

Doherty EPI Study Proposal

February 27, 2018

Subject: Proposal for the Review of Epidemiology Studies from the Open Literature Being Considered for a Basis for Regulatory Action

To: Office of Pesticide Program Managers

From: John D. Doherty, Ph.D.  
(DABT: 1982-2017)

Email: Ex. 6

With regard to the situation that has developed over the past several years with chlorpyrifos that is mainly based on an epidemiology report from Columbia University, I would like to make the following proposal for reviewing epidemiology studies to minimize controversy in the future. Quite frankly, based on my rather rocky participation in the chlorpyrifos project until I was ordered to terminate all review work on this chemical, I rather strongly believe that the current situation could well have been prevented or at least minimized.

In particular, the review process in which an epidemiology study (or any study that appears in the open literature) needs to be standardized before any decision with regard to its use in the regulation of the chemical is deemed appropriate and necessary.

**A Call for the Standardization of the Review of an Epidemiology Report in the Open Literature – Production of the Record of Review (ROR)**

To achieve this end, I would like to introduce the following procedure:

The study needs to have a formal record of review (ROR) with a series of signatures of representatives for the several subdisciplines that are involved in the support of the conclusions of the study. In addition, a signature of a senior program official would be required. The roles of the several committees and individuals that would be signing the ROR are as follows:

1. **Endpoint Evaluation Committee:** Depending upon the lesion/condition claimed by the publication, the endpoint evaluation would be an expert committee in cancer, behavioral response, or other appropriate committee for interpretation of the significance of the lesion/condition. This evaluation should not be left to one individual.

This evaluation would limit its conclusions with regard to how well the character of the endpoint was assessed for and whether or not the data presented supports the increase in the lesion/condition reported. Some conclusion examples would be as follows:

The study supports the associated of *chemical* with an increase in lesion/condition.

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There are problems with the identification of the lesion/condition to render a conclusion for an association between *chemical* and the lesion/condition unsupported. (Refer to pages --- of this ROR).

**2. Statistical Evaluation Committee:** The sole role of the statistical evaluation is limited to determining if the statistical methods were/were not appropriate and adequately conducted to support the conclusion of the report. A committee of statisticians with expertise in epidemiological studies may need to be established for this evaluation. Although statisticians may disagree about the methods, it is problematic to have just one statistician make this decision. Some conclusion examples would be as follows:

The statistical methods were/were not appropriate and adequately conducted.

The statistical methods were appropriate but there was insufficient information available to determine if the statistics were adequately conducted and the study conclusions are not supported. (refer to pages --- of this ROR).

The statistical methods were in appropriate and the study conclusions are not supported. (Refer to pages ---- of this ROR).

**3. Exposure Assessment Committee:** The role of the exposure assessment committee is limited to determining that the methodology used to determine the exposure of the cohort is adequate and appropriate. Some conclusion examples would be as follows:

The exposure of the individuals in the study cohort was adequate to support the association between *chemical* and lesion/conclusion.

There were serious problems with the assessment of the individuals in the cohort for exposure to *chemical* such that the conclusions of the study could not be supported. For example, some of the exposure information was obtained via telephone calls and relatives of the allegedly exposed person provided the information long after the exposure was alleged to occur. Refer to pages ---- of this ROR.

There was insufficient information to eliminate confounding factors such as simultaneous exposure to other chemicals to conclude that *chemical* is associated with lesion/condition.

**4. Analytical Chemistry Assessment Committee:** The role of the analytical chemistry committee is limited to determining if the analytical techniques/methodology was appropriate and adequate for the study. Some conclusion examples would be as follows:

The methods of analysis were/were not appropriate and adequate to determine that *chemical* was associated with lesion/condition.

There were no analytical chemistry data presented in the report. (In this case, no committee review is needed by a qualified chemist should sign the document and if necessary make a statement as to why analytical chemistry data are/are not needed.

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[For the above assessments, it is important to have subdiscipline committees review the study so that the biases of just one reviewer are minimized.

**5. Animal Toxicity Assessor:** A committee is not necessary for this evaluation since the hazard based on animal studies should already be established by committees. This assessor would normally be the person most responsible for reviewing the guideline studies (animal as well as mutagenicity). This assessor will also include studies from the open literature suggesting the association of the lesion with the chemical in animals. However, any publication supporting the association will need its own ROR signed by two qualified toxicologists. Their role is limited to determining if the lesion/condition is known to occur in laboratory animals and is some cases suggestive by *in vitro* studies. If the lesion/condition occurs in animals, it can support the epidemiological findings. If not, it does not automatically dismiss the epidemiological findings. Some conclusion examples would be as follows:

The lesion/condition has been demonstrated in the guideline study (or studies, name species) so that the conclusions associating *chemical* with lesion/condition are supported.

There is no evidence for the occurrence of lesion/condition associated with *chemical* in the guideline studies or in animal studies in the open literature.

Although there is no evidence for the occurrence of lesion/condition associated with *chemical* in the guideline studies, there is/are publication(s) reporting an association. Refer to pages --- of this DER.

**6. Senior Official:** The senior official (needs to be determine if this is a Branch Chief, Program Director or Assistant administrator) has the final determination of deciding if the study demonstrates an association between *chemical* and the lesion/condition. Their conclusion must be inclusive of dismissing the significance of the objections of any of the five subdisciplines listed above. Some conclusion examples would be as follows:

There is near (or otherwise) unanimous agreement among the subdisciplines that *chemical* is associated with the lesion/condition in humans. Therefore, *chemical* is considered a direct cause of lesion/condition and the exposure data causing this lesion/condition can be used for risk assessment.

There were serious reservations from the assessors to preclude an association between *chemical* and lesion/condition. Therefore no further regulatory action is considered required at this time. Refer to pages --- of the ROR.

[There are many combinations of the conclusions of the individual subdisciplines that would allow the Senior Official to conclude that the study still demonstrates a plausible/probable association with the lesion condition. The Senior Official will have to justify their decision to conclude that there is a concern for an association in spite of the objections of the individual subdisciplines.] Example:

The association of *chemical* with the increased occurrence of lesion/condition was supported by the endpoint evaluator and the statistician and but not the exposure assessor or the animal toxicity

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assessor and there were no analytical data presented. However, overall, the study is considered to demonstrate an association between *chemical* and lesion/condition. The lesion/condition can be used for risk assessment at the exposure levels reported. Refer to pages ---- of this ROR for a more detailed discussion to support the association of *chemical* with lesion/condition and justification for minimizing the deficiencies in the exposure assessment.

The reservations of both the exposure assessor and the analytical chemistry assessor preclude establishing an association of between *chemical* and lesion/condition in spite of the conclusions of the endpoint evaluator and the statistician. Refer to pages --- of this ROR.

### **The ROR Product:**

The ROR would include separate sections for detailed commentary of each of the five assessment committees or individual assessors listed above. These sections should clearly demonstrate that the committee/assessors independently reviewed the study (or provided their input) without influence of others. Once the first five committee/assessors finish their respective sections, they meet together with the Senior Official to discuss their findings and conclusions. The Senior Official then makes the overall decision but may consult with others as needed. Ultimately, the decision may go to an SAP for confirmation.

The cover page of the ROR will have a table where the first row identifies the study, authors, affiliations, location and duration of the observation period. The actual study publication will be appended to the ROR. This table will have rows for the names and signatures identifying each of the five subdisciplines and the Senior Official with the first column identify the individual in type, the persons signature and date signed and in the second column, their conclusion as indicated above. An additional row for the conclusions of a SAP review would also be present in the table. The first column would identify the SAP chairman, the date of the review. The second column would state in a few sentences the recommendation of the SAP and the reference to where the SAP report can be found.

Note: In some cases there may be more than one person from each subdiscipline that reviews the report. Separate names and signatures as well as conclusions would then be incorporated into the table.

### **Purpose:**

The purpose of this procedure is to assure that responsible persons for each of the critical subdisciplines independently review the study in terms of their expertise. Rather than have the publication be accepted by one individual based on the study's face value, the public can see that experts in appropriate subdisciplines evaluated the study.

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The Senior Official is something of a referee that eventually decides on the significance of the study after taking into consideration the inputs from the subdisciplines that may differ in the relative importance or acceptability of the study for regulatory purposes. The Senior Official and the subdiscipline committees own the decision are responsible for defending it.

If industry objects to the conclusions, they can address the conclusions of the Senior Official and the subdisciplines that supported the Senior Officials decisions.

Similarly, if concerned groups object to the conclusions again they will need to address the conclusions of the subdisciplines and the Senior Official.

Therefore the decisions in the resulting ROR should be transparent. The current system renders too much power to individuals who can profit by making career projects for themselves based on the face value of the publication.

I am well aware that a publication in the open literature associating a chemical with a lesion/condition in an epidemiological study is going to be controversial. However, preparing a ROR for such studies with the several subdisciplines all contributing to the Agency's determination of the conclusions in the report will greatly help to minimize controversies. Industry and/or the public can see right away why the Agency made its decisions with regard to the study and protection of public health.

The ROR is not a final conclusion of the study (no documents in EPA should be considered final) and as new information is generated, the ROR can be updated and the recommendations for use (or otherwise) can be adjusted as appropriate. The ROR will also be presenting data or other deficiencies that the authors of the publication can address.

I am looking forward to receiving any comments on this proposal.

email:

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