RESIDUE CHEMISTRY BRANCH

STANDARD EVALUATION PROCEDURE

Residues in Meat, Milk, Poultry and Eggs: Dermal Treatments

Prepared by:

Richard A. Loranger

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3. Recipient's Accession No. PB88-243217/AS

4. Title and Subtitle
HAZARD EVALUATION DIVISION: STANDARD EVALUATION PROCEDURE Residues in Meat, Milk, Poultry and Eggs: Dermal Treatments

5. Report Date
JULY 1988

6.

7. Author(s)
Richard A. Loranger

8. Performing Organization Rept. No.
540/09-88-092

9. Performing Organization Name and Address
U.S. Environmental Protection Agency/OPP/HED/TS-769C
401 M Street SW
Washington, D.C. 20460

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address
Same as #9

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

This document describes how the Residue Chemistry Branch reviews studies conducted by registrants to determine residues of a pesticide in animal tissues, milk, and eggs following dermal treatment (spray, dip, pour-on, etc.) of livestock. It informs the public and registrants of what factors are considered in the review process with respect to the handling of the animals, the actual application of the pesticide, the collection and storage of milk/egg/tissue samples, and the analysis of the latter for residues of the pesticide and its toxic metabolites. The availability of this document for public comment was announced in the Federal Register on March 23, 1988 with the deadline for comments being May 23, 1988. No comments relative to this SEP have been received as of June 16, 1988.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
Unclassified and freely available	Unclassified	14
	20. Security Class (This Page) Unclassified	22. Price A03

STANDARD EVALUATION PROCEDURE

PREAMBLE

This Standard Evaluation Procedure (SEP) is one of a set of guidance documents which explain the procedures used to evaluate environmental and human health effects data submitted to the Office of Pesticide Programs. The SEPs are designed to ensure comprehensive and consistent treatment of major scientific topics in these reviews and to provide interpretive policy guidance where appropriate. The Standard Evaluation Procedures will be used in conjunction with the appropriate Pesticide Assessment Guidelines and other Agency Guidelines. While the documents were developed to explain specifically the principles of scientific evaluation within the Office of Pesticide Programs, they may also be used by other offices in the Agency in the evaluation of studies and scientific data. The Standard Evaluation Procedures will also serve as valuable internal reference documents and will inform the public and regulated community of important considerations in the evaluation of test data for determining chemical hazards. I believe the SEPs will improve both the quality of science within EPA and, in conjunction with the Pesticide Assessment Guidelines, will lead to more effective use of both public and private resources.

Anne L. Barton, Acting Director
Hazard Evaluation Division

RESIDUE CHEMISTRY BRANCH

STANDARD EVALUATION PROCEDURE

Residues in Meat, Milk, Poultry and Eggs: Dermal Treatments(1)

I. INTRODUCTION

(A) Purpose of the Standard Evaluation Procedure

This Standard Evaluation Procedure is designed to aid Residue Chemistry Branch reviewers in their evaluations of residue studies reflecting dermal treatment of livestock including poultry. The document also informs pesticide manufacturers and the public of the considerations involved in review of such data.

(B) Background Information

Animal treatment studies are required under 40 CFR 158.125 when a pesticide is requested for registration for direct application to livestock* under the amended Federal Insecticide, Fungicide, and Rodenticide Act. The section of the Residue Chemistry Guidelines (Subdivision O) dealing with such studies is 171-4(c)(3).

These animal studies are also needed to set tolerances for residues of pesticides in meat, milk, poultry and eggs under Section 408 of the Federal Food, Drug and Cosmetic Act. Exposure of the public to pesticide residues from ingestion of these raw agricultural commodities can then be estimated.

(C) Objective of Feeding Studies

As noted in 40 CFR 180.6 a conclusion must be made whether finite residues of a pesticide and "its conversion products" will be found in meat, milk, poultry and eggs

---

(1) Livestock feeding studies and feed-through uses of pesticides will be addressed in a separate Standard Evaluation Procedure being developed concurrently.

* The term "livestock" refers to cattle, goats, hogs, horses, poultry and sheep.

when animals are "fed agricultural products bearing... pesticide residues," when pesticides are used "directly on the animal," or when pesticides are "administered purposely in the feed or drinking water." To make this conclusion direct animal treatment studies and/or feeding studies (discussed in separate Standard Evaluation Procedure) are required to determine the extent to which the pesticide transfers to meat, milk, poultry and eggs. Such experiments should measure the "total toxic residue" (parent pesticide plus its degradation products, metabolites and impurities of toxicological significance) in these commodities following oral ingestion and/or dermal treatment depending on the proposed uses of the chemical. If the data then show that finite residues are expected from such uses, the studies will be used to determine the appropriate tolerances.

II. INFORMATION TO BE SUPPLIED

The submitted study should include all the information needed to describe completely the handling of the animals, the actual application of the pesticide (i.e., the treatment portion of the study), the analyses of the tissues, milk, and eggs for the residue of concern, and the handling/storage of samples between collection and residue analysis. Appendix 1 lists the basic information required for review of livestock dermal studies. This list represents a shortened version of the Data Reporting Guidelines to be developed in FY 87.

Useful Standard Evaluation Procedures and Data Submission Guidelines related to this document include those on Analytical Methods, Animal Metabolism, and Storage Stability (being developed concurrently).

III. THE DATA EVALUATION PROCESS

(A) Determine Need for Study

Animal treatment studies are required whenever a registration is requested for direct application of a pesticide to livestock (including poultry). Such uses include dusts, sprays, dips, pour-ons, dust bags, backrubbers, and ear tags. Treatment of livestock premises (which is an indirect application to animals) will be covered later in a separate Standard Evaluation Procedure.

Separate studies are required for cattle, swine, and poultry (assuming dermal uses requested for all three). Depending on the routes of entry of the chemical (i.e., its absorbency through skin versus oral ingestion by licking/grooming; levels of residues found in cattle and hogs), additional studies may be required for other species (goats, sheep, horses).

Data reflecting exaggerated treatments are desirable but generally not required unless the registrant wants to show the use falls under Category 3 of 180.6 (i.e., no reasonable expectation of finite residues in meat/milk/eggs). In that case (as with feeding studies) the registrant has to show that no detectable residues are incurred following exposure to 10X the desired rate.

(B) Read Study and Identify Data Gaps

Next, the reviewer reads the study to determine whether the information listed in Appendix 1 has been submitted. Any omissions which are significant enough to prevent a complete examination of the study should be noted in the review. Such data gaps must be clearly identified so the registrant can be informed by the Product Manager of the need for additional data and/or details on the conduct of the study.

(C) Assess the Appropriateness and Adequacy of the Data

- The reviewer then considers the adequacy of the supplied data/information. In doing so, the reviewer should keep in mind the following major points:

  - Did the animals receive the maximum dermal treatment with respect to the types of formulations (i.e., those likely to give highest residues) and concentration, number, and frequency of application?
  - Were animals sacrificed within the proposed preslaughter interval?
  - Were the proper tissues and r.a.c.'s (milk/eggs) sampled for both control and treated animals?
  - Did the registrant provide storage stability data to show residues would not degrade between sample collection and analysis?
  - Was the total toxic residue determined in tissues, milk and eggs using a validated analytical method?

For a more detailed list of points the reviewer should consider, refer to Appendix 2. In addition to the latter, the technical guidance available in reviewer aid materials such as the Residue Chemistry Guidelines and sources listed in Appendix 3 should be utilized.

Having considered all the points involved (Appendix 2) the reviewer writes a summary of the study clearly outlining
(1) data gaps/omissions (as noted above in (B)) and
(2) deficiencies in the reported data (such as spray/dip concentrations too low; toxic metabolites not measured; preslaughter interval too long).

(D) Make a Regulatory Determination

As noted under the Introduction, a determination must be made as to whether finite residues of the pesticide will be found in tissues/milk/eggs and, if found, what tolerances are appropriate to cover such residues.

If data gaps/deficiencies prevent such a determination, the reviewer so indicates and outlines what corrective steps need to be taken. If the study is adequate, the reviewer categorizes the proposed use of the pesticide under 40 CFR 180.6(a). (In many cases the ^{14}C metabolism study indicates whether the chemical transfers to animal products.) For the use to be placed under Category 3 of 180.6(a) (i.e., no reasonable expectation of finite residues) no detectable residues should be found after exposure to the pesticide at 10X the proposed rate. In that case no tolerances are required for the chemical in animal products.

The presence of detectable residues from the 10X or lower exposure levels means the use falls under Categories 1 or 2 of 180.6(a) ("finite residues will actually be incurred" or "there is a reasonable expectation of finite residues"). In that case the reviewer must determine what tolerance levels are appropriate. This generally involves using the maximum residues found in animals treated at the maximum proposed rate. This should reflect multiple modes of exposure if the label so permits (for example, dermal sprays plus backrubber). Also, if residues of the pesticide are found on feed items, tolerances must be set high enough to cover both dermal and oral routes of exposure. For this purpose it is generally assumed that residues from from oral ingestion and dermal treatments are additive. It should also be noted that the tolerances are almost always set to one significant figure (e.g., 0.01, 0.2, 0.5 ppm) for those $\leq$1 ppm. On occasion, fractional values greater than 1 ppm may be acceptable, although whole numbers are still preferrable.

Although separate tolerances are established for meat, fat and meat byproducts (latter include liver and kidney), they are often set at the same numerical value. However, if residues concentrate in fat, the latter may receive a higher tolerance. Likewise, when milk residues are found to partition mostly into the milk fat, the tolerance is generally set on the latter with the equivalent whole milk value (1/25X milk fat tolerance) expressed parenthetically (e.g., "milk fat [reflecting 0.02 ppm in whole milk]..... 0.5 ppm"). If liver or kidney has significantly higher levels than other tissues, a separate tolerance is established for that organ. The meat byproduct tolerance is then qualified to show the separation of that tissue as in the following example: meat byproducts (except kidney) ..... 0.1 ppm; kidney ..... 2 ppm. For dermal uses on swine and chickens it is likely that separate higher tolerances will be required for hog and poultry skin.

Unlike the situation with residues on feed items (wherein cattle tolerances are automatically extended to goats, horses and sheep), tolerances are established only for those species to be listed on product labels.

Having completed the various considerations discussed above, the reviewer states whether the meat/milk/egg tolerances (existing or proposed depending on the type of registration action) are appropriate. If they are not, the proper ones are listed so the Product Manager can inform the registrant of the requirement for revised tolerances (i.e., a new tolerance petition or a revised Section F in a pending petition). In some cases, efficacy considerations permitting, the reviewer may also be able to suggest changes in the use pattern (application rate, number and timing of treatments) so that revision of tolerances is not necessary.

IV. REVIEWER AIDS

There are a large number and variety of source materials that are available to assist the data reviewer in the evaluation process. A listing of some of the more useful references that reside within the Branch is provided in Appendix 3 to this document.

- APPENDIX 1 -

INFORMATION REQUESTED OF PETITIONER FOR DERMAL LIVESTOCK STUDIES

1. Identity of active ingredient (a.i.) and relative levels of a.i. and impurities.

2. Type of formulation (WP, EC, dust, pour-on), % active ingredient, amount of a.i. per gallon for liquids, and % of each inert ingredient.

3. Mode of application (high pressure spray, ULV spray, dip, backrubber, pour-on, dust, ear tag).

4. Treatment rates-concentration and time for dips; spray concentration plus volume per animal; quantity of pour-on formulation per animal.

5. Number and frequency of treatments.

6. Identity of solvent/diluent and any spray adjuvants.

7. Identity of animals and number per treatment level.

8. Housing, diet composition, and feeding/milking schedules during acclimation and treatment periods.

9. Sampling dates for milk and eggs; sample compositing technique if applicable.

10. General health, body weights, feed consumption, and egg/milk production prior to and during treatment period.

11. Mode and date of sacrifice (time in hours from final application of pesticide) and organs sampled (compositing of latter if applicable).

12. Conditions and length of sample storage (including shipping if applicable) prior to extraction/analysis.

13. Detailed description of analytical method and chemical species determined.

14. Recovery data demonstrating validity of analytical method.

15. Dates of sample extraction and analysis of extract (also storage conditions of extract if applicable).

16. Data demonstrating stability of residues under observed storage of samples (and extracts if applicable).

17. Measured residue levels in muscle, fat, liver, kidney (except poultry), poultry and hog skins, milk, and eggs.

18. Representative raw data and chromatograms of control, spiked, and treated samples supporting reported residues and recoveries.

19. Names/addresses of organizations/personnel involved in the feeding and analytical portions of the study.

20. Quality assurance procedures - measures/precautions to ensure fidelity of study and analyses (such as animal identification, proper labeling/coding of samples, record keeping procedures, high quality equipment and reagents, etc.).

-APPENDIX 2-

POINTS TO CONSIDER IN EVALUATING DIRECT ANIMAL TREATMENT STUDIES

Application of Pesticide to Animals

- Was the material applied clearly identified as to its chemical structure and purity? Is there any impurity of concern (such as hexachlorobenzene)?

- Were the proper animals treated with the pesticide? Cattle, swine and poultry each require a separate study for dermal uses. Healthy animals should be chosen with dairy cows in mid-lactation and chickens in full lay. For sheep the data should reflect use on shorn and unshorn animals unless the label specifies treatment at only one of these stages. Data may not be required for goats and horses (and perhaps sheep) if the cattle study shows low residue accumulation for similar uses.

- Did each treatment level involve an adequate number of animals? A poultry study should include 10 birds per level (allowing 3-4 samples per composite), while only 3 individuals are needed for cattle and other livestock (swine, goats, horses, sheep). Each study should also include untreated (control) animals (10 for poultry, 3 for larger animals).

- Did feed consumption, body weights, and milk/egg production decrease drastically after treatment started? If so, animals did not receive an adequate acclimation period or the pesticide is producing deleterious effects. Toxicology Branch should be alerted as to the possible hazard of dermal use of the pesticide.

- What formulations and modes of application were employed? Generally, each formulation and application technique should be tested. However, data from dips and high pressure wetting sprays can cover use of dusts (but not vice versa) and pour-ons (provided ca the same amount of active ingredient is applied per animal). If a product can be diluted with an organic solvent, data using the proper diluent will be required (i.e., data using water as the solvent will not cover uses of other diluents). Data are often not required for ear tag uses as long as studies are available on full body treatments (sprays, dips) or backrubbers.

- How many separate studies or trials were conducted? For dermal uses it is advisable to perform several unrelated tests or at least allow applications by various individuals to see if applicator differences affect residue levels.

- Were adequate quantities of pesticide applied per treatment? At a minimum animals should receive the highest exposure to pesticide permitted by the label. For sprays this entails the maximum solution concentration and spray volume per animal. For dips the most concentrated solution and longest exposure time in the tank should be employed. Pour-on studies must use the maximum amount of solution permitted per animal. Free access should be given to backrubbers and dust bags. Studies at exaggerated concentrations/doses are desirable, but only required if the registrant wants to prove the use can be classified under Category 3 of 40 CFR 180.6 (a).

- How many applications were made to the animals? What was the frequency of treatment? Animals should receive the maximum number of applications with the minimum retreatment interval specified on the label. However, if the petitioner can demonstrate that milk residues have declined to non-detectable levels within the minimum retreatment period, data for multiple applications to dairy animals would not be necessary. For meat animals biopsy samples of fat tissue could be used for the same purpose. In those cases where daily exposure is involved (dust bags, backrubbers, ear tags) data is required to show that residues plateaued in milk or tissues by the time of sacrifice.

- Were treated and control animals housed separately? Since animals (especially cattle) often groom and lick each other, the controls should be kept separate from treated animals. The latter should be allowed free access to each other to simulate actual animal husbandry. However, in some cases it may be useful to restrain a few additional treated animals in harnesses to demonstrate the extent of absorption through the skin (versus oral ingestion by licking the fur).

Sample Collection and Analysis

- What sampling procedure was utilized for milk and eggs? Milk and eggs should be collected and analyzed daily until residues have plateaued. This procedure should be repeated after each dermal application unless the residues have declined to non-detectable levels within the retreatment interval (in which case multiple applications do not have to be examined at all). Milk samples from different cows should not be pooled, although up to 3 eggs may be composited. Analyses must be conducted on whole milk and eggs (yolk and white). In addition, several milk samples should be analyzed to determine how residues partition into milk fat. Sometimes information on the latter may be found in the metabolism study.

- Were animals sacrificed within the proposed preslaughter interval? Generally, we do not accept PSI's longer than 3 days as being practical (although we have accepted 5 days and longer in certain cases). In any case, the animals should be sacrificed within the PSI on the label (provided it is a practical one). However, with dermal treatments residues may not peak until a week or so after treatment. Therefore, if the label PSI is short (1-3 days), additional data reflecting longer intervals are advisable to establish the true maximum residue levels for tolerance calculations.

- Which organs were sampled? Were samples composited? For cattle, goats, hogs, horses and sheep, analyses are required for muscle, fat, liver and kidney. Hog skin should also be analyzed after dehairing and steaming as in commercial slaughterhouses. Data on fried pork skins are also needed, although the tolerance is set on the uncooked commodity as the raw agricultural commodity. If residues concentrate upon frying, a food additive tolerance will be required for the fried skins. For poultry, samples include muscle (breast, thigh), liver, skin, and fat. Tissues should not be composited except in the case of poultry where it is acceptable if at least 3 unique samples are analyzed per feeding level (i.e., 3-4 tissues per composite if 10 hens per level).

- Were all samples frozen as soon as possible after collection/sacrifice? Is storage stability data available reflecting intervals from collection to extraction and from extraction to residue quantitation? Refer to separate Standard Evaluation Procedure on Storage Stability for more details.

- Was the total toxic residue measured by a validated method? Has the method been tested by EPA and published in the FDA Pesticide Analytical Manual? Parent compound plus all metabolites and impurities of toxicological concern should be determined in milk/eggs/tissues. Recoveries should be $\geq$ 70%. For more details on analytical methodology refer to the Standard Evaluation Procedure (SEP) on that topic. For background on how to determine the "total toxic residue" refer to the S.E.P. on Animal Metabolism.

- Was the method sufficiently sensitive? The sensitivity should be 0.01-0.05 ppm or less.

- Were control values less than the method sensitivity? If samples from untreated animals are found to contain apparent residues, the validity of the study is questionable. Keeping controls and treated animals in the same enclosed area may lead to such results due to grooming between individuals.

- Did the submitter provide raw data and chromatograms to support the reported residue levels? Representative chromatograms should be presented for control, fortified and treated samples of each commodity. Actual values should be reported for each sample rather than an average for an entire group.

- Was there reasonable agreement between samples from the same exposure level? If one value is considerably higher than the others, can it be discarded as an outlier?

Other Considerations

- Are the results of the cold dermal study consistent with the radiolabeled metabolism study? The levels of the residue of concern should be similar provided comparable amounts of active ingredient were applied per animal using the same mode of treatment, pre-slaughter intervals and numbers of applications.

- Has a Registration Standard been issued for this chemical and, if so, is it being used in evaluation of the dermal study?

- Is the pesticide undergoing Special Review? If so, has any relevant information been submitted under that process?

- Is there any other unpublished (such as data submitted in earlier petitions, Section 18 and 24(c) requests) or published information (such as Codex/FAO Monographs) known to us about feeding of this pesticide to livestock? If so, this information should be consistent with the results of the new study.

- APPENDIX 3 -

REVIEWER AIDS MATERIALS

Following is a listing of some of the more useful source materials within the Residue Chemistry Branch that could prove helpful in reviewing livestock dermal studies:

(1) Federal Food, Drug, and Cosmetic Act, as amended, §§ 408-409.

(2) Federal Insecticide, Fungicide, and Rodenticide Act, as amended.

(3) Subdivision O [Residue Chemistry] of the Pesticide Assessment Guidelines, § 171-3 and § 171-4, prepared by OPTS/EPA, 1982.

(4) Subdivision D [Product Chemistry] of the Pesticide Assessment Guidelines, prepared by OPTS/EPA, 1982.

(5) Code of Federal Regulations [40 CFR 158 and 180; 21 CFR 193 and 561], General Services Administration, Washington, D.C., updated annually.

(6) Pesticide Chemical News Guide, R. E. Duggan, editor, Food Chemical News, Inc., Washington, D.C., 1982, updated monthly.

(7) "Guidelines for Data Acquisition and Data Quality Evaluation in Environmental Chemistry," Anal. Chem. 52, 2242-2248 (1980).

(8) Acceptable Common Names and Chemical Names for the Ingredient Statement on Pesticide Labels, 4th ed., C. R. Blalock, et al., editors, OPP/EPA, 1979, available from National Technical Information Service, Springfield, VA.

(9) Farm Chemicals Handbook, Meister Publishing Co., Willoughby, OH, updated annually.

(10) Nanogen Index: A Dictionary of Pesticides and Chemical Pollutants, K. Packer, editor, Nanogens International, Freedom, CA, 1975 (updated periodically by supplements).

(11) F.D.A. Pesticide Analytical Manual, Volumes I and II, available from the National Technical Information Service, Springfield, VA.

(12) Guidelines on Supervised Studies to Provide Data on the Nature and Amount of Pesticide Residues in Products of Animal Origin, Codex Committee on Pesticide Residues, draft dated Nov. 5, 1984.

(13) Statistical Methods Applied to Experiments in Agriculture and Biology, 7th. ed., G. W. Snedecor, Iowa State College Press, 1980.

(14) Registration Standards on various individual pesticides, prepared by OPTS/EPA, (several issued each fiscal year).

(15) Directory of Professional Workers in State Agricultural Experiment Stations and Other Cooperating State Institutions, published by U.S. Dept. of Agriculture.

(16) Various reference texts and journal publications of a scientific or agricultural nature, including FAO/Codex Monographs; Residue Reviews (assorted volumes); Analytical Chemistry (assorted issues); Journal of Agricultural and Food Chemistry (assorted issues); Journal of the Association of Official Analytical Chemists (assorted issues).

(17) Residue Chemistry Branch files: petition and registration files; reviewer aids; policies; subject files; reading files; cultural practices files (cattle, poultry, swine); et al.