in *EHP* does not mean the NIEHS condones, endorses, approves, or recommends the use of any products, services, materials, methodology, or policies stated therein. Conclusions and opinions are those of the individual authors and advertisers only and do not reflect the policies or views of the NIEHS.”¹⁴

Two of the authors of the 2016 *EHP* article are EPA officials. Does this Disclaimer mean that the views stated in the article are only theirs, and not the EPA’s? Is this even a meaningful distinction given their ranking positions at the EPA?

Given the EPA’s discontinued work on the 2010 Draft Framework, we are concerned that the agency seems to have abandoned transparency and is instead making epidemiological policy behind closed doors.

The aforementioned lack of transparency should be discarded and instead the EPA should implement a completely public and open process--with a public record for later use—which will ensure a comprehensive review of the pros and cons of the use of epidemiological data. A transparent process is necessary in order to promote DQA compliance and provide “transparency and scientific integrity,” to use the EPA’s own words in the 2010 Draft Framework.

¹³ <http://ehp.niehs.nih.gov/1308062/>

¹⁴ <http://ehp.niehs.nih.gov/journal-information/>

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THE 2010 DRAFT FRAMEWORK IS A GOOD PLACE TO START

The SAP review of the EPA's Draft Framework exemplifies this open and transparent process that is necessary. There was a Federal Register notice of this SAP meeting and there is a permanent online transcript of the report. Furthermore, the public was able to attend and comment to the SAP.

The 2010 Draft Framework and the resultant SAP report represents considerable time, resources and dedicated work by a large cadre of talented scientists and the interested public. There is no justification for the EPA's apparent abandonment of all this work and knowledge. Consequently, the agency's development of epidemiological Standard Operating Procedures should begin with the 2010 Draft Framework.

The Draft Framework relies heavily on modified Bradford Hill Criteria.¹⁵ The 2010 SAP supported using the Bradford Hill Criteria as a starting point. The report offered additional criteria for determining whether epidemiological data can be used for a regulatory purpose:

- A. Was the epidemiologic study conducted primarily in a hypothesis generation or a hypothesis testing mode?
- B. Was the method of assessing exposure accurate and reliable?
- C. Were inclusion and exclusion criteria clearly stated and reasonable to provide a representative sample with regard to exposure and health outcome so as to provide a relatively unbiased and representative estimate of effect?
- D. Was the method of assessing the criteria for determining the health outcome clearly stated, valid, and reliable; e.g., confirmed with histopathology, and were they designed to detect newly diagnosed (rather than prevalent) cases so that it was reasonably possible to determine the exposure preceded disease?
- E. Was appropriate information on potential confounding factors, such as socio-demographic, behavioral and dietary factors collected for both exposed and unexposed groups for cases and controls in the same way, and were they appropriately controlled in the analyses of the data? Were data on co-morbid conditions collected? (i.e., factors that are associated with the health condition of interest as well as factors associated with exposure).
- F. Did the study sample the population or individuals of interest? (i.e., was selection bias minimized and generalizability optimized?) How does the study population relate to the universe of potentially exposed populations?

¹⁵ See pages 9, 27, 28, and 33, at <http://www.thecre.com/forum8/wp-content/uploads/2016/05/EPA-Framework.pdf>

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G. Did the study examine individuals with a wide range of exposures? (i.e., ability to detect a dose-response and to generalize to other populations) Did the study include unexposed populations or individuals?

H. Did exposures examined in the study relate to past or current situations? (e.g., acute versus chronic exposures and the targeted health end points)

I. Did the study have adequate statistical power to detect meaningful differences for outcomes between the different groups of exposed and unexposed or less exposed individuals while controlling for important confounding factors? Does the sample size take into account the expected incidence of the target health effect in the study populations? (e.g., Page 13, 7th bullet of the EPA Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment [January 7, 2010] – specify the statistical power of the sample size to detect an effect after adjusting for confounders). Was the study powerful enough to detect as statistically significant meaningful differences while adjusting for confounding variables and exposure measurement error which typically reduce statistical power?¹⁶

These SAP criteria should be part of the EPA's epidemiological Standard Operating Procedures.

CONSIDER THE LONDON PRINCIPLES

In the mid-nineties, a similar issue surfaced regarding the potential use of epidemiological studies in conducting risk assessments for chemicals introduced into the market place. The issues raised at that time regarding the shortcomings of epidemiological studies are similar to those being discussed now for pesticides.

In response to these concerns, Federal Focus, the non-profit research foundation affiliate of the Center for Regulatory Effectiveness, recognized the need for uniform epidemiology principles and convened a conference of 19-member expert panel members in 1994. The papers from that conference were compiled and edited by Professor John Graham and published by Elsevier Science B.V. in *The Role of Epidemiology in Regulatory Risk Assessment*, ISBN 0-444-82201-1.

In 1995, a second 18-member expert panel met in London, England, and drafted a set of such principles -- often referred to simply as the "London Principles." Federal Focus staff prepared a conference report incorporating both the Principles and separate

¹⁶ Pages 16-17, at <https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0851-0059>

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recommendations for risk assessment guidelines to implement the intent of the Principles.¹⁷

The aforementioned [panel](#) consisted of a number of the nations' most influential toxicologists and epidemiologists.

The *London Principles* are available [here](#).

The London Principles and the record of their development should be useful to development of the EPA's epidemiological Standard Operating Procedures.

LEVERAGE AGENCY-WIDE AND INTER-AGENCY EXPERTISE AND RELY ON THE SAP

The EPA has the good fortune of having a wide range of expertise in the relevant subject areas. EPA personnel have a long-standing regulatory responsibility in pesticide issues. The Office of Children's Health Protection has also been involved. Other operating elements within the EPA should have input to the decision process comparable to the OCHP. The Associate Administrator for Policy should also be heavily involved in the development of epidemiological Standard Operating Procedures because this Office is the primary policy arm of EPA, and it provides multi-disciplinary skills to interagency reviews.

For reasons stated above, the USDA should be involved in the development process, including but not limited to USDA's Office of the Chief Economist, which includes the Office of Risk Assessment and Cost-Benefit Analysis.¹⁸

Any interagency review of the methods to integrate epidemiological data into risk assessment should, in addition to utilizing the talented staff of the OPP, enlist personnel in the Office of Science Policy, the National Center for Computational Toxicology and the National Center for Environmental Assessment.

Finally, the EPA should provide ample opportunity for public comment, and review by at least one SAP and preferably multiple SAPs.

¹⁷ *Principles for Evaluating Epidemiologic Data in Regulatory Risk Assessment*, ISBN 0-9654148-0-9, and "Recommendations for Implementing the 'London Principles' and for Risk Assessment Guidance," Federal Focus 1996.

¹⁸ See USDA Office of Chief Economist site at http://www.usda.gov/oce/risk_assessment/

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CONSEQUENCES OF NOT DEVELOPING STANDARD OPERATING PROCEDURES

Failure to develop Standard Operating Procedures before using epidemiological data for pesticide assessment and registration will cause unnecessary delay, confusion, inconsistencies and bad science. These wholly avoidable results would violate the Data Quality Act and a number of other good government laws.

For example, the EPA must demonstrate that the agency's information disseminations containing epidemiological data meet DQA standards, including DQA pre-dissemination review requirements.¹⁹ As discussed above, multiple SAPs have provided specific guidance to the agencies on the quality standards necessary for epidemiological data during pesticide assessment and registration.²⁰ These SAP reports provide a foundation for DQA compliance in the event epidemiological data is used for product specific reviews. The EPA's disregard of the SAP reports would violate the DQA and violations of the DQA requirements are subject to Requests for Correction.²¹

As another example, the EPA will need OMB to approve new Information Collection Requests ("ICR") for any pesticide assessments and registrations using epidemiological data. During its ICR review, OMB "reviews the extent to which the information collection is consistent with applicable laws, regulations, and policies related to privacy, confidentiality, security, **information quality**, and statistical standards."²² OMB will not approve epidemiological ICRs if they don't meet DQA standards.

As a final example, the launch of an entirely new approach to the pesticide registration process that incorporates epidemiological data is in fact a rule, not sub-regulatory guidance. It will, therefore, be subject to review by OMB under Executive Order 12866.²³

¹⁹ See, e.g., EPA IQA Guidelines, Sections 1 and 7, at <https://www.epa.gov/sites/production/files/2015-08/documents/epa-info-quality-guidelines.pdf>

²⁰ See <https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0274-0064> (2008 Final Report); <https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0851-0059> (2010 SAP Minutes); <https://www.epa.gov/sites/production/files/2015-06/documents/041012minutes.pdf> (2012 SAP minutes); and https://www.epa.gov/sites/production/files/2016-05/documents/fifra_sap_04_19_16_to_04_21_16_final_transcript.pdf (2016 SAP meeting transcript)

²¹ See, e.g., EPA IQA Request for Correction site at <https://www.epa.gov/quality/epa-information-quality-guidelines-requests-correction-and-requests-reconsideration>

²² OMB/OIRA ICR FAQ website, at <http://www.reginfo.gov/public/jsp/Utilities/faq.jsp> (emphasis added). See also EPA ICR site at <https://www.epa.gov/icr>

²³ See, e.g., Executive Order website at http://www.reginfo.gov/public/jsp/Utilities/EO_Redirect.jsp

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REQUESTED ACTIONS

CRE requests that the EPA and the USDA co-chair an interagency working group charged with the development of Standard Operating Procedures for using epidemiological data during pesticide assessment and registration.

The discharge of this responsibility must be achieved by the direct actions of the two affected agencies, **not** by contracting with a third-party who is not subject to the Federal Advisory Committee Act.

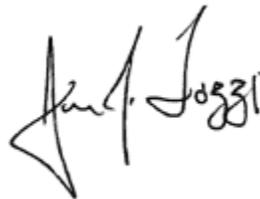
The EPA should provide for ample public participation in this process.

The EPA should charge the SAP with reviewing drafts of the Standard Operating Procedures for the use of epidemiological data.

Until the EPA has published final epidemiological Standard Operating Procedures that result from the process discussed above, they should not use epidemiological data for pesticide assessment and registration. In all cases involving the use of epidemiological data, the EPA should always certify in the administrative record that they have complied with the quality standards required by the DQA and SAP Reports discussed in this letter. This certification should identify evidence of compliance in the administrative record for each and every use.

With respect to the Government Performance and Results Act of 1993 (GPRA), the EPA IG states: “EPA is considered a leader in implementing GPRA because of the innovative approach it has taken to align its planning, budgeting, analysis and accountability processes.”²⁴ To this end, CRE requests that the EPA amend its National Program Manager Guidance (VII. PROGRAM-SPECIFIC GUIDANCES FOR THE OFFICE OF PESTICIDES PROGRAMS) to include the development of Standard Operating Procedures for use of epidemiological data in pesticide assessment and registration.²⁵

Respectfully submitted,



²⁴ Page 3, at <https://www.epa.gov/sites/production/files/2015-12/documents/gpra.pdf>

²⁵ EPA’s National Program Manager Guidance is at https://www.epa.gov/sites/production/files/2015-04/documents/ocspg_final_2016-2017_national_program_manager_guidance2.pdf

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