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Defined Formats Proposal: Increased Efficiency and Reduced Costs in the Submission and Review of Pesticide Studies

J.D. Doherty, Ph.D., D.A.B.T. (primary author)
William Irwin, Ph.D., D.A.B.T. (secondary contributor)

Executive Summary

This proposal defines a system to *improve efficiency* and to reduce taxpayer costs in the review of the toxicity, chemistry, fate and exposure studies submitted in support of the registration of pesticides to the Office of Pesticide Programs of the Environmental Protection Agency. This Defined Formats approach can save OPP $ millions/year in staff and contract work expenses derived from the taxpayers. Since the format was first proposed in the mid 1990's, OPP could have saved over $50 million in contract and staff expenses across all the disciplines. The Defined Formats system simply allows the pesticide companies to write the pesticide draft study analysis from the full study reports which are then reviewed by the EPA, saving taxpayer money and greatly speeding up the registration process. The pesticide companies are the experts on the study results and it would be much more efficient if they wrote the evaluation analysis and the EPA simply reviewed the evaluations for accuracy. The Defined Formats would better allow the EPA to meet the deadlines and obligations of FIFRA, FQPA and PRIA, for increased protection of children at decreased cost to the taxpayers. The Defined Formats approach to company data evaluation has applications in other offices across the Agency for further savings to the taxpayers. The computer technology to support this proposal has been available for decades.

I. Introduction

In this proposed system, the OPP reviewers will still retain all authority and responsibility to classify the study, identify study deficiencies, identify all responses to treatment, write a discussion on their interpretation of the data and write the executive summary. The purpose of this proposal:

-Increase the efficiency and decrease the taxpayer expense of assessing pesticide studies

[1]Previous versions have been prepared since approximately 1992. Modifications in this current version have been made partly in response to comments by various OPP staff.

Sierra Club v. EPA 18cv3472 NDCA Attachments Prod 1 ED_002061_00039082-00001

across all disciplines in OPP (toxicology, chemistry, fate, exposure, etc)

- Utilize the reviewers' time more *efficiently* so that more quality time is spent actually analyzing the data and better supporting the Food Quality Protection Act (FQPA, unamiously approved by Congress) to protect children's health.

-Provide a more balanced product that assures that all customers including the public that the peer review committees considered both the study author's conclusions and the EPA reviewer's conclusions and is supported by the FIFRA statute.

-Provide a more useful product for other government agencies that utilize OPP's reviews of pesticide toxicity data such as WHO, CALEPA and Canada.

-Improve the OPP ability to meet PRIA deadlines, often missed in the current review system.

-Provide an assurance against the "cut and paste" plagiarism promoted by the current OPP system.

This proposal provides that the *study authors* complete *specifically defined supplements or formats that will be designed by the Office of Pesticide Programs (OPP) staff* and toxicologists from other governmental agencies that contain the facts of the study including the methods and materials and obvious responses to treatment in the test animals. The formats present the facts of the study and not the interpretation of the study for regulatory purposes.

The basic tenet that justifies this proposal has been valid for many years. FIFRA clearly states that the burden of proof for a pesticide's safety is on the registrant. The registrant is therefore obligated to provide a document that can be used for the Agency's purposes that does not have to be rewritten at government expense of time and resources. The pesticide company has already written the full study reports and they are the experts on the information, it is easy for them to write the summary Data Evaluation Records (DERs) from the full study documents. The Defined Formats approach requires that the full study report have a defined format which would make it much faster to write the draft study DERs. The Defined Formats system could speed up the pesticide registration process by up to one year if the EPA was not responsible for this step in the process. The EPA would still have the authority to revise the draft DERs to meet their policies.

The conduction and review of toxicity studies are a means to an end. It is the *quality of the study* that satisfies the data requirement, characterizes the toxicity of the chemical and drives a meaningful risk assessment. The quality of the study is related to the design, preparation, conduction and reporting at the laboratory and by the people who performed the study (often the

pesticide companies/registrants). The proposed supplements are a form of reporting the study. A DER prepared by OPP/HED staff or its contractors, no matter how well polished with fancy outlines and tables, does not improve the quality or render added value to the study. Having contractors write DERs actually gives the HED reviewers two documents to review for each study and decreases efficiency.

II. **Factors that Justify a Consideration of this Proposal.**

1. Conduction of the study and the generation of toxicity data.

Since the current 870 series study protocols are so specifically designed to meet a particular guideline, there should be no need to copy over the methods and materials for each study review, except for deviations that may invalidate the study. Such information related to the particular properties of the test chemical, the test animals used and the procedures used for all analyses and tissue preparation are better presented directly by the study author or the pesticide company, they are the experts in the study results and conduct.

Toxicity studies consist of the generation of data that is gathered by direct observation such as clinical signs, assessment of the behavioral parameters in neurotoxicity studies, counting of fetuses and their visible malformations in developmental toxicity studies and necropsy. In the case of direct observations, when the event occurs, only the observer can record it and note its severity and duration. The reviewer cannot change the data and observations made by direct observations. Again, this information is best reported in the evaluation record (DER) directly by the laboratory or the pesticide company for the toxicity, chemistry, fate and exposure studies.

In the case of data such as hematology, clinical chemistry and urinalysis that are mostly generated by modern and highly sophisticated analytical instrumentation, there is nothing the reviewer can do to change the readings as presented in the study report. The reviewer's responsibility is to be able to identify inconsistencies in the data that would suggest something is wrong with the instrumentation that may have given a false result or to spot other indications of possible error.

In the case of histopathology data, the pathologist reading the slide has total control of the observation and diagnosis. The OPP toxicology reviewers cannot see what is on the slides. Any question regarding the pathology diagnosis in the report has to be directed to OPP's consulting pathologists. The reviewer can look for consistency in the gross pathology and histopathology reports but this should not require that the reviewer copy over the study report tables. Also, when gross necropsy tables are prepared, the current DER does not provide that an animal by animal comparison with the histopathology be provided.

Another compelling reason for having the study author or company prepare the data in a defined format is when the study author is a specialist in some particularly narrow field

of toxicology. Only such specialists can best present the data with the tissue slides, chromatograms and hard data directly available to them, not provided to the EPA with the full study reports.

2. The study authors already identify the critical responses to the pesticides and indicate responses that may be related to treatment but in their opinion do not relate to treatment.

The EPA reviewer needs to spend time trying to identify responses to treatment not already indicated by the study author. Any subtle responses that a EPA reviewer identifies that are not already indicated by the study authors are controversial and require resolution of their significance by peer review groups. The HED reviewers need to spend quality time to make a case that these subtle responses are indeed significant, rather than spending large amounts of time simply transcribing information into study DERs.

3. The OPP Peer Review Committees and Risk Assessors and other governmental review groups have emerged as the principal customers of the reviews of toxicity studies.

The 1995 and later 2001 versions of the Data Evaluation Record (DER) formats were specifically designed to meet the needs of the various OPP peer review committees. OPP has committed to harmonize its reviews so that they can also be used by other governmental regulatory groups such as CALEPA, Canada and WHO. These groups are now very important customers of EPA's reviews of pesticide toxicity studies. Thus, a product that produces a first hand account of the study in the format that will be a part of the review product as well as OPP/HED reviewer's interpretation that would result from this proposal better suits the needs of its principal customers. For example, they can directly compare the facts presented by the study author and the EPA reviewer.

4. The current system of DER production does not provide an assurance against "cut and paste".

Completing the DER as per the current instructions requires the reviewer to include the methods and materials and the obvious responses to treatment. All of this information is routinely taken from the full study report and incorporated verbatim into the OPP DER, which could much easier be done by the company. In the current system there is no way for someone reading the DER to tell if the information entered in the table are the same as from the study author's data tables or if the conclusions entered by the reviewer are the same as the study author's. The proposed defined formats system clearly indicates what was provided by the study author and what the EPA reviewer contributed. Thus, the defined formats system provides a better assurance that the OPP review was not cut and pasted.

5. OPP scientists are customers too.

In the Total Quality Management (TQM) paradigm, customer satisfaction is the driving force. The products submitted to customers are supposed to satisfy their needs. OPP

scientists provide products in the form of reviews for their customers such as the Peer Review Committees. The OPP toxicologists, chemists, physicists and exposure scientists are also customers of the products that are submitted to them for review. It stands to reason that they can ask for products that more efficiently satisfy their needs.

6. Study audits.

The most appropriate way to demonstrate that study discrepancies have occurred in a study would be to audit that study on site. The OPP reviewers would still have the authority to request a study audit if there is a reasonable suspicion of study discrepancies.

III. **The Roles of the Study Author and Reviewer.**

The roles of the study author and toxicology reviewer (either an OPP staff or a contractor) would be as follows:

Study Author. The study author completes the study and prepares and submits the entire study*. The study author also prepares defined formats DERs as a supplement that strictly follows prescribed instructions as provided by OPP scientists for describing certain specific factual aspects of the methods and materials used, certain factual data that demonstrate the proficiency of the study (i.e. survival or pregnancy rate etc depending on the study type) and the effects of the test material. The obvious responses to treatment include those parameters that are statistically significant in the treatment groups as well as those parameters that the study author believes to be treatment related. The NOAEL and LOAEL as determined by the study author for each of several investigational parameter groups would be presented in the Table of Concurrence/Non-Concurrence (see below).

[*Note: The Formats as designed by the HED scientists can eventually be incorporated as the study report so that the author does not have to prepare two documents.]

OPP Reviewer. The OPP reviewers would first review the study report, ascertain that the study is valid and identify all study deficiencies (if any) as well as identify the responses to treatment using the summary tables and the raw data. The reviewers then ascertain that the supplements contain all the necessary methods and materials parameters and that the obvious and suspected effects of the test material are consistently presented.

OPP reviewers should be trained to know what to assess, expect from and interpret in a toxicity study. *Thus, a good review depends on the work habits of the individual reviewer.* Trained reviewers should welcome this proposal because it frees them from simply transcribing the mundane aspects of the study and allows them to use their judgment and expertise more efficiently. This proposal raises the level of professionalism of OPP's science reviewers.

If the reviewer identifies an effect of the test material that was not identified by the study author, the reviewer can enter these data in a Table in the reviewer's discussion Another item that can be included in appendixes are reanalysis of the data by statistical methods not already used by the study author if the alternate statistical analysis renders a different interpretation.

The reviewer then completes a Table of Concurrence and Non-Concurrence in which the many parameter groups of a study are listed in one column, the study author's conclusion in the second and the reviewer's statement as to whether or not they concur with the study author. The design of the Table of Concurrence and Non-Concurrence would be different for each guideline study type to assure that all of the key parameter groups were addressed.

The reviewer then prepares a Discussion section. The discussion of the study is where the reviewer interprets the data for regulatory purposes. The Table of Concurrence/Non-Concurrence will have paragraph reference numbers to refer the reader to the relevant section of the discussion to explain why there was differing opinions.

The reviewer then prepares an executive summary.

The reviewer then assembles the Record of Review (RR)[2] as follows.

Item	Preparation
Cover Page	EPA Reviewer
Executive Summary	EPA Reviewer
Classification statement	EPA Reviewer
Methods and Materials Supplement	Study Author*
Results Supplement	Study Author*
Table of concurrence/non-concurrence	EPA Reviewer
Discussion (study deficiencies and comments)	EPA Reviewer
Appendix (if required)	EPA Reviewer

*Included only after having been verified by the EPA Reviewer.

IV. **Principal Advantages of the Proposal**

1. A more thorough assessment of the study would result.

The reviewer would be spending a larger portion of the review time challenging and assessing the entries made in the supplements provided by the study author as well as identifying omissions by the study author. If the study author/company prepared the draft DERs

[2]The term Record of Review (RR) would replace the term DER to distinguish the two products.

more effort could be devoted by OPP scientists evaluating mechanistic evaluations, fulfilling FQPA statute obligations and meeting PRIA deadlines. The current procedure of preparing DERs requires the reviewers to follow specific outlines that are time consuming and require much polishing and creation of data tables showing the obvious results of the study and rewriting the methods and materials sections—unnecessary and wasteful effort by OPP staff. The current procedure just transcribes the study report information at taxpayer expense. The time spent polishing the DER as they are now prepared would be better spent assessing and interpreting the actual raw data of the study to fulfill FQPA and PRIA statutes. The current OPP system of pesticide study review takes at least 2 years. The proposed Defined Formats approach could speed up pesticide registrations by one year.

2. The public has a better assurance that the EPA reviewer (or its contractor) did not "cut and paste" to produce the DER.

Since the defined format supplements are clearly indicated as being provided by the study author (see section below on logistics and mechanisms) and the other sections are clearly indicated as being authored by the EPA reviewer, the public knows where all of the information in the Record of Review originated. The public can judge what both the study author and reviewer contributed to the Record of Review.

3. The table of Concurrence/Non-Concurrence provides both a source to indicate that the EPA reviewer takes responsibility for each phrase of the study and a source to indicate where there are differences between the study author and the EPA reviewer. Thus, this Defined Formats approach is transparent and EPA scientists and review committees still retain the final authority of the study conclusions.

Since the EPA reviewer must commit to concur or otherwise with the several phrases of the study, the reviewer must assess the data to satisfy themselves that the data support the author's conclusion (concur) or the conclusion that the reviewer decides (non-concurrence). When the EPA reviewer does concur, the necessary data would already be in the supplement provided by the study author. When the EPA reviewers do not concur, the reviewer would be making a separate data table to illustrate the points and this table would be in either the discussion section or an appendix.

In this Defined Formats system, the peer reviewers as well as other governmental review groups and the public can see immediately where the reviewer and the study author did not agree and can formulate their own conclusion by assessing both data evaluations as provided by the author and EPA reviewer.

4. A first hand account of the study methods and materials and results would be presented to the Peer Review Committees.

In the Defined Formats, the study author whom wrote the DER/supplements

would be providing a first hand account of the study methods, materials and results to maximize DER accuracy to the various Peer Review groups. The current system of preparing DERs conveys a second hand account of the study and only the reviewer's viewpoint in selecting data for the tables conveying the information. In the defined formats proposal, the various customers of the product are assured that the viewpoints of both the company and EPA scientist are considered for transparency.

In the Defined Formats approach, there will be less mis-transcription errors by the EPA reviewers simply transcribing copying numbers from the full study reports which occurs in the present system.

5. The proposed system is "market driven" to produce thorough supplements by the study authors and reviews by OPP scientists.

Pesticide testing is a competitive business. A study laboratory or pesticide company would strive to prepare thorough supplements that require a minimum of critical comments made by the EPA, to protect the integrity and reputation of their laboratory/company. The laboratories that are owned by the companies/registrants would also be pressured to produce quality studies and reports that are not rejected by the Agency because this would reduce the delays in having their products registered.

The system is also "market driven" for the EPA reviewers. The EPA reviewers would not want some other reviewer or reviewer groups to identify a response to treatment or study deficiency that they did not recognize. Thus, the EPA reviewers would be conscientious in completing the review to fully identify and assess the impact of study deficiencies as well as identify subtle responses to treatment and explain why these responses should be considered as potential risk findings. The EPA reviewers would also not want to magnify a trivial response to treatment.

6. The products sent to the peer review groups would be more uniform for all studies.

Since the Defined Formats will be rigidly designed, the EPA peer reviewers will see products that are more uniform, thus more efficient to review and meet PRIA deadlines.

7. The Record of Review would be more useful to other regulatory agencies.

In many cases, the reviews of all studies for pesticides produced by EPA are sent to other regulatory Agencies in states within the USA or to other countries such as Canada or to the WHO. When the reviews include the defined format supplements, the other regulatory scientists can readily see the conclusions of the study author and the conclusions of the EPA reviewer, as well as the indications of study commentaries as indicated by the EPA reviewer. Thus, when the Record of Review contains the defined formats supplements, the other regulatory

groups can resolve to their own standards the differences in conclusions between the study author and the EPA reviewer.

8. Savings in time, labor, tax money, paper and other supplies.

DERs are typically 5-15 pages but some are 40 or more pages long. Several drafts of each DER are often made. The current system amounts to much use of time, labor, paper and other supplies at the taxpayer expense. Since the study authors are already preparing the methods and materials sections as well as results in their reports, they are the experts on the study, thus they can more efficiently prepare the supplements using less time and paper than an EPA reviewer would expend.

V. **Logistics and mechanistics of the proposal.**

1. Identifying the contributions from the study author and EPA reviewer.

In order to identify the contributions that were provided by the study author, it is proposed that the supplements will be submitted in a form that cannot be altered by EPA staff such as on watermarked paper or unalterable electronic disks. The contributions made by the EPA reviewer will be on paper with an identifying header.

2. Compatibility with the proposed electronic submission of data.

The defined formats proposal is entirely compatible with proposed electronic submission of toxicity data. The electronic submissions are useful for extracting data for independent analysis by alternate methods and this will be very useful in the proposed system for review of toxicity studies.

VI. Conclusions

The Defined Formats system would increase the efficiency of pesticide study reviews in all disciplines, potentially saving OPP and other EPA offices $ millions each year in contractor expenses. The Defined Formats would better allow OPP to meet FIFRA, FQPA and PRIA obligations for improved protection of children.

Sample Table of Concurrence and Non-Concurrence. For a Chronic feeding Study

Parameter	Study Author's Conclusion	OPP Reviewer's Conclusion[2]
Analytical Report	N/A[1] (Only the reviewer may comment on this in this table.)	-Report Adequate OR -Report not adequate. Needs homogeneity data refer to item 1 of discussion.
Statistical Methods	N/A	-Statistical methods adequate. OR -Inappropriate statistical methods used refer to item 2 of discussion.
Clinical signs and mortality.	NOAEL and LOAEL = 100 and 200 ppm. Tremors. At 600 ppm deaths.	-Concur with study authors -NOAEL and LOAEL = 50 and 100 ppm, respectively. Tremors in 6 males considered significant and adverse.
Body Weight and Food Consumption	NOAEL and LOAEL = 100 and 200 ppm.	-Concur with study authors
Hematology	NOAEL and LOAEL = 200 and 600 ppm. Decreases in leucocytes.	-Concur with study authors
Clinical Chemistry	NOAEL and LOAEL = 200 and 600 ppm. Increases in ASAT and LDH.	-Concur with study authors
Urinalysis	NOAEL and LOAEL > 600 ppm.	-Concur with study authors
Organ Weights	NOAEL and LOAEL = 200 and 600 ppm.	-Concur with study authors
Pathology	NOAEL and LOAEL = 200 and 600 ppm. Liver hypertrophy.	-Concur with study authors -Kidney data needs re-evaluation, refer to item 6 in discussion.
Carcinogenicity	Positive for liver tumors.	-Concur with study authors -Positive for liver tumors and brain tumors, refer to item 7 of discussion and Table 3 below.
Overall NOAEL and LOAEL	100 and 200 ppm based on tremors.	-Concur with study authors -50 and 100 ppm based on tremors.
Study Classification	N/A	STUDY ACCEPTABLE (870.xxxx) for regulatory purposes OR PENDING. Needs reassessment of the kidney histopathology.

[1] N/A means that the study author will not be making entries for this parameter.

[2] Sample entries that the reviewer would be making. In some cases more than one sample is presented for illustrating how this table would be completed by the reviewer.