Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment

PROCEDURES FOR REVIEWING RELEVANT EFFECTS DATA PUBLISHED IN THE OPEN LITERATURE
FOR USE IN OPP's HUMAN HEALTH RISK ASSESSMENTS

8/28/2012

Office of Pesticide Programs
U.S. Environmental Protection Agency

Table of Contents

1. Introduction 3
1.1. Purpose 3
1.2. Organization of the Document 3
2. Screening the Open Literature Studies 4
2.1. Accepted Journal Articles/Publications by OPP 4
2.2. Documenting Relevant Journal Articles/Publications 4
3. Reviewing the Open Literature Studies 5
3.1. Study Categorization 5
3.2. Guidance for Open Literature Study Review 6
3.2.1. Guidance for Evaluating the Acceptability of Open Literature Studies 6
3.2.2. Guidance for Differentiating Between Qualitative and Quantitative Studies 8
3.2.3. Special Notes on Epidemiologic Data 10
3.3. Completion of Data Evaluation Records (DERs) for Journal Articles 11
3.3.1. Completion and Submittal of Journal DERs for Data Used Quantitatively 12
3.3.2. Completion and Submittal of Journal DERs for Data Used Qualitatively 12
3.3.3. Completion and Submittal of Journal DERs for Unacceptable Studies 12
4. Use of Open Literature in OPP's Risk Assessments 13
4.1. Use of "Quantitative" Open Literature Data in Risk Assessment 13
4.2. Use of "Qualitative" Open Literature Data in Risk Assessment 13
5. References 15

Attachment 1: Criteria for Invalidation of Open Literature Studies 16

1. Introduction

1.1. Purpose

Toxicological and metabolism data for pesticide chemicals (active and inert ingredients) are provided by the registrants as required in 40 CFR Part 158. Guidelines for conducting studies to meet these requirements are available on the OCSPP Harmonized Test Guideline webpage: http://www.epa.gov/ocspp/pubs/frs/home/guidelin.htm. In addition to the information submitted by the registrants, effects data from studies published in the open literature may also be considered in risk assessments conducted in the Office of Pesticide Programs (OPP).

The purpose of this document is to provide further information and clarification to assist in the selection and review of relevant publications available in the open literature (*i.e.*, non-test guideline studies) for use in hazard and dose response assessment. This guidance was developed to assist OPP scientists and is intended for use in OPP's risk assessments. This guidance draws from OPP's long standing experience and guidance for review of registrant-submitted studies submitted in response to the 40 CFR Part 158 data requirements. It is intended to ensure consistent consideration, use, and documentation of information in the open literature by OPP scientists and risk assessors when evaluating the potential adverse effects on human health. This document is also intended to make transparent how OPP judges the scientific quality of open literature publications of relevance and importance to human health risk assessment.

Although this guidance focuses on mammalian *in vivo* toxicity studies, its general principles and criteria also apply to pharmacokinetic/metabolism, mechanism of toxicity and *in vitro* studies.

1.2. Organization of the Document

This guidance is divided into the following three sections:

- **Screening the Open Literature Studies**: Discusses how to determine which journal articles / publications to consider relevant to the specific purpose of human health risk assessment.

- **Reviewing the Open Literature Studies**: Provides study categorizations, criteria for study reviews, and preparation of documentation of reviewed open literature [*i.e.*, preparation of a Data Evaluation Record (DER) or Abbreviated Data Evaluation Record (AbDER)].

- **Use of Open Literature Studies in Risk Assessment**: Provides guidance for use of quantitative and qualitative data in OPP's risk assessments conducted for Registration Review and Registration actions.

2. Screening the Open Literature Studies

When evaluators conduct a literature search, the evaluator should keep the search parameters and the results of the literature search as a record. It is possible a large amount of published papers will be identified that are of possible interest. An initial screening process is needed to identify those papers that are appropriate for the purposes of addressing the critical questions of human health risk assessment (*e.g.*, what are the potential toxicities of the chemical, at what doses are effects found, what lifestages are impacted, how does the chemical causes its toxicity). The purpose of this section of the guidance is to discuss the screening process used to identify potentially suitable and useful open literature journal articles/publications. The screening criteria for accepted journal articles/publications that are described below in **Section 2.1** are taken from the Pesticide Reregistration Rejection Rate Toxicology document (USEPA.1993).

2.1. Accepted Journal Articles/Publications by OPP

In order to be eligible for consideration, journal articles/publications need to meet the following minimum criteria:

1. The toxic effects are related to defined chemical exposure;
2. The toxic effects are on an appropriate test animal species;
3. The presence or absence of toxicological effects is observed;
4. A chemical concentration/dose or application rate is reported;
5. An explicit duration of exposure is included;
6. Toxicology information is reported for the chemical of interest or its structural analog;
7. The article is available in the English language;
8. The study results are presented as a full article (i.e., not an abstract);
9. The paper is a publically available document;
10. The paper is the primary source of the data;
11. Treatment(s) are compared to acceptable controls;
12. The location of the study (e.g., laboratory vs. field) is reported;
13. Adequate data are provided on the chemical tested (i.e., test article characterization);
14. Adequate data are provided on the species tested;
15. The study results (findings) are adequately reported; and
16. The study findings are relevant to assessing human health risks

2.2. Documenting Relevant Journal Articles/Publications

Once the determination is made that the open literature article/publication is eligible for consideration (based on the screening criteria discussed in **Section 2.1**) and may be used quantitatively or qualitative in risk assessments, a Master Record Identification number (MRID), for the article should be requested. The purpose of assigning an MRID to the open literature study is to ensure that the study is documented as part of the study bibliography for the chemical

in the Office of Pesticide Program's Information Network (OPPIN) and electronically available via Documentum. In order to obtain an MRID number for an open literature study, an electronic copy of the study should be provided to the Alternate Contracting Officer Representative (ACOR) of the Data Management Contract in the Information Technology Resources and Management Division (ITRMD). Currently, the ACOR point of contact in ITRMD is Teresa Downs (703-305-5363, downs.teresa@epa.gov). An electronic copy of the study should be provided to the ACOR in an email and the MRID number is typically assigned within 2 to 10 days. Once the MRID is assigned to the open literature study, the citation for the study will appear in the OPPIN bibliography. In addition, a ".tif" file of the study will be available in Documentum approximately one month after the MRID is assigned to the study.

Journal articles are sometimes submitted to the Agency by outside stakeholders such as environmental groups or the registrant. When this occurs, the article is processed in the same manner as standard test guideline studies (*i.e.*, scanned into Documentum, entered into OPPIN and assigned an MRID by ITRMD).

3. Reviewing the Open Literature Studies

All open literature journal articles/publications that are identified as potentially useful based on the selection criteria discussed in **Section 2** should be reviewed, categorized, and documented. A description of the open literature study categorizations, guidelines for study reviews, and completion/documentation of open literature data summaries is provided in **Sections 3.1 through 3.3**, respectively.

3.1. Study Categorization

Open literature studies that may provide additional information on measurement doses/endpoints should be reviewed and categorized as to their usefulness in a risk assessment. The three general categories for open literature studies are:

- Quantitative: Appropriate for quantitative use [*i.e.*, establishing a point of departure such as No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL), Benchmark Dose (BMD), cancer slope factor, etc.] in risk assessment;
- Qualitative: Not appropriate for quantitative use, but is of sufficient quality, relevant to issues and questions within the risk assessment of a chemical, and can be used descriptively in the weight of the evidence and risk characterization; and
- Unacceptable: Inappropriate for quantitative or qualitative use in risk assessment because it is of insufficient quality and lacks scientific reliability and defensibility.

Further description of the guidelines for open literature study categorization as "quantitative", "qualitative", or "unacceptable" is provided below in **Section 3.2**.

3.2. Guidance for Open Literature Study Review

This guidance will enable scientists to consistently differentiate open literature studies into the three categories outlined in **Section 3.1**. The scientist must also use best professional judgment, in addition to the considerations discussed below to determine the appropriate study categorization for open literature studies. While a single factor may result in categorization of the study as unacceptable (*e.g.*, excessive control mortality), more typically, several issues combine to render the study of questionable reliability and utility.

3.2.1. Guidance for Evaluating the Acceptability of Open Literature Studies

Consistent with guidance to determine whether a study meets the criteria outlined in pesticide testing guidelines, general information that should be considered as important in determining the reliability and utility of an open literature study in risk assessment includes the following:

- **Nature of the test substance (percent active ingredient).** The study needs to indicate the exact nature and source of the pesticide; the percent active ingredient and/or the purity of the test compound should also be reported. If a solvent vehicle is used, the vehicle should not interfere with the absorption, distribution, metabolism or the elimination (ADME) of the test substance nor alter the behavior/response of the test organisms. Studies which use a solvent vehicle should also include solvent vehicle controls.

- **Test organism**. Species, age, sex, size, health and life stage and source of the test species should be reported. Any observed diseases and treatment need to be reported.

- **The number of organisms tested per concentration and the number of concentrations or dosage levels evaluated**. This type of information should be reported and be sufficient to yield statistically sounding data. An inadequate number of test organisms per test level can also produce unreliable results. The appropriate comparable guideline study Standard Evaluation Procedure (SEP) should be consulted for further information on the adequate number of test organisms per test level.

- **Husbandry conditions.** Guideline studies have been developed using particular species to establish conditions under which the test organisms are most likely to thrive and where husbandry conditions will not confound the interpretation of the study. Reviewers need to be cognizant of husbandry conditions and verify whether the environmental conditions of the study are adequately described and/or addressed to ensure that the test organisms are not adversely affected. This description should include the number of animals per cage or test container (*i.e.*, biological loading rate); nature and composition of bedding used for mammalian studies (if available); ambient temperature and humidity; photoperiod; description of the diet; source of the animal feed; dimensions of the test container.

- **Exposure method, route, and frequency of administration and length of the treatment period.** The dose administered (test substance plus carrier) to each organism (in feed or water) at each time administration is made need to be reported. In addition, the frequency of administration and duration of the exposure need to be reported. For all studies, the exposure conditions need to be clearly described and documented. Additionally, the reviewer needs to consider whether test conditions may not sufficiently preclude exposure to other chemicals that could potentially confound the study. In such cases, the reviewer should consider the variability associated with the measured endpoints from the controls.

- **Controls.** A suitable number of controls need to be run to test whether study conditions are adequate. Control performance should be used as an indicator of whether study conditions and animal performance are adequate. To this end, controls need to be run concurrent with the study; failure to do so would render the study unacceptable. As mentioned previously, studies which rely on solvent vehicles should report concurrent solvent controls. As an indicator of study conditions, control performance in terms of mortality and disease should be carefully evaluated to determine the adequacy of the study. Mortality of greater than 10% in controls for most test species is sufficient to conclude that the study is unacceptable. Ideally, studies should also report the measured concentrations of test chemical in the controls.

- **Performance of test species.** Normal development times (where available) should be compared to those reported for the test species. Where the development time for the control animals differs substantially from normal reported values, the reviewer needs to determine whether study conditions have impaired the animals' ability to thrive. In cases where development time is substantially different than what is typically observed for the test organisms, the study should be considered as unacceptable as the study's ability to distinguish treatment effects is uncertain.

- **Macroscopic observations of the test animals.** During the course of the study, a detailed description of the nature, incidence, time of occurrence, severity, and duration of all observed toxic effects, including death and any other abnormal or unusual signs and symptoms (*i.e.*, sub lethal effects) should be reported.

- **Microscopic observations of the test animals.** Tissues and organs for microscopic examination should be fixed in 10% buffered formalin or recognized fixative. Reporting of microscopic evaluations should consist of accurate diagnosis of all non-neoplastic (*e.g.*, atrophy, hypertrophy, hyperplasia, and dysplasia) and neoplastic (*i.e.*, tumors) lesions observed in the control and treated groups. Neoplastic findings (*i.e.*, tumors) where applicable, may be reported as benign and malignant. This evaluation is important for integrated interpretation of the findings to identify and characterize the histopathological findings of a study. Microscopic evaluation of the slides should follow the guidelines established in the Society of Toxicological Pathology's Best Practices Guideline paper (Toxicological Pathology 32:126-131; 2004).

- ***In vitro* studies** should include the following data: description of the test system/test method; purity/composition/origin of the test substance; data on dose/concentration tested; data on solubility, impurities, and pH; presence of absence of metabolic activation; appropriate negative/positive controls; and the appropriateness of the method of analysis performed.

- **Statistical method used to derive the test endpoints.** Verification of the statistical analysis is an integral part of the data evaluation process. As such, studies should provide descriptive statistics that report measures of central tendency (*e.g.*, means, medians) and measures of dispersion (*e.g.*, standard deviations, standard errors) along with associated sample sizes (N values). The report should state which methods of statistical comparison (*e.g.*, t-test, ANOVA, chi square) were used and the presumed nature of the data (parametric versus nonparametric) and whether the data supported use of parametric analyses.

- **Information necessary to provide a complete and accurate description of test procedures and evaluation of the test results**. Each report should include a summary of the data, a description of the statistical analysis of the data, and a statement of conclusions drawn from the analysis that allows the reader to independently understand the conclusions of the author. Sometimes it is important to obtain raw data from the study authors.

- **Important information missing from the study.** Inconsistencies or deviations with recommended methodologies, as discussed in the appropriate comparable guideline study SEP and/or 870 guideline for each of the respective studies, should be addressed. SEPs and/or 870 test guidelines can provide additional measures of gauging the reliability of study conditions.

- The toxic effects must be able to be attributed to exposure from the chemical.

An acceptable open literature study may have some limitations but will still contribute information to the assessment. Unacceptable open literature studies, however, are those that are not considered scientifically sound and as such do not provide useful/reliable information. These can include studies that were performed under conditions that deviated significantly from scientifically accepted methods or recommended protocols such that the scientific integrity of the study is uncertain and the results should not be used to support risk assessment. In addition to the guidance discussed in this section, a list of additional factors that could result in an open literature study being categorized as 'unacceptable' is provided in **Attachment 1**.

3.2.2. Guidance for Differentiating Between Qualitative and Quantitative Studies

If a study is considered to be acceptable based on the guidance described in **Section 3.2.1.** and/or **Attachment 1**, a determination is made regarding whether the information provided in the study is adequate for "qualitative" or "quantitative" use in risk assessment. For OPP's purposes, "qualitative" refers to data that can be used in a weight of evidence evaluation to support

conclusions regarding potential hazard. "Quantitative" means the dose response data from the study can be used for establishing a point of departure for risk assessment.

To be used quantitatively, the data reported in the open literature need to meet all of the following criteria:

- The dose from the open literature study is lower *(i.e.,* more sensitive) than the lowest dose from a comparable registrant-submitted study;
- The open literature data are reported in (or have the ability to be converted to) units that can be compared to other study results; and
- Sufficient information is provided in the open literature to substantiate whether the study conclusions/endpoints/doses are accurate, reliable, and reasonable and a judgement can be made that the study findings could potentially be replicated (as per Section 3.2).

If a scientifically valid study does not meet any of these three criteria, the data from the study should be categorized as "qualitative." OPP recognizes that the third criterion (*i.e*., sufficient information is provided to substantiate whether the conclusions/endpoints/doses are accurate) requires best professional judgment. The most reliable means of determining whether study conclusions can be verified is through access to the raw data; however, it is recognized that very few open literature journal articles/publications provide this type of information. Therefore, the quantitative use of open literature requires that the study provide a relatively comprehensive understanding of the conditions under which the study was conducted and of the data generated by the study. If the open literature study is important to the risk assessment and this comprehensive understanding is not provided, the reviewer should attempt to obtain missing information from the study, including the raw data from the study authors.

To assess the third criterion the reviewer should consider whether the study reports relatively detailed measures of the variability associated with the data and the methods used to analyze the data. Reviewers should note whether the statistical tests used in the study are appropriate to the design of the study, the nature of the measurement endpoint, and of the data generated in the study. Tests using parametric statistics should indicate whether the conditions for such tests (*i.e.*, normal distribution and homogeneity of variance) have been met.

Where raw data cannot be obtained or are not available to verify the study results, the reviewer needs to discuss the uncertainties associated with quantitative use of the data relative to studies where raw data are provided. Consideration needs to be given as to the extent to which results are aligned with other lines of evidence. Open literature values that are inconsistent with similar measures of toxicity should be carefully scrutinized to determine their reliability.

Ultimately, distinguishing between data that can be used qualitatively versus quantitatively will largely depend on professional judgment.

3.2.3. Special Notes on Epidemiologic Data

In addition to experimental toxicological evidence, OPP is interested in querying the peer review literature for observational epidemiology studies of potential adverse acute and chronic health effects linked to pesticide use. Epidemiologic research utilizing cohort, case-control or cross-sectional study designs may provide information to strengthen OPP's understanding of the potential hazards, exposure-response characterization, exposure scenarios or assessment methods, and ultimately risk characterization (Van den Brandt, 2002). In addition, at times compelling case reports or case series analysis may illumine a health effect or mechanism of action previously unidentified.

Recently, OPP has developed *draft* guidance for incorporating epidemiologic research into the risk assessment process. OPP anticipates increased use of these types of data in our risk assessment process as epidemiologic cohorts such as the National Cancer Institute's Agricultural Health Study, among others, continue to mature (increased time on study), and associations between pesticide use and adverse cancer and non-cancer outcomes are refined and clarified.

To perform a query of the published epidemiologic data, OPP scientists utilize biomedical search tools such as MedLine/PubMed, Web of Science, and Google.scholar. These three biomedical search tools are among the most well-developed and characterized for use by epidemiologists (Falagas 2006). Working in conjunction with EPA reference librarians, internal data query experts, and using best professional judgment, OPP scientists develop a search string appropriate to the research question of interest. Use of Medical Subject Heading (MeSH) indexing is particularly helpful in developing a comprehensive search string. Manually searching reference lists of key/pivotal articles (secondary level searching) is also recommended. Using the ISI/Web of Science search tool, OPP scientists can also perform citation mapping in which articles that cite key/pivotal research are automatically identified. In this way, additional studies potentially pertinent to the research question may be identified. Ultimately, the particular needs of the risk assessment will dictate the level of sophistication of the biomedical literature review. In all cases, search string variables, date of search, and original reference lists can be retained to delineate literature search methodology and allow replication, if needed.

Regarding the selection of epidemiologic studies identified in the peer reviewed literature for use in risk assessment, OPP is currently in the process of developing a guidance document detailing the characteristics of epidemiology studies deemed desirable for this purpose. The guidelines discussed in this document with respect to querying the experimental toxicological literature may or may not be used for the purposes of selecting observational epidemiology studies.

Generally speaking, the quality epidemiologic research, sufficiency of documentation of the study (study design and results), and relevance to risk assessment will be considered when selecting epidemiology studies from the open literature for use in OPP's risk assessments. These include:

1. Clear articulation of the hypothesis, even if the study is hypothesis-generating in nature;
2. Adequate assessment of exposure for the relevant critical windows of the health effects, the range of exposure of interest for the risk assessment target population, and the availability of a dose/exposure-response trend from the study, among other qualities of exposure assessment,
3. Reasonably valid and reliable outcome ascertainment (the correct identification of those with and without the health effect in the study population),
4. Appropriate inclusion and exclusion criteria that result in a sample population representative of the target population, and absent systematic bias,
5. Adequate measurement and analysis of potentially confounding variables, including measurement or discussion of the role of multiple pesticide exposure, or mixtures exposure in the risk estimates observed,
6. Overall characterization of potential systematic biases in the study including errors in the selection of participation and in the collection of information, including performance of sensitivity analysis to determine the potential influence of systematic error on the risk estimates presented (*e.g.,* Greenland's formula)
7. Evaluation of the statistical power of the study, if under-powered to observed an effects, appropriate discussion and/or presentation of power estimates,
8. Use of appropriate statistical modeling techniques, given the study design and the nature of the outcomes under study.

OPP will finalize the *draft* Framework for incorporating epidemiology into risk assessment, including factors to consider when selecting studies for inclusion in qualitative or quantitative aspects of the risk assessment. FIFRA Scientific Advisory Panel comments on OPP's draft framework can be found at:
http://www.epa.gov/scipoly/sap/meetings/2010/020210meeting.html#transcripts

3.3. Completion of Data Evaluation Records (DERs) for Journal Articles

Once a journal article has been determined useful for risk assessment (qualitatively or quantitatively), OPP staff should complete a DER (or AbDER) for the review using the standard toxicology template form that is the best fit for the type of study described in the article following the established Standard Operating Procedures (*e.g.,* HED SOP 2001.02 and 2001.03).

The purpose of completing the DER is to ensure an efficient and consistent process for documenting reviews of open literature and avoiding duplicative and possibly conflicting efforts associated with study. The procedures for completion and submittal of DERs for endpoints that are categorized as "qualitative," "quantitative" or "unacceptable" are described below in **Sections 3.3.1** through **3.3.3**, respectively.

An MRID number needs to be obtained for any open literature used or qualitatively or quantitatively in risk assessments (based on the screening criteria discussed in **Section 2.1**). See **Section 2.2** for instructions on obtaining an MRID number. Once the risk assessor has obtained

an MRID number and completed the journal DER (including secondary and/or peer review), the journal DER should be out-processed as for any other OPP work.

3.3.1. Completion and Submittal of Journal DERs for Data Used Quantitatively

Review summaries of open literature data that are used quantitatively (*i.e.,* to establish endpoints and points of departure for risk assessment) should include all available information that would normally be included as part of the current guideline/non-guideline DER templates. Although the journal DER should include the same type of information, it is expected that they will be reduced in length and detail as compared to standard DERs because raw data are generally not available for review and only the data in the published study are being evaluated. The basic study requirements should be verified and reported using the standard DER template that best fits the article content. The review should document all statistically or biologically significant effects. In addition, the duration of exposure, the magnitude of the effect, and the test concentration (nominal, measured, and time-weighted average, if it can be determined) at which the effect was observed should be documented. In addition, the reviewer is encouraged to include relevant figures and tables from the study that include key findings; table and figure captions should properly cite the relevant publication if the figure and/or table is copied from the publication.

All open literature studies that are categorized as "quantitative" need to undergo secondary review and/or peer review within OPP.

3.3.2. Completion and Submittal of Journal DERs for Data Used Qualitatively

At the discretion of the evaluator, DERs may be completed for open literature studies that include data to be used qualitatively in the risk assessment. The evaluator should consider preparing a DER for studies that provide novel information and are critical to the conclusions of the assessment. In addition, DERs for qualitative assessments should include the same type of information and level of detail as reviews that are completed for quantitative assessments. DERs for qualitative data need to include descriptions of the study limitations which preclude their quantitative use. These DERs should undergo secondary review.

3.3.3. Completion and Submittal of Journal DERs for Unacceptable Open Literature Studies

Literature studies that are determined to be unacceptable do not require a DER since they will not be considered for use in the OPP risk assessment. However, DERs should be completed for unacceptable studies that are submitted to the Agency by outside stakeholders. The level of

detail for an "unacceptable" review relative to "quantitative" and "qualitative" reviews should be significantly reduced. The DERs for unacceptable studies should be condensed into 1–2 pages and focus on the limitations of the study which preclude its use in hazard/risk assessment. Detailed description of the experimental design is not required for studies that are categorized as "unacceptable."

4. Use of Open Literature in OPP's Risk Assessments

The extent to which open literature data categorized as either "qualitative" or "quantitative" should be used in the risk assessment is discussed below in **Sections 4.1.1** and **4.1.2**, respectively. Open literature studies that pass the initial screen and are determined to be "unacceptable" based on the risk assessor's review should not be included in the risk assessment.

4.1. Use of "Quantitative" Open Literature Data in Risk Assessment

As previously discussed in **Section 3.2.2**, endpoints and points of departure from the open literature that are more sensitive (or lower) than the lowest registrant-submitted study and are categorized as "quantitative" may be used for establishing a point of departure for risk assessment.

Where data from open literature are deemed to be of sufficient quality to permit their use quantitatively in OPP's risk assessment, the assessment needs to provide a relatively comprehensive review of the open literature study associated with the dose/endpoint. Any open literature data that are categorized as 'quantitative' and used for endpoint and dose selection in the risk assessment needs to be fully described in the toxicological effects section of the assessment, with particular emphasis on those open literature endpoints that result in lower values than those used in previous risk assessments. In addition, the risk assessor should cite the DERs for all 'quantitative' endpoints and doses in the risk assessment. If applicable, the risk assessor needs to provide clear and transparent rationale for quantitatively using the open literature data over guideline and GLP-compliant data. As described in more detail in **Section 3.2.**, the criteria used to evaluate test guideline studies and best professional judgment should be used to determine the appropriate use of an open literature study in risk assessment.

4.2. Use of "Qualitative" Open Literature Data in Risk Assessment

Although data from the open literature that are categorized as "qualitative" are not appropriate for quantitative use (*i.e.*, dose selection), they should be discussed in the toxicological effects and risk characterization sections of the risk assessment as additional lines of evidence to support risk conclusions regarding metabolism, adverse effects of concern, life stage susceptibility, and mode of toxic action. A clear rationale should be provided in the effects section that describes why the data were not used quantitatively. These reasons might include limitations in the study design, lack of sufficient information to substantiate whether the conclusions/endpoints/doses are

accurate, and other uncertainties that confound the ability to discriminate a dose-related effect. As previously stated, best professional judgment should be used to determine the appropriate use of an open literature study in risk assessment.

Conclusion

In summary, this document provides guidance for the use of open literature publications and criteria for judging its quality and relevance in support of OPP human health risk assessments. To permit independent review of the study findings, the study method and findings need to be sufficiently documented and transparent. In principle, the more details of the methodology and findings, the greater the confidence in the publication's reliability. Studies that use scientifically sound and appropriate methodology and relevant routes of exposure are important to consider because they may provide valuable information for the risk assessment.

5. References

Crissman et al (2004) Best Practices Guideline: Toxicologic Histopathology. Toxicologic Pathology 32: 126–131.

Falagas (2006) Peer Review in Open Access Scientific Journals. Open Medicine Vol.1, No.1.

Klimisch, H.J., Andreae, M. and Tillman, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25: 1–5.

Society of Toxicological Pathology's Best Practices Guideline paper (Toxicological Pathology 32:126–131; 2004).

U.S. Environmental Protection Agency (USEPA). Series 870 Health Effects Test Guidelines (http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm)

USEPA. 1993. Pesticide Reregistration Rejection Rate Analysis Toxicology. Office of Prevention, Pesticides, and Toxic Substances. EPA 738-R-93-004.

U.S. EPA. 2010. Evaluation Guidelines for Ecological Toxicity Data in the Open Literature, Procedures for Screening, Reviewing, and Using Published Open Literature Toxicity Data in Ecological Risk Assessments; November 4, 2010

Van den Brandt *et al.* (2002) The Contribution of Epidemiology. Food and Chemical Toxicology Vol. 40 Issues 2–3: Feb.-March 2002: 387–424.

Attachment 1:

Criteria for Invalidation of Open Literature Studies

- Lack of characterization of the test substance
- Lack of characterization of vehicle/solvent controls used
- Inadequate or missing analytical data
- Insufficient number of animals tested
- Poorly controlled test environment
- Insufficient number of dose levels tested
- Insufficient number of parameters evaluated
- Lack of clinical pathology data
- Lack of macroscopic and/or histopathology data
- Lack of appropriate statistical methodology
- Deficiencies in reporting of study data