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EPA

Pesticide Reregistration Rejection Rate Analysis Residue Chemistry

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 24 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Dear Interested Party,

I am pleased to send you the first chapter of EPA's Rejection Rate Analysis, on the scientific discipline Residue Chemistry. This document is the first in a series of guideline-by-guideline analyses which will identify the factors that most frequently cause studies required for pesticide reregistration to be rejected.

EPA believes that the submission of unacceptable studies is the most significant factor in delaying production of Reregistration Eligibility Documents, or REDs. Unless study rejection rates are significantly reduced, EPA's Office of Pesticide Programs (OPP) will not meet its REDs production schedule.

Thus, OPP has launched an intensive effort, with the cooperation and active involvement of the pesticide industry, to analyze rejected studies, to determine why they were found to be unacceptable, and to find ways to improve the quality and increase the acceptability of studies submitted to EPA in the future.

The Rejection Rate Analysis will enable OPP to provide pesticide registrants with information on rejection factors to minimize their reoccurrence in future studies; reassess the adequacy of its guidance to registrants and internal review processes and criteria; and determine the appropriate regulatory response to future rejected studies. As a result, the quality and acceptance rate of studies submitted for pesticide reregistration are expected to improve.

The first chapter of the Rejection Rate Analysis focuses on the discipline Residue Chemistry. This chapter was produced through a workgroup effort involving OPP scientific and regulatory staff, ten scientists representing the pesticide industry, and the IR-4 Program. As you will notice in reading the document enclosed, "Industry Comment" and "EPA Response" are provided for each rejection factor considered.

OPP will continue to involve the pesticide industry in its development of future chapters of the Rejection Rate Analysis. We plan to issue other completed chapters during the rest of 1992, and to complete the entire study early in fiscal year 1993.

We encourage all pesticide producers and all pesticide testing laboratories to read and use the Residue Chemistry chapter enclosed, when providing new pesticide studies to EPA and when upgrading existing studies in support of pesticide reregistration. About a dozen pesticide companies already have made a commitment to conduct their own study rejection rate analyses. OPP commends these companies, and we encourage others to take similar action.

We will keep you informed of the progress of the Rejection Rate Analysis, and of voluntary efforts on the part of the industry to comply with its findings and recommendations, in the "Pesticide Reregistration Progress Report." If you are not already receiving this quarterly publication and would like to be added to the mailing list, please contact the Special Review and Reregistration Division (H-7508W), Office of Pesticide Programs, US EPA, 401 M Street, SW, Washington, DC 20460, telephone 703-308-8000. We are also interested in receiving your comments and reactions regarding the enclosed Residue Chemistry chapter.

Thank you for your attention, and again, we encourage your voluntary, active participation in this program to reduce pesticide study rejection rates.

Sincerely yours,

Douglas D. Campt, Director
Office of Pesticide Programs

Enclosure

REJECTION RATE ANALYSIS

RESIDUE CHEMISTRY

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REJECTION RATE ANALYSIS

I. INTRODUCTION

This rejection rate analysis has been undertaken by the Special Review and Reregistration Division (SRRD), the Health Effects Division (HED) and the Environmental Fate and Effects Division (EFED) in the Office of Pesticide Programs (OPP) of the Environmental Protection Agency (EPA). The purpose of this guideline-by-guideline analysis is to identify those factors that most frequently cause guideline studies required for reregistration to be rejected. This information will enable OPP to (a) provide registrants with information on rejection factors to minimize their reoccurrence in future studies, (b) reassess the adequacy of its guidance, (c) determine the appropriate regulatory response to a future rejected study, and (d) make any internal changes in process, procedures or criteria deemed appropriate.

The decision to analyze these factors was made after a FIFRA Reregistration recosting analysis, conducted in the Spring of 1991, indicated that rejected studies posed the most significant potential for delays in the production of Reregistration Eligibility Documents (REDs). Reregistration eligibility decisions require that reasonable risk assessments be performed for all relevant human health and ecological end points for each chemical. Performing such risk assessments requires a "substantially complete" data base. A "substantially complete" data base requires that registrants submit studies of acceptable quality. A significant reduction in rejection rates for most disciplines is required for OPP to be able to meet its production schedule for REDs.

II. SCOPE OF ANALYSIS

The scope of this analysis is limited almost entirely to an examination of rejected studies. While a scientist's review of a study may result in a finding of acceptable, upgradable, unacceptable or supplementary, rejected (i.e. unacceptable) studies are the focus here because a rejected study will more than double the amount of time and resources required to satisfy that guideline. Upgrading a study usually doesn't require as much time to accomplish as repeating the study. A rating of supplementary by a scientist might require substantial new work and add additional time delays to the process.

For residue chemistry, 6 percent (44/722) of the reviewed studies were rated as supplementary. Sixty one percent (27/44) of these supplemental studies are concentrated in two guidelines - animal metabolism (171-4B) and storage stability (171-4E). For these two guidelines, an analysis of the supplemental studies augments the analysis of the rejected studies.

The scope of this analysis is also limited to List A studies. The analysis was confined to List A because (1) List A chemicals represent those chemicals with the longest reregistration history - each chemical case had a Registration Standard published between 1980-1988, (2) List A chemicals are the high-volume food-use chemicals, which could pose the greatest potential risk to human health and the environment and therefore have the highest priority in reregistration, and (3) List A chemicals generate the most extensive data requirements.

To what extent are List A rejection factors representative of Lists B, C, and D? Unfortunately, it is not possible at this time to make such a determination since a random sample of List A, B, C, and D studies was not chosen as the basis for this analysis. Such a sample was not feasible since List B chemicals have only recently completed Phase 4 (FY91); List C chemicals will complete Phase 4 this fiscal year (FY92), and List D chemicals won't complete Phase 4 until next fiscal year (FY93). Consequently, there was not an adequate pool of reviewed studies across lists for each guideline to support a randomly drawn data base. Furthermore, many List B and C study reviews, conducted in Phase 4, were based on examination of the summaries only. For consistency, the decision was made to limit this analysis to consideration of full study reviews only.

The rejection factors identified in this assessment of List A rejected studies could plausibly either <u>overstate</u> or <u>understate</u> the number of rejection factors likely to be found in any future assessment of List B, C, and D rejected studies. On the one hand, many List A studies were initiated in response to the Registration Standards prior to both the 1982 guidelines and

development of acceptance criteria in Phase 3 (1989) and consequently may have been rejected by criteria that were not in place at the time the study was conducted. In this case the corresponding rejection factors are not likely to be repeated in List B, C, and D studies since the data-call-ins have all been issued subsequent to OPP's publication of its guidelines and acceptance criteria. On the other hand, many of the studies judged to be acceptable now may be repeat studies. Consequently, the rejection factors identified here may omit factors that were responsible for previous submissions being rejected.

Process

First, the Agency reviewed the data evaluation records (study reviews) on a guideline-by-guideline basis in order to:

(1) identify those factors that most frequently caused each guideline study to be rejected;

(2) determine the rejection rates and trends (where the sample size was adequate) for each guideline requirement;

(3) assess the adequacy of EPA's guidance documents with respect to each rejection factor; and

(4) for each rejection factor determine if it is "avoidable."

Secondly, a draft was provided to an industry workgroup of residue chemists for review and comment in order to (1) obtain from a user's perspective the adequacy of EPA's guidance documents corresponding to each rejection factor, and (2) better understand why the rejection factors occur. The industry workgroup included: Chuck Baer (Dupont), Judy Ball (Uniroyal), Jim Campbell (Nor-Am), Rick Holt (Dupont), Bob Larkin (Rohm and Haas), John Magnussen (Dow Elanco), Paula Paul (Nor-Am), Fred Pearson (ICI), Bill Stellar (American Cyanamid), and John Thornton (Miles). Industry and EPA scientists met on April 23, 1992 to discuss the problem areas in order to develop a better understanding of them.

The revised residue chemistry chapter explicitly includes industry comments on each rejection factor and EPA's response to them.

Finally, the revised chapter was sent to the IR-4 program for comment. Their comments are included in this final residue chemistry chapter.

III. RESIDUE CHEMISTRY CHAPTER

This chapter examines the results of the residue chemistry rejection rate analysis. The following information is discussed: (1) a description of the discipline of residue chemistry, (2) the current rate of rejection of residue chemistry studies, (3) a list of the most common factors that have led to the rejection of these studies, (4) industry comments on each rejection factor, (5) EPA response to comments, (6) internal EPA obstacles, and (7) conclusions and recommendations.

IV. DESCRIPTION OF DISCIPLINE

Residue chemistry data are used by the EPA to estimate the exposure of the general population to pesticide residues in food and for setting and enforcing tolerances (maximum permissible level) for pesticide residues in food or feed. The following is a description of the residue chemistry studies that are required by EPA for reregistration:

Metabolism in Plants and Animals (guidelines 171-4A,B). The purpose of conducting metabolism studies is to determine the qualitative metabolic fate of the active ingredient, i.e. examine what happens to it when it is applied to a plant or administered to an animal. This is commonly referred to as the "characterization" of residues of the compound. To obtain this information, the pesticide is labeled with a radioactive atom, to follow the compound to see if and where it breaks down within a plant or animal. Sometimes the "parent" compound (original active ingredient) breaks down into other compounds (metabolites). Metabolism studies are required to document what happens when the compound(s) breaks down within the plant or animal. The determination of whether the residues have been sufficiently characterized is dependent on many factors. Often 90% of the "total radioactive residue" (TRR) is required to be identified for complete characterization. Plant metabolism studies are usually required for a minimum of three diverse crops (unless the pesticide is to be used on only one or two crops). If the metabolism in each of these crops is similar, then the metabolism in other crops is assumed to be similar. If the pesticide is applied to crops used for animal feed, or if the pesticide is intended for treatment of livestock, then animal metabolism studies are required in addition to plant metabolism data. Animal metabolism studies are generally carried out on ruminants (cows or goats) and poultry (chickens).

Significant Metabolites and Tolerance Expression. Using the results of plant and animal metabolism studies, EPA determines which metabolites are of concern and need to be included in the tolerance expression. In each case, this decision is based on (1) the toxicity of the metabolite, and (2) the magnitude of its residue. Metabolites that are toxicologically significant and occur at significant levels require a suitable analytical method. The pesticide active ingredient and any significant metabolites are together called the "total toxic residue" (TTR).

Analytical Methods (guidelines 171-4C,D). Based on plant and animal metabolism study results, EPA requires tolerance petitioners to develop analytical methods to determine all components of the TTR. In some cases, it is not possible to develop a single method that can determine all components of the residue, and several methods are required. Pesticide analytical methods are used to obtain residue data on which dietary exposure

assessment and tolerances are based, and to enforce the tolerance after it is established. Enforcement methods are validated by an independent laboratory before submission to EPA as required by PR Notice 88-5. EPA then validates each new analytical method using a method trial, to ensure that the procedures can actually be used for tolerance enforcement.

Residue Field Trial Data (guideline 171-4K). Once the metabolism data indicate what to look for, and methods are developed to measure the TTR, field experiments are conducted to determine the magnitude of the pesticide residue in or on raw agricultural commodities (RACs). Field trials are required to reflect pesticide use patterns that could lead to the highest possible residues. The pesticide must also be applied at known application rates and in a manner similar to the use directions intended for the pesticide label. Data are normally required for each crop or crop group for which a tolerance and registration is requested and for each raw agricultural commodity derived from the crop.

Storage Stability (171-4E). These studies are required to validate the rate of decomposition of the TTR in or on the RAC between the time of harvest and the final analysis of residues.

Determining the Tolerance Level. A petitioner to obtain a tolerance proposes a tolerance level, based on residue field trial data, which reflects the maximum residue that may occur under "worst-case" conditions as a result of the proposed use of the pesticide. The tolerance must include significant metabolites and must be high enough to cover all components of the TTR. If one component of the residue is significantly more toxic than other components, two levels may be included in the tolerance expression.

Processing data (171-4L). Processing studies are required to determine whether residues in raw commodities may be expected to degrade or concentrate during food processing. If residues do concentrate in processing, one or more food or feed additive tolerances must be established. However, if residues do not concentrate in processed commodities, the tolerance for the RAC itself applies to all processed food or feed derived from it.

Feeding Studies (171-4J). Whenever pesticide residues are detected in feed items, data on the transfer of residues to meat, milk, poultry, and eggs are required. These studies are also required if a pesticide is to be applied directly to animals. Data from these studies determine which components of the TTR are present and at what concentration secondary residues could result in meat, milk, poultry and eggs in order to set appropriate tolerances.

Summary

From the rejection rate perspective, the most critical residue chemistry guideline requirements are the metabolism studies for plants and animals. All other residue chemistry guidelines are contingent upon the adequacy of their results. Since pesticides often undergo significant metabolic changes within crops and livestock, the composition of the toxic residues must first be characterized before the amount of residue present can be determined. Additionally, analytical methods capable of adequately detecting the TTR must be developed prior to conducting field residue trials. Once the TTR is known and adequate methods are developed, field trials can proceed. Storage stability studies, processing studies, and livestock feeding studies may then be conducted.

V. CURRENT REJECTION RATE

The following graphs demonstrate the current and historical rejection rates for each of the residue chemistry guidelines. The historical rate does not include studies that were submitted prior to the publication of the Registration Standards. Due to the limited number of cases, none of the results reported in this section have been tested for statistical significance, and therefore caution should be exercised in their interpretation.

Figure 1 illustrates the overall rejection rate for residue chemistry, which is now estimated at approximately 12 percent. This is down from the overall rate of around 47 percent prior to 1986. As indicated in Figure 1, the overall rejection rate for residue chemistry guidelines has decreased by about 25 percent every year since 1986. However, within the residue chemistry discipline, there are large discrepancies in the rejection rates between guidelines. Therefore, the following graphs show trends by guideline. Some residue chemistry guidelines with an insufficient number of studies were omitted. These guidelines include 171-2, 171-4F, 171-4G, 171-4H, 171-4J, and 171-5.

Figure 2 illustrates what the Agency believes is the current rejection rate within each guideline. The current rate refers to all post-1988 studies that were reviewed by the EPA. The rejection rate (percentage of rejected studies) is given at the top of each guideline bar and the number of rejected studies over the number of studies reviewed are listed inside each bar. Figure 2 depicts the discrepancy in the rejection rate between guidelines.

In order to explore the reasons for such varying rates of rejection, Figure 3 illustrates the rejection rates over time. For each guideline, the rejection rates from three time frames are listed for comparison. The time frames include (a) pre-1986 (not including information received for Registration Standards), (b) from 1986 to 1988, and (c) post 1988. In this figure, the trends across guidelines have been quite different, with no consistent pattern. This comparison illustrates the drop in the rejection rate over time for some guidelines including 171-4B, 171-4D, and 171-4K, and a slight increase over time in the rejection rate for guideline 171-4A. Guideline 171-4C experienced a 14 percent increase in the rejection rate from 1986 to 1988, which dropped to zero again since 1988.

Figure 4 portrays the trend in the crop field trial (171-4K) and livestock metabolism (171-4B) guidelines, which have experienced a dramatic drop in the rate of rejection since pre-1986. The livestock metabolism rejection rate dropped from 80 percent before 1986 to 9 percent since 1988. The crop field trial rejection rate dropped from 45 percent before 1986 to 16 percent since 1988. While the livestock metabolism rejection

rate decreased, the plant metabolism increased slightly during the same time period. The trends for plant metabolism (171-4A) and processed food (171-4L), which have remained relatively constant over time, are portrayed in Figure 5.

Summary

Key implications that might be drawn from these graphs include:

(1) overall rejection rates in residue chemistry appear to have gone down dramatically;

(2) the livestock metabolism (171-4B) and crop field trials (171-4K) guidelines have shown substantial declines in their rejection rates;

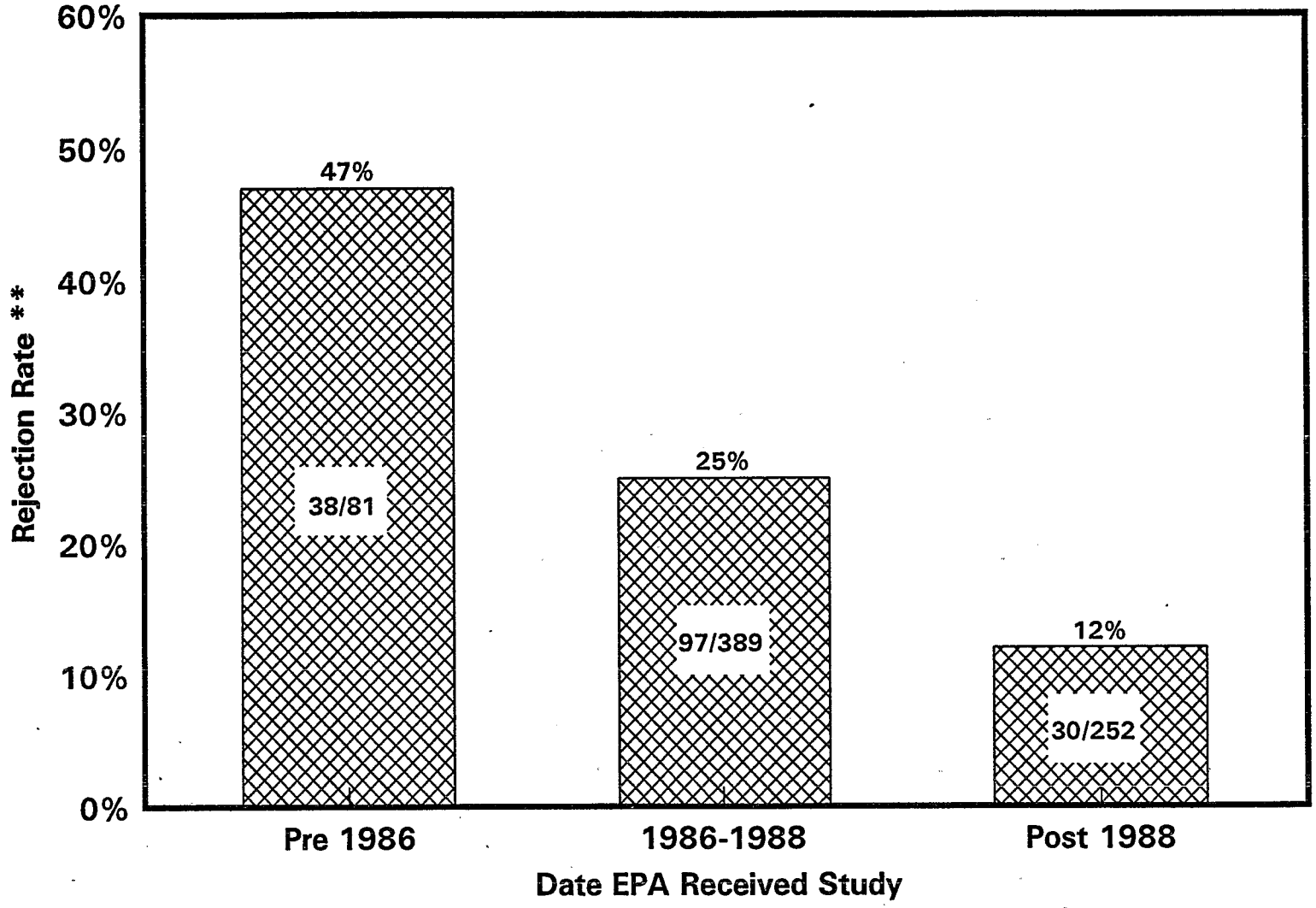
(3) for the plant metabolism (171-4A) and processed food (171-4L) guidelines, the rejection rate trends do not reflect substantial improvement;

(4) processed food (171-4L), plant metabolism (171-4A) and crop field trials (171-4K) still have high rejection rates;

(5) none of the implications discussed above are based on statistically significant results, and therefore caution should be exercised in interpreting them.

FIGURE 1

LIST A - REJECTION RATE FOR ALL RESIDUE CHEMISTRY GUIDELINE REQUIREMENTS



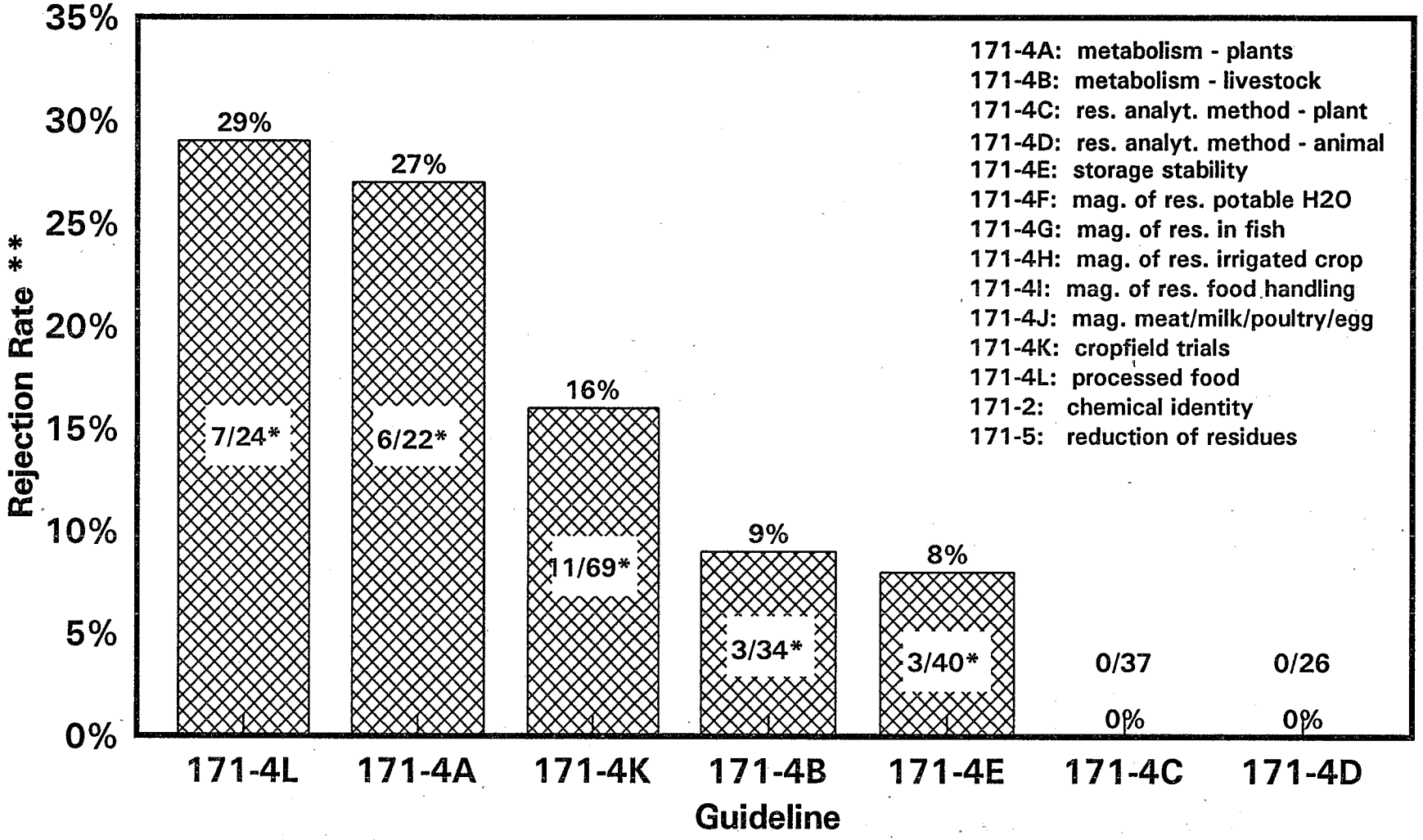
* Numerator = the number of rejected studies; denominator = the total number of reviewed studies.

** Of the total studies reviewed for all guidelines, the percentage of studies that were rejected.

NOTE: Rejection rates do not include studies submitted prior to Registration Standards.

FIGURE 2

LIST A - CURRENT (POST 1988) REJECTION RATE BY RESIDUE CHEMISTRY GUIDELINE



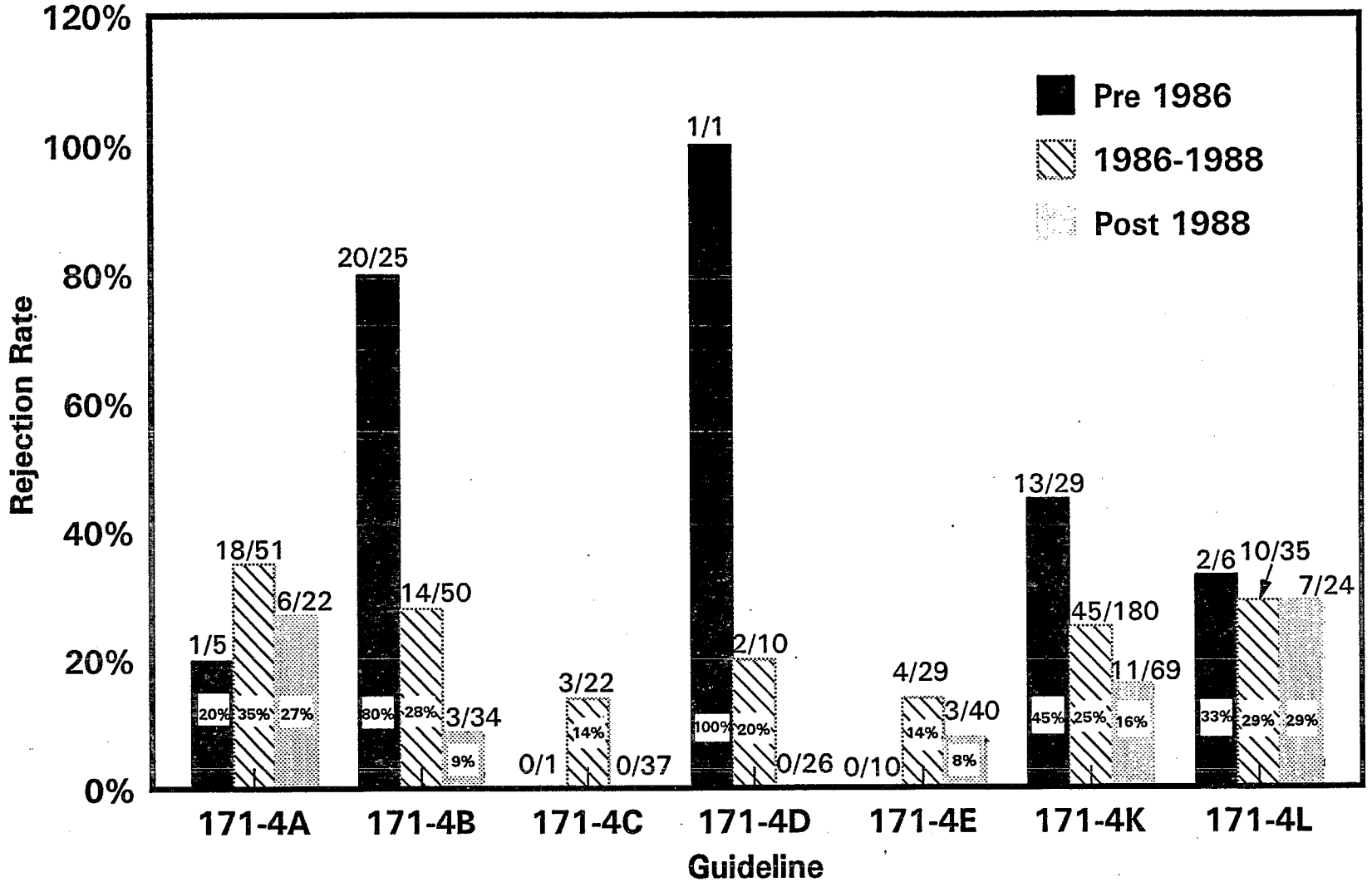
* Numerator = the number of rejected studies; denominator = the total number of reviewed studies.

** Of the total studies reviewed under that guideline, the percentage of studies that were rejected.

Note: insufficient data to evaluate 171-2, 171-4F, 171-4G, 171-4H, 171-4I, 171-4J, AND 171-5.

FIGURE 3

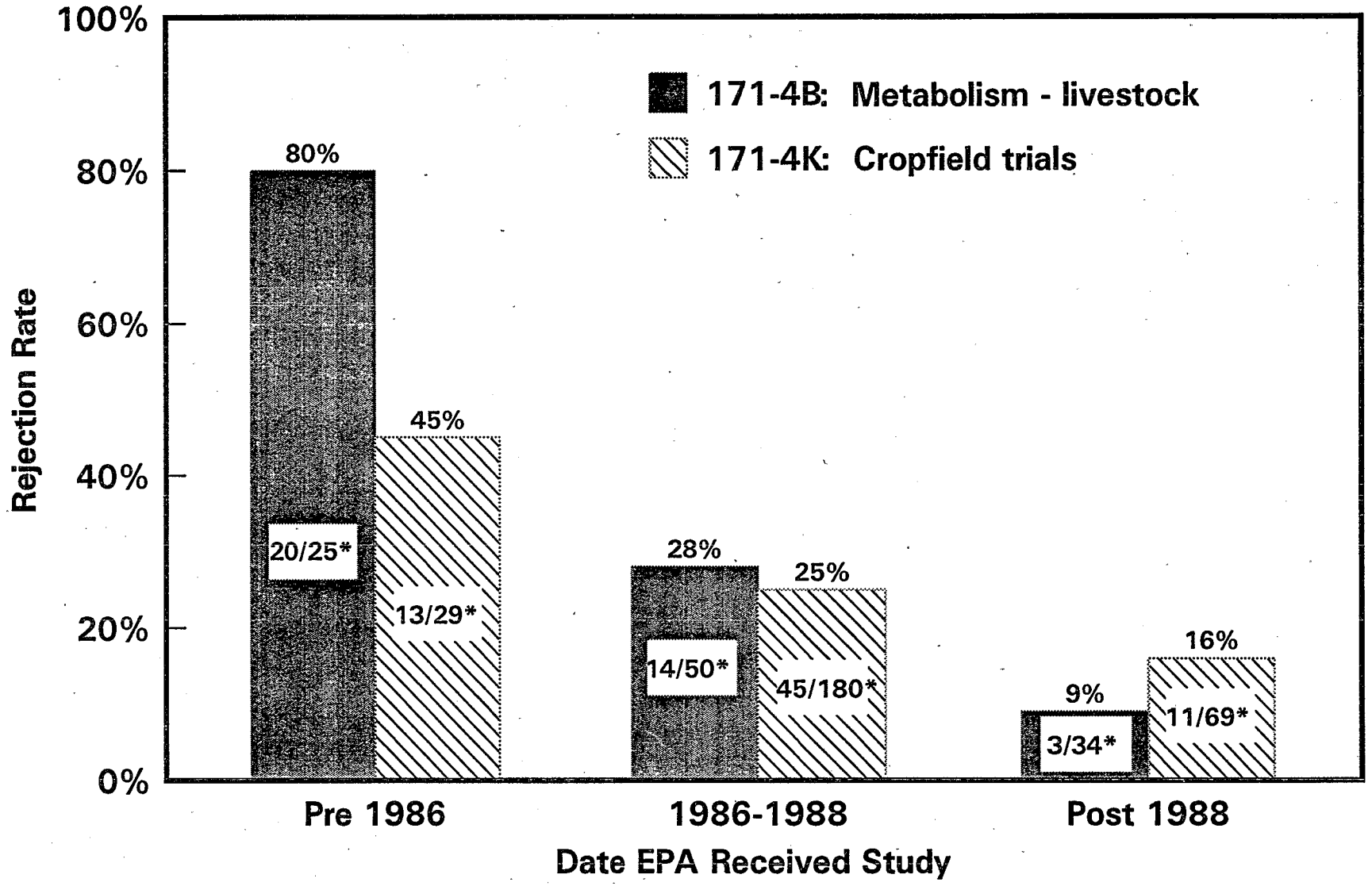
LIST A - RESIDUE CHEMISTRY REJECTION RATE BY GUIDELINE SINCE BEFORE 1986



Note: Insufficient data to evaluate 171-2, 171-4F, 171-4G, 171-4H, 171-4I, 171-4J, and 171-5
Rejection rates do not include studies submitted prior to Registration Standards.
Number of rejected studies over the number of reviewed studies shown above eachbar.
Percentage of rejected studies shown inside each bar.

FIGURE 4

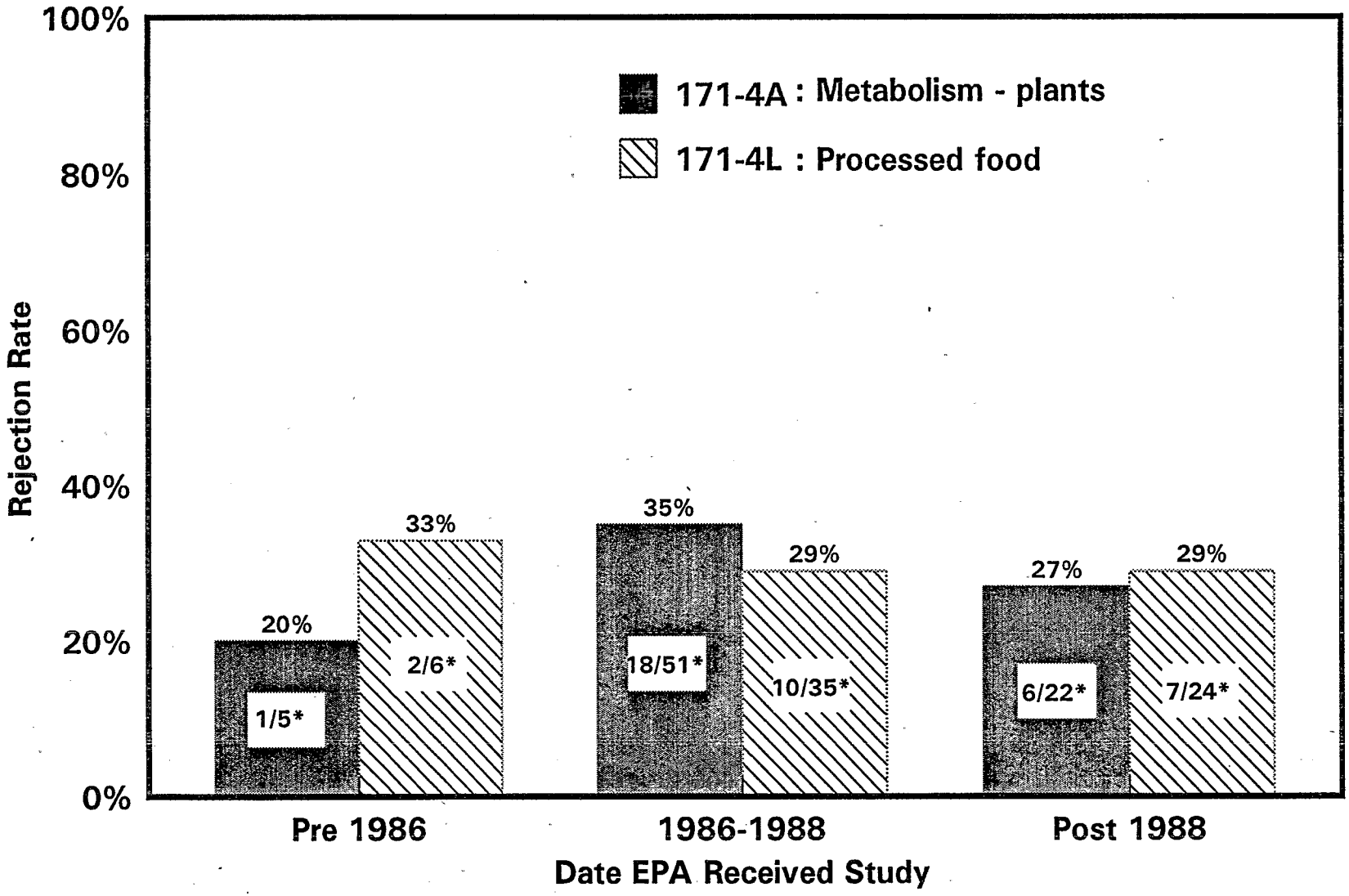
LIST A - RESIDUE CHEMISTRY GUIDELINES WITH LOWER REJECTION RATES OVER TIME



* Numerator = the number of rejected studies; denominator = the total number of reviewed studies.

FIGURE 5

LIST A - RESIDUE CHEMISTRY GUIDELINES WITH CONSTANT REJECTION RATES



* Numerator = the number of rejected studies; denominator = the total number of reviewed studies.

VI. REJECTION FACTORS

The following residue chemistry guidelines were analyzed to determine the most common reasons that studies submitted to meet these guidelines were rejected. EPA scientists listed these rejection factors below in ranking order according to the frequency of their occurrence. After each rejection factor, specific references to EPA guidance addressing that factor are given. The EPA guidance is analyzed and is referred to in this report, to determine if the guidance documents available to registrants adequately cover the areas where problems have occurred. (A list of all guidance documents available for residue chemistry studies is provided in Appendix A, at the end of this document.)

After each rejection factor and the corresponding references to EPA guidance, an Industry Comment section has been provided with the industry scientists' (a) assessment of the adequacy of the EPA guidance, (b) explanation of technical difficulties, if any, associated with the rejection factor, and (c) recommendations. Following each Industry Comment section is EPA's response to that comment.

After each guideline, the rejection factors are assessed in terms of the registrants' ability to avoid the factor in the future. This is presented in a list, which represents what EPA would consider to be rejection factors that could/should be avoidable on the part of the registrants. It is the intention of the Agency in the future to take the appropriate regulatory action should such "avoidable" factors cause a future study submission to be rejected. This standard will not be applied retrospectively to the studies analyzed in this assessment.

GUIDELINE 171-4A PLANT METABOLISM STUDIES

1. Rejection Factor: **Essentially no characterization of residues in crop parts used for food or feed.**

EPA Guidance on this Factor

Guidance on this topic appears in Subdivision O-Residue Chemistry Guidelines (pages 10-12) and in a 7/25/89 memorandum from Richard Schmitt to Dietary Exposure Branch Staff, which is included in the Overview of Subdivision O portion of the Phase 3 Guidance package-(pages E-25 through E-27). It is also included in the acceptance criteria (#8) as follows: "Major components or portion of the terminal residue identified (preferably by at least two techniques-e.g., Thin Layer Chromatography, High Performance Chromatography, Mass Spectrometry)" [see page C-363 of the Phase 3 Guidance].

The metabolism study is the key study in residue chemistry because it defines the residue to be quantified in later studies such as crop field trials. On page 10 of the Guidelines it states that "The composition of the terminal residue must therefore be determined before complete residue detection methodology and residue quantification data can be developed." On page 11 one of the purposes of an adequate plant metabolism study is noted to be to "identify the major components of the terminal residue".

In the past registrants could argue that residues were simply too low to even attempt their characterization. However, clear guidance has been issued on this topic in the 7/25/89 R. Schmitt memo. The latter discusses "trigger values" that serve as guides to the degree of characterization needed in metabolism studies. For example, if total radioactivity is <0.01 ppm in a crop part or animal tissue treated at a sufficiently high rate, no characterization is necessary. However, for radioactivity ≥0.01 ppm attempts to extract the activity and then to characterize the extractable activity are required.

Industry Comment

1. Under Plant Metabolism Rejection Factors (p. 16), the Agency has listed the memorandum from Richard Schmitt to the Dietary Exposure Branch Staff as a guidance document for plant metabolism studies. This document does not really emphasize plant metabolism!

2. If this document is to be used for plant metabolism study guidance, the EPA should change the document title to include "plant metabolism" and the guidance portion on plant metabolism

should be expanded.

3. In general, Dr. Schmitt's memo has been extremely helpful for animal metabolism studies.

EPA Response

The Agency agrees that additional guidance in the area of metabolism studies, especially for plants, is needed. The Agency agreed to develop a "Metabolism Guidance Paper" to address topics such as the need for identification by two techniques, techniques that should be used in attempts to release bound residues, and the clarification of trigger values for bound residues. This guidance paper will also include a roadmap of acceptable techniques to be tried before giving up on releasing bound residues.

2. Rejection Factor: Partial characterization of residues

In these studies portions of the residue have been characterized, but not a sufficient percentage to completely delineate the metabolism of the pesticide. This is a "gray area" and it is not possible to define an exact percent of the residue that has to be identified in all cases. Although the EPA normally states that registrants should strive for 90% identification, it is often not possible to reach this level. The final decision as to whether the residue has been adequately characterized depends upon factors such as the actual level (ppm) of unidentified activity, the importance of the matrix containing the residue as a food or feed, the chemical structure and toxicity of the active ingredient, and the toxicity of similar chemicals (pages 10-11 of Residue Chemistry Guidelines). Another factor which involves judgement is how the dosage or application rate in the metabolism study compares to the actual use of the pesticide (see 7/25/89 R. Schmitt memo).

EPA Guidance on this Factor

Due to this complexity involved in making the final decision, the EPA does not have formal guidance on the percent of the total residue that must be identified. Determination of the adequacy of metabolism studies must be done on a case-by-case basis.

Industry Comment

1. The terms "identification" and "characterization" seem to be used interchangeably by the Agency and this is very confusing. This confusion alone could be the number one reason for rejection of plant metabolism studies. "Identification" is a much more precise and difficult goal to attain than is "characterization".

We believe that "identification" means pretty much the same to everyone, whereas "characterization" may mean different things to different people (especially study directors vs. reviewers).

We would propose that the Agency always use the term "identification/characterization" together when they are speaking in general terms, and that they clearly delineate what they require when they use the terms individually (i.e. identification = structure elucidation, match with standards, etc., and characterization = aqueous vs. organic solvent soluble, polar vs. non-polar, acidic, basic, bound, etc.)

2. Due to the low residue levels generally found in samples from the plant metabolism studies, registrants are often faced with the task of trying to identify/characterize fractions representing very low levels of extractable or nonextractable radioactivity even though these fractions represent a significant proportion (>10%) of the total radioactive residue (TRR). As stated in the rejection document, work with these types of fractions often falls into a "gray area" which is not well defined in the guidelines. As a result, this has led to the perception that decisions dealing with these matters are often based on the reviewer's own personal views. Issuance of the Schmitt memo has helped to somewhat temper this perception by defining what needs to be done with extractable residues; however, additional guidance is still needed on the "trigger values" for bound or nonextractable (NE residues).

As stated in the Schmitt memo, further characterization of NE residues should be attempted when the NE activity is greater than ≈0.1 ppm or 10% of the TRR. For samples containing a TRR of less than 1.0 ppm, this could result in the need to characterize NE residues which are considerably less than 0.1 ppm. Thus guidance is sought on how to deal with NE residues which represent more than 10% of the TRR but represent ≈0.01 ppm or less in the original sample; ≈0.01-0.05 ppm in the original sample; and greater than 0.05-0.1 ppm in the original sample. In addition, input is also sought on whether NE residues from crops treated at rates higher than the maximum label rate can be factored down (e.g., if the NE or bound residues are from samples treated at a 2x rate, can the residue levels they represent be divided in half for purposes of deciding what additional characterization needs to be done?).

3. When residues in the RAC are too low for meaningful characterization, we would solicit the Agency's view on the possibility or need for characterizing other plant parts which may contain significant residue but are of no regulatory concern, in order to gain insight into the type of metabolic alterations which might be taking place. We would equate this situation to identifying activity found in urine and feces in animal metabolism studies.

4. A difficult task for the registrant is deciding how far to

go in identifying structures of water-soluble, highly polar metabolites that have undergone multiple molecular transformations. These metabolites are the most challenging and time-consuming to extract, purify, and identify/characterize. In addition, because of the number of "detoxifying" steps they have undergone, they represent the least value for the effort since they are highly unlikely to be toxicologically significant.

EPA Response

With regard to the first comment, the Agency agrees that the terms "characterization" and "identification" should not be used interchangeably. An effort will be made to use the terms as industry has described them. As discussed above for the previous rejection factor, additional guidance will be developed to address identification of bound residues (Comment 2). With regard to Comment 3, identification of residues on inedible plant parts can be useful. However, EPA prefers that some evidence be provided to show similar residue profiles for edible and inedible plant parts to accept such data. In response to the fourth comment on water soluble residues, EPA will address identification of such residues in the "Metabolism Guidance Document".

3. Rejection Factor: Characterization conducted on only immature crop parts or cell cultures as opposed to mature plants.

The third most frequent factor for rejecting a study is that the characterization of residues is conducted on immature crop parts or cell cultures, where the use of mature plants is required.

EPA Guidance on this Factor

This subject is addressed on the bottom of page 11 of the Residue Chemistry Guidelines: "The metabolism studies should be carried to plant maturity whenever possible, so that the composition of the residues is indicative of that in the terminal residues at harvest." Although the acceptance criteria do not mention mature plants by name, they do note that the major components of the "terminal residue" should be identified (criterion #8-page C-363 of Phase 3 Guidance). In addition, criterion #5 refers to plant parts used for human food or animal feed. Thus, both criteria imply that plant parts associated with harvest of the mature crop should be analyzed. However, registrants should be reminded to examine mature crops in metabolism studies. EPA suggests in many cases that the residues on the immature crop be characterized in addition to those at harvest. This is especially true for at-planting or early season uses where the immature crop usually has much higher residues than the crop at harvest.

Industry Comment

1. The Agency "suggests in many cases that the residues in the immature crop be characterized in addition to those at harvest", even though they have just stated in the first sentence of the paragraph, that the "composition of the residues" should be "indicative of that in the terminal residues at harvest". They give as their reason that for at-planting or early season uses the immature crop usually has much higher residues than the crop at harvest". This may be true, but the residue in the immature crop may have no bearing on the most prevalent (qualitatively and quantitatively) metabolites in the terminal residues.

Unless the immature crop is used as a feed item (green wheat forage), the Agency should not suggest that this type of metabolism work be done. The emphasis should always be on the "terminal residue".

If the Registrant wishes to do this type of work to supplement the terminal residue work, that should be alright, but if the Agency suggests it should be done, some reviewers and Study Directors may believe that this is a requirement, and unnecessary time and effort may be expended for no good reason.

2. Even though the guidelines wisely state that metabolism studies should be carried to plant maturity **whenever possible**, some reviewers ignore the words in bold. Especially troublesome are those situations where the level of agrochemical needed to be applied to incorporate sufficient activity into the mature plant is lethal to the plant, thus maturity is unattainable.

EPA Response

This topic will be addressed in the Metabolism Guidance Document. The Agency agrees that emphasis should be on the terminal residue. However, in cases where it can't be identified, additional work on the immature crop (or mature crop parts other than the rac) may be required. Prior to studies being conducted EPA will not state that use of immature crop is required (unless it is an animal feed), but will continue to suggest its use as an aid to identify residues.

4. Rejection Factor: Treatment of plants with wrong material such as an isomer of the pesticide or pesticide radiolabeled in a potentially labile site which could preclude our ability to track that portion of the molecule of potential toxicological significance.

EPA Guidance on this Factor

The first acceptance criterion for 171-4a states "Pesticide

radiolabeled in non-labile portion of molecule (tritium label strongly discouraged)" [Page C-363 of Phase 3 Guidance]. The second paragraph on page 10 of Subdivision O-Residue Chemistry Guidelines also addresses this issue. It is noted that ring labeling is preferred for most aromatic or cyclic compounds. If a potentially labile side chain or tritium labeling is chosen, the study is acceptable only if all significant activity is identified and found to be associated with the basic structure of the pesticide, not with loss of the label or side chain.

Industry Comment

Industry agrees that this is an appropriate cause for rejection.

5. Rejection Factor: **Application of pesticide at less than maximum registered rates such that very low radioactivity resulted in crop parts.**

EPA Guidance on this Factor

This factor is addressed in the Residue Chemistry Guidelines and the Acceptance criteria. On the bottom of page 11 of the Residue Chemistry Guidelines it notes that the minimum application rate should approximate proposed label rates. It further states that "exaggerated rate studies may be necessary in order to obtain sufficient activity for identification." Acceptance criterion #4 (page C-363 of Phase 3 Guidance) specifies that the pesticide be applied to the plant in a manner simulating the expected use. This point has been emphasized to registrants over the years in reviews and at meetings.

Industry Comment

Guidelines are clear concerning the need to use at least the maximum label rate in metabolism studies. The problem is in the need for exaggerated use rates to obtain sufficient activity for identification when these rates prevent normal growth of the plant. Does a sick plant metabolize a xenobiotic the same way a healthy plant does?

Are there any criteria based on plant morphology or other phytotoxic effects which could help in determining what the maximum tolerated application rate should be?

EPA Response

This will also be addressed in the Metabolism Guidance Document. The latter will have a maximum exaggerated rate (e.g., 10x) to be used in plant metabolism studies. If this maximum exaggerated rate kills the plant, the plants should be treated just to the point of phytotoxicity (analogous to maximum

tolerated dose concept in animals).

6. Rejection Factor: Need for confirmation of residue identities by second technique.

EPA Guidance on this Factor

Although Subdivision O does not specify confirmation of identities, this is addressed in the Phase 3 Guidance package on pages E-6 and C-363. On page E-6 it states that residues should be identified by matching Rf values in at least two different solvent systems if TLC is the only procedure used. "If possible, we really prefer that two separate techniques (e.g., TLC and MS) be used to identify residues". The last acceptance criterion on page C-363 also mentions identification "preferably by at least two techniques-e.g., TLC, HPLC, MS". Confirmation of identities has also been discussed in our Standard Evaluation Procedures on "Metabolism in Food Animals: Qualitative Nature of the Residue" (page 8, paragraph 5) and on "Qualitative Nature of the Residue: Plant Metabolism" (page 9, paragraphs 1 and 2).

Industry Comment

1. In some cases, the low levels of radioactivity available may preclude the exploitation of a totally separate technique. A realistic requirement might be the use of two sufficiently different aspects of the same procedure such as HPLC with different solvent (or column) systems, if that would qualify as a "separate technique".

2. The guidelines state that "Major components or portions of the terminal residue be identified **preferably** by at least two techniques". Reviewers ignore the term in bold and demand two techniques even when levels are low.

EPA Response

As noted above under rejection factor 1, this will be addressed in the Metabolism Guidance Document. EPA notes that it normally would be acceptable to identify minor metabolites (low percent of total residue, not likely to be toxic) using only one technique. With regard to what constitutes a second technique, the Agency feels that use of a different column or adsorbent is acceptable. However, use of a second solvent system with the same column or adsorbent is questionable.

GUIDELINE 171-4B LIVESTOCK METABOLISM STUDIES

Several of the rejection factors discussed under 171-4A are also relevant to livestock metabolism studies. These include partial characterization of residues, treatment with wrong material (isomer; labile site for radiolabel), and need for confirmation of identities. The guidance described for these factors under 171-4A is also applicable to livestock metabolism. Acceptance criteria 1 and 10 for 171-4B also deal with these rejection factors (page C-367 of Phase 3 Guidance package). Two additional causes for rejection of livestock metabolism deserve more discussion: no characterization of residues and dosing with a mixture of compounds.

1. Rejection Factor: No characterization of residues

EPA Guidance on this Factor

Many livestock metabolism studies were rejected in the past due to no (or perhaps minimal) characterization of residues in tissues, milk, and eggs. In many instances this was due to dosing at a too low level. This problem has been addressed by the 7/25/89 R. Schmitt memo (pages E-25 to E-27 of Phase 3 Guidance). This memo specifies that the minimum dose should be 10 ppm in livestock metabolism studies. It also provides guidance ("trigger values") as to the degree of characterization required in metabolism studies based on the total radioactivity observed in a tissue, crop part, etc.

Industry Comment

See Industry Comment at the end of this section.

2.Rejection Factor: Dosing with a mixture of compounds

Some livestock metabolism studies have been rejected in the past due to dosing with a mixture of radiolabeled chemicals (e.g., parent plus metabolites) rather than a pure compound. When dosing with such a mixture, it is impossible to determine whether plant metabolites are also animal metabolites. Therefore, animal metabolism studies should reflect feeding of only one compound, usually the parent. If a plant metabolite comprises a major portion of the residue on feed or is not found to be an animal metabolite, additional animal metabolism studies involving dosing with that plant metabolite may be required.

EPA Guidance on this Factor

Guidance on this factor was issued on page E-7 of the Phase 3 Guidance package. (The latter points out that this does represent a change from the Residue Chemistry Guidelines in that they state "The material fed should simulate the terminal

residues in feed items as closely as possible ....") The feeding of a single compound is also specified on page 3 of the Standard Evaluation Procedure on Metabolism in Food Animals: Qualitative Nature of the Residue.

Industry Comments on This Section

Industry acknowledges that many of the comments on identification/characterization for plant metabolism also hold true for animal metabolism.

When referring to the 7/25/89 memo by R. Schmitt, the Agency should emphasize that the minimum dose of 10 ppm referred to is 10 ppm in the feed and not 10 ppm by body weight. This is very important.

In some livestock metabolism studies, the bulk of the radiolabel is excreted and exaggerated doses are required to produce radioactivity in the tissues. It is possible that extreme doses of compound or vehicle can produce anomalous results.

EPA Response

The Agency will emphasize the 10 ppm in the feed (i.e., 10 mg pesticide per kg feed) in the Metabolism Guidance Document.

General Industry Comments on Metabolism Studies

The following industry comments regarding metabolism studies were not directed at any specific rejection factor.

Reviewers tend to interpret technical guidance too conservatively by ignoring the statements about identification of activity "above the ppm trigger value are not absolute requirements, but rough guides as to how much characterization is adequate."

There should be an intermediate step in the registration process in which the Agency will quickly review the registrant's metabolism data, and the Agency and the registrant can agree on what should constitute the total toxic residue, so that work on an appropriate method can proceed.

If this type of procedure cannot be accomplished in an expedient fashion, then clear "trigger values" for toxicity of metabolites should be developed, so that the registrant and the Agency use the same criteria in deciding if a metabolite should be included in the analytical method or not.

EPA Response

With regard to reviewers' interpretations of guidance, all

reviews are examined by a section head and branch senior scientist for consistency with branch policy and are often changed to ensure such consistency. The Agency tends to ask for additional data in those situations that are close calls. Registrants can challenge such requests for additional data.

For chemicals undergoing reregistration the Agency is not willing to delay field trials while metabolism studies are being reviewed. However, metabolism studies have been placed in high priority review status in reregistration to allow decisions on the total toxic residue to be made as soon as possible. Registrants are also encouraged to consult with EPA as soon as possible when questions arise regarding the need to regulate a recently discovered metabolite.

In the case of new chemicals registrants are encouraged to request pre-registration conferences to discuss metabolism results. EPA suggests that summaries of available toxicology data (including rat metabolism and acute studies) be submitted prior to such conferences. Literature searches on the toxicity of any known metabolites would also be useful.

Animal Metabolism - Supplementary Assessment

Twelve animal metabolism studies on five chemicals were classified as supplementary. Upon analysis of the reviews, the following was determined: six studies should have been classified as rejected; three studies are supplementary because they were done using the wrong animals (rats and non-lactating goats); two studies are interim reports; and one study was not accepted, but could be upgraded, due to insufficient characterization.

Examples of "Avoidable Rejection Factors" for Metabolism Studies

In assessing the factors above and other reasons that studies submitted to the EPA might get rejected, the following is a list of what EPA believes would be avoidable rejection factors on the part of the registrants. Should these factors cause a future study submission to be rejected, the Agency would likely consider taking the appropriate regulatory actions. This assessment would only be applied to future studies submitted to the Agency. This judgement would not be applied retroactively.

1. No attempt to extract or characterize radioactivity at levels ≥0.05 ppm unless such activity resulted from application rates or dosages well above the actual use of the pesticide.

2. Studies which fail to identify significant portions of the residue and in which the radiolabel was placed in a potentially labile site.

3. Plant metabolism studies which fail to identify significant portions of the residue and in which the pesticide was applied at well below label rates.

4. Livestock metabolism studies which fail to identify significant portions of the residue and in which the pesticide was fed to animals at well below expected dietary burdens or well below 10 ppm in those cases where low residues are present in feeds.

5. Livestock metabolism studies in which animals were dosed with a mixture of compounds unless an adequate rationale for doing so is presented.

171-4(C and D) - ANALYTICAL METHODS

1. Rejection Factor: **Method inadequately validated (recovery data, radiovalidation, independent lab validation, interference data)**

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) pp. 13-17
- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)
- Standard Evaluation Procedures: Analytical Methods/Residue Chemistry (1990)
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-369 through C-371, and E-8 through E-9.
- PR Notice 88-5: Tolerance Enforcement Methods - Independent Laboratory Confirmation by Petitioner

In many cases, methods rejected due to validation deficiencies may be upgraded by the submission of additional data/information.

Industry Comment

No comments were recorded on this factor.

Example of an "Avoidable Rejection Factor" for Analytical Methods Studies

In assessing the factor above and other reasons that studies submitted to the EPA might get rejected, EPA believes that circumstances such as where no validation data are submitted would constitute an "avoidable" rejection factor on the part of the registrant. Should this kind of factor cause a future study submission to be rejected, the Agency would likely consider taking the appropriate regulatory actions. This assessment would only be applied to future studies submitted to the Agency. This judgement would not be applied retroactively.

171-4E - STORAGE STABILITY

1. Rejection Factor: **Samples not fortified with all components of the total toxic residue**

EPA Guidance on this Factor

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp C-372-3.

- Position Document: Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data. (1987)

Industry Comment

1. The phrase "all components of the total toxic residue" needs to be clearly defined as applying only to residues of toxicological concern. Magnitude of the residue studies, crop processing studies, and their companion storage stability studies need to be sequentially scheduled after plant and animal metabolites are completed. Adjusting the Reregistration time frames to allow identification of the components of the total toxic residue before subsequent studies are conducted would reduce the number of requests for waivers and time extensions.

2. Obtaining EPA's evaluation of the total toxic residue before proceeding with the remaining residue studies is ideal. Magnitude of the residue, processing and storage stability studies are often initiated in conjunction with the growing season, and are conducted before EPA's "sign-off" on the total toxic residue.

EPA Response

Registrants should consult with the Agency as soon as possible if questions arise as to what residues to include in the TTR. EPA also advises that some control samples be spiked when field trial samples are collected even if a method is not available to do the zero day analyses.

2. Rejection Factor: **Fortification with a mixture for which the analytical method is not able to quantitate residues individually**

Other causes for rejecting storage stability studies involved the fortification with a mixture where the analytical method did not determine residues individually or the method gave low and variable recoveries.

EPA Guidance on this Factor

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp C-372-3.

- Position Document: Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data. (1987)

Storage stability studies that do not provide data regarding the stability of each individual component of the total toxic residue are unlikely to be upgradable.

Industry Comment

Fortification with a mixture is suitable for all products which meet the following conditions:

- The total toxic residue shows no appreciable degradation.

- None of the mixed compounds has a specific toxicological concern.

Conversely, it is not appropriate to use the analytical method, either total or specific to each compound in the mixture, to determine when to fortify with a mixed spike.

EPA Response

Spiking with a mixture is acceptable in those instances where the method is capable of measuring each component of the residue separately. In those cases where the method converts all residues to a common moiety the Agency is concerned about the possibility of the disappearance of one component being masked by the presence of the other components of the mixture. Therefore, spiking with mixtures or using weathered residues is not encouraged with such analytical methods. The type of chemical and toxicity involved would determine the acceptability in these cases. For example, with chemicals like alachlor or triazines where similar chronic toxicity concerns exist over numerous components of the residue, spiking with a mixture followed by use of a common moiety method is probably acceptable. On the other hand, it would not be acceptable to use a common moiety method for cholinesterase inhibitors where significant differences in toxicity may occur as the parent compound oxidizes to assorted metabolites. In other words, in the latter case the method would need to detect each of the metabolites separately.

3. Rejection Factor: **Use of an Analytical method which gives low and variable recoveries**

EPA Guidance on this Factor

For a summary of guidance in the analytical method area, refer to 171-4 (C and D). Storage stability studies conducted using invalid analytical methods are unlikely to be upgradable.

Industry Comment

"Low" and "variable" need to be defined. It is standard practice to allow limits of a residue method to vary between 70% and 120% (Subdivision O, p. 14). To reduce variability in a fortified storage stability study, the registrant may take certain measures such as spiking with an adequate level, averaging results of duplicate samples for each stability time point, and preparing additional samples for use if method recoveries do not fall within the allowed limits. To correct for variability in the method, stability recovery data may also be corrected for the method recovery data obtained with each set of stored samples.

EPA Response

"Low" recoveries normally means <70%. "Variable" depends upon the level of residues present. A much higher variability is acceptable for residues of 1 ppb than for those at 1 ppm. The Agency recommends that spiking levels in storage stability studies be at least 10x the limit of detection with the minimum being 0.1 ppm. Preferably, spiking levels should be close to typical residue levels observed in the field.

4. Rejection Factor: **Insufficient information regarding dates, storage conditions, and descriptions of analytical methods**

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 19
- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)
- Standard Evaluation Procedures: Storage Stability Study/Residue Chemistry
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp C-372-3, and C-387 through 390.
- Position Document: Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data. (1987)

In many cases, studies rejected due to storage stability data problems may be upgraded by the submission of additional data/information.

Industry Comment

Concerning storage conditions for a stability study, the above information should be provided.

Once the stability is proven for representative crops (fruit, oilseed, non-oily grain, representative by-products) stored under a set of related storage conditions (frozen), these core studies should be considered as a unit to define the storage stability pattern.

Producing storage stability data mimicking exact conditions under which the magnitude of the residue or processed commodity samples have been stored is quite difficult. If stability has been demonstrated in representative crops, then no further storage stability studies should be required. Representative stability data should be adequate to support pre-GLP or pre-Phase 3 guidance residue studies, where only the approximate storage conditions are known.

EPA Response

As noted above under EPA Guidance, storage stability studies rejected for lack of details on dates, storage conditions, etc. may be upgraded by submission of that information.

A cohesive document on storage stability will be prepared to address topics such as representative commodities and temperatures to be examined in these studies. In general, the studies should be conducted at the same temperature at which field trial samples were stored. To cover older field trials the Agency suggests conducting storage stability studies at two temperatures (e.g., -5C and -20C) to address the uncertainty regarding exact temperature at which older samples were stored.

5. Rejection Factor: Failure to include a sufficient range of commodities

Another frequent cause for incomplete storage stability data was the failure to include a sufficient range of commodities. In general, one crop from each crop grouping having tolerances should have been examined. In addition, some representative processed commodities such as fruit juice, pomace, milled products (e.g. flour bran), and oil should be included.

EPA Guidance on this Factor

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp E-9-10.

- Position Document: Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data. (1987)

Industry Comment

1. A revision of Subdivision O of the Pesticide Assessment Guidelines incorporating the Agency's most current views (Phase 3 Guidance, for example) would enable registrants to plan storage stability studies that are acceptable to the Agency and logistically feasible to conduct.

2. The Phase 3 Guidance allows combining crop groups, and conducting stability studies on representative crops, i.e., an oilseed, a fruit, and a non-oily grain, and representative processed products. The 1990 "Storage Stability Study" SEP (p. 10) reminds the reviewer to consider storage stability data for the test compound on other commodities, thus acknowledging the usefulness of related storage stability data.

3. Once a compound has been shown to be stable in representative crops stored under similar conditions, the registrant need not continually demonstrate that stability. If instability is shown in any of the representative crops then additional data may be required on other crops. Generating excessive stability data, as suggested in the 1987 Position Document, "Effects of Storage (Storage Stability)", is prohibitively expensive. It can cost more than the RAC residue studies or processing studies themselves, without contributing to the validity of those studies.

4. We also recommend that storage stability <u>not</u> be required for samples analyzed within 30 days from harvest, provided samples are frozen after harvest. In most field-trials one month is needed to ship samples and schedule them for analysis.

EPA Response

As stated previously, EPA plans to prepare a cohesive document on storage stability that would address the concept of representative commodities. This paper will follow and expand upon the guidance issued in the Phase 3 Guidance Package.

Unless a compound is otherwise known to be volatile or labile, the Agency agrees that storage stability data are not needed for samples stored frozen for <30 days.

Additional Industry Concerns

EPA lists five rejection factors for storage stability studies. Industry has concerns regarding piecemeal issuance of storage stability requirements, and requests for increasing numbers of crops and commodities. The expanding and conflicting requirements doom storage stability studies to be considered inadequate, especially for studies which are in progress or in queue for EPA review.

Studies performed before the issuance of any new requirement should be reviewed according to the regulation in effect when the study was conducted.

Increasing and conflicting requirements, both written and verbal from reviewers, for storage stability studies are the principle reasons why residue chemistry studies are considered deficient at the time they are reviewed. The varying regulations need to be combined, after industry comments are considered, into one cohesive document so that once established, it will provide a framework for acceptable studies.

The concurrent storage stability requirement specified in the 1987 position Document requires preparation of a set of stability samples for virtually every set of treated samples. This entails preparing stability spikes and performing a 0-day analysis on the day samples are placed in storage. Thus, analytical methods must be validated on all matrices, including processed products, at the time the samples arrive at the analytical lab. Also, samples of processed products may not be available in advance of shipment to the analytical laboratory, and, therefore, method development and validation may not be completed at the time samples are shipped.

EPA Response

A cohesive document will be prepared addressing issues such as representative commodities, temperatures, and the need for concurrent storage stability data. With regard to the latter, such data are not required in most cases. However, in instances where residues are known or suspected to be unstable, concurrent studies may be needed. The Agency advises that control samples of all crops be spiked at the time field trial samples are placed into storage in case stability questions arise at a later time.

Storage Stability - Supplementary Assessment

Fifteen storage stability submissions on four chemicals were classified as supplementary. Upon analysis of the reviews, each submission was an interim report for the full study.

Examples of "Avoidable Rejection Factors" for Storage Stability Studies

In assessing the factors above and other reasons that studies submitted to the EPA might get rejected, the following list are what EPA believes would be "avoidable" rejection factors on the part of the registrant. Should these factors cause a future study submission to be rejected, the Agency would likely consider taking the appropriate regulatory actions. This assessment would only be applied to future studies submitted to the Agency. This judgement would not be applied retroactively. The following are examples:

1. Lack of storage stability data provided for key components of the total toxic residue.

2. There are no method validation data provided or referenced.

3. No information regarding sample storage conditions or intervals are provided.

171-4J - MEAT/MILK/POULTRY/EGG STUDIES

These studies are very rarely rejected. Registrants should keep in mind the following key factors when conducting livestock feeding studies:

(1) Feed the appropriate material (parent pesticide and/or metabolites) at sufficient levels (normally 1, 3 and 10 times the anticipated dietary burden for the species of interest).

(2) Continue dosing until residues plateau in milk or eggs (minimum of 28 days even if residues plateau earlier).

(3) Sacrifice animals within 24 hours of the final dose.

(4) Use a validated analytical method to measure the total toxic residue in edible tissues, milk, and eggs.

(5) Provide storage stability data to show behavior of residues during storage of samples prior to their analysis.

EPA Guidance on this Factor

Sources of guidance for this study include pages 22-23 of Subdivision O, pages C-382 to 384 and E-13 and 14 of the Phase 3 Guidance package, and the Standard Evaluation Procedure entitled Residues in Meat, Milk, Poultry and Eggs: Feeding Studies/Feed-troughs.

Industry Comment

The Agency indicates that dosing should continue "until residues plateau in milk or eggs (minimum of 28 days even if residues plateau earlier)." Industry believes the Agency should simply set a certain duration for the feeding studies (28 days, 30 days, 35 days, 40 days, 50 days, or something), and not leave this so open-ended.

These studies are very costly, and they require more than the average amount of man-power for a residue chemistry study. In these studies it is sometimes very difficult to keep up with the residue analyses to verify that a plateau has been reached so that the dosing can be stopped. In addition, the number of doses to be prepared is never known exactly in the current situation.

EPA Response

Although it is rare that residues do not plateau in 28 days, this has been observed with some pesticides. In order to cover those cases where residues may not plateau for a long time

period, the Agency prefers to maintain the present requirement of "until residues plateau ... (minimum of 28 days) ..."

171-4K - CROP RESIDUE STUDIES

1. Rejection Factor: Method inadequately validated or described

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) pp. 13-15
- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)
- Standard Evaluation Procedures: Analytical Methods/Residue Chemistry (1990)
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-369 through C-371, C-387 through C-390, and E-8 through E-9.

In many cases, crop residue studies rejected due to method problems may be upgraded by the submission of additional data/information.

Industry Comment

Industry agrees that this is an appropriate rejection factor.

2. Rejection Factor: Insufficient geographical representation

The second most frequent reason for rejection was geographical distribution, where field trials were not conducted in states that represent a sufficient portion of U.S. crop production. These deficiencies are difficult to resolve without further field trials.

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) pp. 19-20
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-387 through 390 and E-28 through E-30.

In most cases, additional field trials were needed when there was inadequate geographical representation.

Industry Comment

1. Vague guidance on this subject has led to a variety of

interpretations by reviewers regarding the adequacy of data. Questions are raised about insufficient number of sites per state and per crop. Reviewers have commented that residue trials must cover both ends of a state, with test sites at each end. Registrants have also been told that two sites in a geographically similar area count as only one site.

The Agency should provide more specific guidance on requirements for number of sites per state, number of sites per crop, and geographical distribution of test sites within a state. We believe that unless there is a distinct climatic difference within a state, geographical distribution of sites within a state is not relevant, and all sites within a state should be considered valid.

We recognize that providing this guidance is not easy. Therefore, we propose that representatives of EPA, USDA, IR-4, and industry jointly address this topic, to resolve the ambiguities for both registrants and reviewers.

2) Guidance varies regarding the specific states where residue tests should be conducted. For example, the 1985 NACA "Guidelines for Conducting Agricultural Chemical Residue Field Trials in the USA" lists TX, NM, and WA as the major crop producing states for bulb onions, based on USDA's 1985 Agricultural Statistics. EPA's Phase 3 Technical Guidance (p. E-28) lists NY, MI, OR/WA, and ID or CO for that crop, based on a 1983 list prepared for IR-4. Only one state is common to the two lists. One List A Registration Standard required residue tests for bulb onions in CA, NY, and ID/OR. Which guidance should the registrant follow? The only safe choice is to cover all the states listed by the three lists, but that defeats the purpose of guidance documents.

We propose that the group of representatives mentioned above also address proper geographic representation for the various crops. A single reference source for crop production statistics should be identified or prepared as guidance for all crops.

3) The phrase, "a sufficient portion of U.S. crop production" is too vague. The Phase 3 Technical Guidance lists CA, FL, TX/AR, NY/NJ, CO and WA as required states for lettuce. Based on the 1985 Agricultural Statistics, these states comprise 95% to 97% of U.S. lettuce production. However, for peaches the Phase 3 document lists the states of CA, GA/SC, MI, NJ/PA, and WA, representing 80% to 88% of U.S. production. This guidance does not consider the number of states to be required for major vs. minor crops, or for non-detectable vs. detectable residues.

The group defined above should also define the percent of crop production that must be accounted for. We propose that trials in states representing 75% of crop production be considered adequate.

EPA Response

EPA suggests that industry working in conjunction with IR-4 prepare a package for Agency review that addresses the definition of a site, the number of sites needed for various crops, the states in which trials should be conducted, and the percent of national production to be accounted for. The Agency believes that the number of sites in each state/region for a given crop should be weighted to follow the distribution of the production of that crop. The Agency is also concerned about setting 75% of crop production as adequate for any commodity. EPA considers geographic variability as well as climate and growing seasons. Defining geographic areas rather than individual states might be considered.

3. Rejection Factor: No data for aerial/sprinkler application on label

Chemistry Branch/HED policy regarding the need for field trials reflecting aerial application has recently changed such that aerial field trial data will be required less frequently.

EPA Guidance on this Factor

- Letter dated December 6, 1991 from Robert S. Quick, Acting Chief, Chemistry Branch I/HED to Dr. Richard F. Holt, Chairman, NACA Registration Committee.

Prior to this change in policy, the following guidance on aerial data requirements was available:

- Subdivision O: Residue Chemistry Guidelines. (1982) pp. 19-20

- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-387 through 390

The present policy is if the registrant is willing to amend their label(s) such that the product is applied in $\geq$ 2 gal water/acre ($\geq$ 10 gal water/acre for orchard crops), no field trial data specifically for aerial use will be required (i.e., this rejection factor may be satisfied by a label change if the registrant is willing to pursue that route).

Industry Comment

Industry agrees that this is an appropriate rejection factor.

4. Rejection Factor: Relevant formulation not tested

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) pp. 19-20
- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-387 through 390

If the registrant wishes to maintain use of the formulation in question, residue field trials in which a representative formulation is used must be conducted.

Industry Comment

Industry agrees that this is an appropriate rejection factor.

5. Rejection Factor: Registered use/minimum PHI not reflected

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) pp. 19-20
- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-387 through 390

Crop residue studies rejected because the registered use/minimum PHI was not reflected may be upgradable only if registrants amend their label(s) such that the existing residue studies reflect the uses specified on the label.

Industry Comment

Industry agrees that this is an appropriate rejection factor.

6. Rejection Factor: Inadequate storage stability data

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 19

- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)

- Standard Evaluation Procedures: Storage Stability Study/Residue Chemistry

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp C-372-3, C-387 through 390 and E-9-10.

- Position Document: Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data. (1987)

In many cases, crop residue studies rejected due to storage stability data problems may be upgraded by the submission of additional data/information.

Industry Comment

Industry addresses this issue in the storage stability section.

7. Rejection Factor: Application number/rate too low

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) pp. 19-20

- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-387 through 390

Crop residue studies rejected because the application number/rate was not reflected may be upgradable only if the registrants amend their label(s) such that the existing residue studies reflect the uses specified on the label.

Industry Comment

Industry agrees that this is an appropriate rejection factor.

8. Rejection Factor: Untreated RAC contaminated

No specific guidance is needed for this factor. It is obvious that a study must be repeated if the reason for rejection was contamination of the control samples.

Industry Comment

Industry agrees that this is an appropriate rejection factor.

9. Rejection Factor: Summary data presented, not supported by raw data

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 37
- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-387 through 390

Crop residue studies rejected due to the absence of representative raw data may be upgraded by submission of the missing data/information.

Industry Comment

The term "raw data" is too open-ended. Registrants have continually been faced with varying expectations for raw data, depending on the particular reviewer. Some want weather data, others don't. Some want hand-written field observation data, others don't. Registrants must try to satisfy all reviewers, which adds extra paperwork, preparation, and review time to every report. To limit this confusion, it is in the Agency's best interest to be consistent in defining what raw data are to be submitted.

Therefore, we propose that the Agency clearly define the term "raw data," and clearly specify which raw data must accompany a report.

EPA Response

The Agency will prepare a document outlining which raw data should be submitted with residue chemistry studies.

10. Rejection Factor: No data on relevant metabolites

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 15
- Data Reporting Guidelines: Residue Chemistry - Addendum

2. (1986)

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-387 through 390

Crop residue studies rejected due to the absence of data on relevant metabolites may, in some cases, be upgradable by additional analysis of stored samples from the residue studies.

Industry Comment

At present, List A compounds are given timelines that require the magnitude of residue in crop study to start concurrently with the nature of the residue in plant study. However, the total toxic residue is not clearly defined until the completion, submission, and review of the nature of the residue study. Such schedules do not allow time for assessment of the components of the total toxic residue in planning residue analyses. If new metabolites of toxicological concern are identified, then new analytical methods must be developed and residue samples must be reanalyzed. Obviously, no freezer stability data are available on the new metabolite. Thus, the registrant is faced with generating freezer stability data to cover a lengthy storage period on the new metabolite or running all new crop trials.

The solution requires two components. First, for products subject to reregistration, allow time for plant metabolism studies to be conducted, submitted, and reviewed before the field residue trials are scheduled to start. Second, the Agency needs a mechanism to quickly determine the residues of toxicological concern after metabolism studies are submitted. Often it is over one year before such a determination is made. This is of special concern for new active ingredients.

EPA Response

This issue is discussed above under "General Industry Comments on Metabolism Studies". The Agency reiterates that metabolism studies have been placed in a high priority review status in the reregistration process. Registrants should also consult with the Agency as soon as possible when questions arise regarding the need to regulate a recently discovered metabolite. In some cases the Chemistry Branch may refer the question to the recently formed HED Metabolism Committee for a final decision.

11. Rejection Factor: No data on relevant commodity

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 18-19 and Table II

- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. E-20 through E-24

In cases where the relevant commodity was not collected for analysis or the sample was treated inappropriately following harvest (e.g., washed), the study will most likely need to be repeated, i.e., the study will not be upgradable.

Industry Comment

Industry agrees that this is an appropriate rejection factor.

Industry Comment Overview

EPA lists 11 rejection factors for crop field trial studies. Industry is concerned about the lack of specific guidance on the number of sites required, the definition of raw data, the identification of metabolites of toxicological concern, and various new requirements being proposed as extensions of the guidelines. After all industry comments are considered, the guidelines and supporting documents need to be upgraded to clearly state the requirements for studies in this area.

At present, registrants are faced with new interpretations of old guidance, new interpretations of vague guidance, and evolving specific requirements based on chemical classes of compounds. We seek more Agency guidance on the vague areas of the guidelines and ask that the Agency not impose new study requirements retroactively. Rather, the Agency should acknowledge that it will take 24 months before new regulations can be met in ongoing crop field studies. Industry agrees that factors 1,3,4,5,7,8 and 11 are appropriate for rejection. Rejection factor 6 is addressed within our storage stability comments.

Other Crop Field Trial Issues from Industry

1. Reviewers have frequently stated that two years of field residue data are required on major crops, while the available guidance documents do not indicate such a requirement. If two years are required, the Subdivision O guidance document needs to be revised to reflect this requirement.

We believe that two years of data should not be needed. Adequate geographic representation of data from one year should also account for the climatic variation needed to evaluate the potential for residues in the various crops.

2. The present guidance on rinsing, cleaning, trimming, or brushing of raw agricultural commodities prior to residue

analysis needs to be clarified.

Subdivision O (p. 18) states: "The samples taken should be of the whole raw agricultural commodity (RAC) as it moves in interstate commerce . . .The sample should not be brushed, stripped, trimmed or washed except to the extent that these are commercial practices before shipment, or to the extent allowable in 40 CFR 180.1(j), the PAM, or the codex Document Alinorm 81/24, Appendix III. It should be noted in the enforcement program, produce is examined for residues on an "as is" basis, regardless of whether it meets any Federal or State quality grading standards with respect to washing, brushing or number of wrapper leaves retained. Because certain crops (cabbage, celery and lettuce) may be shipped without having been stripped or trimmed, samples of these crops should reflect both trimmed and untrimmed samples; only obviously decomposed outer leaves should be removed. The preparation of each sample prior to analysis should be indicated."

Virtually all produce is washed, brushed, stripped or trimmed for direct sale to the consumer before it is moved in interstate commerce. Is there now a conflict between the condition of crops as they move in interstate commerce and as they are examined for residues by FDA on an "as is" basis? How does this impact the samples that should be analyzed for field residue trials?

We propose that extraneous foliage and soil should be removed before the RAC is analyzed for field crop trials. Neither is part of a consumable product.

3. The number of samples required per site needs to be defined. Some reviewers require more samples per site for acutely toxic substances. The Subdivision O Guidelines refer to the 1981 FAO CCPR document which states, ". . . it is usually not necessary to replicate treatment at individual sites. However, it is useful to have three or four replicates at one site to study experimental uniformity and determine within site variations." Some reviewers want replicates from every site.

We propose that the group described above develop firm guidance on this issue.

4. Presently, field residue studies are designed to ensure greatest potential crop exposure to pesticide residues that would be allowed by proposed or registered use patterns (highest use rate, shortest application interval, shortest PHI). Occasionally, a residue data value from one test site is an obvious outlier, where the field data indicate no application irregularity, yet the value is far outside the normal cluster of residue values.

We propose that the Agency should disregard obvious outlier data when establishing tolerances for pesticide residues.

5. In objecting to residue analysis of composited samples, the Agency has argued that all of the residue in the composited sample could come from a single commodity or single fruit. According to such an argument, a ten-apple composite sample having residues of 1 ppm, could consist of one apple with 10 ppm and 9 apples with no residues.

Is the Agency moving toward this position? If so, does this mean individual sampling? If so, how will the Agency regulate? The approach may have merit in specific limited circumstances, but bears further detailed discussion to establish reasonable, realistic guidance.

EPA Response

1. Provided that field trials in one year have adequate geographic representation, studies representing a second year are not mandatory, although such data will be utilized if available. When additional studies are requested, it is usually just due to there being too few studies, not because a second crop year was not represented. However, in certain cases of unusual weather conditions, field trials from a second year may be required regardless of the number of studies done in the first year.

2. As long as removal of extraneous foliage or soil is part of normal harvesting procedures, such treatment of crop samples prior to residue analysis is acceptable. It is currently acceptable to brush root crops such as potatoes to remove adhering soil. An interagency (EPA/FDA/USDA) workshop is developing a regulation on portion of commodities to be analyzed. This regulation will probably specify that root and tuber and bulb vegetables be lightly rinsed in running water to remove adhering soil.

3. Although EPA statisticians think more samples should be required, only one sample per site is presently required. We prefer that more sites (with one sample per site) be included for a given crop versus fewer sites with multiple samples per site. Industry can address this issue in their proposal on geographic representation (states, # sites, etc.).

4. The Agency does discard residue values that it believes are outliers. However, there are numerous ways of determining what constitutes an outlier. EPA recommends that registrants identify outliers and give reasons as to why they should not be used.

5. In the case of acutely toxic pesticides the Agency is developing guidelines that should be issued in fall 1992 (Acute Tolerance Project). The options being considered include continuing to set tolerances on composite samples (but at a level low enough to ensure residues on individual commodities do not present an unreasonable risk), setting separate tolerances on composite and individual samples, and setting tolerances on individual samples. The guidelines will list the specific

commodities for which analyses of individual samples may be required. Public comment on this policy will be requested.

Examples of "Avoidable Rejection Factors" for Crop Field Studies

In assessing the factors above and other reasons that studies submitted to the EPA might get rejected, the following list are what EPA believes would be "avoidable" rejection factors on the part of the registrant. Should these factors cause a future study submission to be rejected, the Agency would likely consider taking the appropriate regulatory action. This assessment would only be applied to future studies submitted to the Agency. This judgement would not be applied retroactively. The following are examples:

1. The method submitted lacks validation data.

2. The key production states are not represented in crop residue trials.

3. The registered use is poorly represented in crop residue trials and there is no indication of intention to amend the label.

4. There are no storage stability data submitted or referenced with the crop field trial.

5. The relevant metabolites or relevant commodity are omitted from crop field trial data with no explanation or rationale for the omission.

171-4L - FOOD PROCESSING STUDIES

1. Rejection Factor: No data on relevant commodity

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 21 and Table II
- Data Reporting Guidelines: Residue Chemistry - Addendum 4. (1988)
- Standard Evaluation Procedures: Magnitude of the Residue - Processed Food/Feed Studies (1988).
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. E-10 through E-12 and E-20 through E-24.

Industry Comment

If "relevant commodity" means a major commodity, such as soybean oil, this is an appropriate reason for rejection. If it refers to a minor commodity, such as soapstock, where the residue in the RAC has been accounted for in other processed products, such as the oil and meal, then this is not a valid reason for study rejection.

EPA Response

In cases where analysis of a given fraction is not possible (e.g., loss of sample), this argument is acceptable as a reason for not rejecting the study. However, if samples of processed fractions listed in Table II of the Guidelines are available, they should be analyzed.

2. Rejection Factor: Method - Inadequate description/validation data

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) pp. 13-15
- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)
- Standard Evaluation Procedures:
    - Analytical Methods/Residue Chemistry (1990)
    - Magnitude of the Residue: Processed

Food/Feed Studies (1986)

- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-369 through C-371, C-391 through C-392, and E-8 through E-9.

In many cases, food processing studies rejected due to method problems may be upgraded by the submission of additional data/information.

Industry Comment

This is an appropriate reason for rejection. However, as the draft report points out, such a study should be upgradable, by submission of the appropriate description and validation data.

EPA Response

EPA agrees that such studies may often be upgraded.

3. Rejection Factor: No processing study available

Industry Comment

If the 408 tolerance for the RAC reflects finite, detectable residues over 0.1 ppm for pesticides applied to fruits or vegetables close to harvest, a processing study would be required. Hence, this would be an appropriate reason for rejection.

However, many pesticides (primarily herbicides) are applied at low rates early in the growing season to crops such as soybeans, corn, and peanuts, long before any harvestable commodity is present or forming. In many of these situations the established tolerance (usually 0.1 ppm) reflects the sensitivity of the analytical method; residue samples show nondetectable residues. Actual residues can be estimated only by extrapolation from samples treated at exaggerated rates.

In these situations there is usually no possibility of residues in the processed commodity that would exceed the 408 tolerance level for the RAC. Unfortunately, essentially all of the Agency guidance on this issue confusedly states, "If detectable residues are found on a crop for which Table II of the Guidelines lists a processed commodity, then a processing study is required, and if the data show a concentration of residues, then a Food Additive Tolerance (FAT) is required." This statement is not equivalent to 40 CFR §190.1(f)(2) which states:

> (f) Where raw agricultural commodities bearing residues that have been exempted from the requirement of a tolerance, or which are within a tolerance permitted under section 408 are used, the processed foods will not be considered unsafe

within the meaning of section 406 if: (2) the concentration of the pesticide in the preserved or processed food when ready to eat is not greater than the tolerance permitted on the raw agricultural commodity.

In order for a Food Additive Tolerance to be required, residues in the processed food product must exceed the tolerance on the RAC, not merely the residue in the RAC. Therefore, in the situation described above, a processing study should not be required. However, a table should be prepared which lists the percentage range of the RAC represented by each processed commodity, so that registrants and reviewers can clearly determine when a processing study should and should not be required. Because of the cost of these studies and the limited facilities available to perform them (e.g. Texas A&M for corn, soybeans, peanuts, etc. and Lake Alfred for citrus), the Agency should not require processing studies when there is no reasonable expectation for residues in the processed commodity to exceed the tolerance on the RAC.

EPA Response

In those instances where the tolerance on the RAC is set at the limit of quantitation and residues in the RAC could not theoretically concentrate above the RAC tolerance, a processing study is not required. An example might be a tolerance of 0.1 ppm (limit of quantitation) for oilseed where residues in the seed are ≤0.02 ppm (limit of detection) and the theoretical concentration factor for oil is 4x.

When processing studies are conducted in situations where residues in the RAC are below the limit of quantitation (LOQ) but above the limit of detection, the observed concentration factor will be applied to the highest residue observed in the RAC in field trials, not to the RAC tolerance. The Agency emphasizes that this concept will be applied only to tolerances set at the LOQ. For those RAC's where real residues are observed above the LOQ, the concentration factor will be applied to the RAC tolerance to determine the food additive tolerance.

4. Rejection Factor: Exaggerated application rate needed

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 21
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. E-10 through E-12

A processing study rejected due to this factor will most likely need to be repeated, i.e., the existing study will not be upgradable.

Industry Comment

We assume that this means that an exaggerated field application rate was needed to obtain residues in the RAC at or near the tolerance for processing purposes. In certain marginal situations where a RAC was processed with no detectable residue, eliminating any possibility of detecting residues in any of the processed commodities, this would be an appropriate reason for rejection. However, the only detailed guidance on the use of RACs from exaggerated rate application [Phase 3 Guidance (1989) p E-12] is difficult to interpret. It pertains more to the later section just discussed with relevance to when a processing study should not be required.

EPA Response

The response to the previous rejection factor is related to this comment. In addition, the Agency notes that the Phase 3 Guidance Package recommends maximum practical exaggeration levels for certain types of applications. For example, 5x is considered to be an upper limit for foliar applications.

5. Rejection Factor: No data on storage conditions/stability

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 19
- Data Reporting Guidelines: Residue Chemistry - Addendum 2. (1986)
- Standard Evaluation Procedures: Storage Stability Study/Residue Chemistry
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp C-372-3, C-391 through 392 and E-9-10.
- Position Document: Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data. (1987)

In many cases, food processing studies rejected due to storage stability data problems may be upgraded by the submission of additional data/information.

Industry Comment

This is an appropriate reason for rejection. However, as the draft report indicates, in most cases such a study should be upgradable with the subsequent submission of the appropriate data.

6. Rejection Factor: Application rate less than maximum

Food processing studies would not typically be rejected because the rate was less than maximum, provided detectable residues of concern were present in the raw agricultural commodity prior to processing.

Industry Comment

Industry agrees with the stated conclusion.

7. Rejection Factor: Relevant metabolite not analyzed

EPA Guidance on this Factor

- Subdivision O: Residue Chemistry Guidelines. (1982) p. 15
- Data Reporting Guidelines: Residue Chemistry - Addendum 4. (1988)
- Standard Evaluation Procedures: Processed Food/Feed Studies (1988)
- FIFRA Accelerated Reregistration - Phase 3 Guidance (1989). pp. C-391 through 392

Food Processing studies rejected due to the absence of data on relevant metabolites may, in some cases, be upgradable by additional analysis of stored samples from the processing studies.

Industry Comment

If this statement means that metabolites in the tolerance expression and in the RAC sample utilized for processing were not assayed in the processed commodities, then this is an appropriate reason for rejection.

Industry Comment Overview

Subdivision O: Table II (Raw Agricultural Commodities and Feeds derived from Field Crops) needs to be updated and revised, incorporating all the changes listed in the Phase 3 Technical Guidance pp. E-20 to E-24. Clarification of the Feed Items is critical since some of the currently listed feed items are not normally part of animals diets and could not substantially contribute to meat, milk, or egg residues. Such atypical or only occasionally used items include such products as rice straw, soapstock, cannery waste, grain dust, wet and dry pomace, citrus molasses, etc. which should probably be removed from this table. Clarification of the uses of commodities such as crude vegetable

oil that may be nothing more than intermediates to some final product, should also be incorporated into this revised table.

A new table is required listing the processed commodities for each RAC and the corresponding proportion of each processed commodity in the RAC. A realistic livestock diet from an authoritative source is needed.

EPA Response

EPA is planning to update Table II with regard to which processed commodities need to be analyzed, which commodities are used as animal feeds, and the percentages of these items in livestock diets. An EPA contract on "What a Cow Eats" is scheduled for completion this fall. Theoretical concentration factors may also be included in the updated table. In the meantime the Dietary Risk Evaluation System has default concentration factors with respect to drying and FDA's Pesticide Analytical Manual-Volume I has information on oil or fat content of various commodities.

Examples of "Avoidable Rejection Factors" for Processing Studies

In assessing the factors above and other reasons that studies submitted to the EPA might get rejected, the following list are what EPA believes would be "avoidable" rejection factors on the part of the registrant. Should these factors cause a future study submission to be rejected, the Agency would likely consider taking the appropriate regulatory actions. This assessment would only be applied to future studies submitted to the Agency, due to the fact that adequate guidance documents may not have been available to registrants in the past. This judgement would not be applied retroactively. The following are examples:

1. The major processed products (outlined in Table II of Subdivision O and in the Phase 3 Guidance package) are not analyzed.

2. The method was submitted without validation data,

3. No storage stability data was submitted or referenced with the processing studies.

4. The relevant metabolites were omitted from the processing data with no explanation or rationale for omission.

VII. SUMMARY TABLE OF REJECTION FACTORS

GUIDELINE	REJECTION FACTOR
PLANT METABOLISM STUDIES: 171-4A	-No characterization of residues -Partial characterization of residues -Characterization conducted on immature crop parts/cell cultures -Plants treated with wrong material such as an isomer of the pesticide or pesticide radiolabeled in a potentially labile site -Application of pesticide at less than maximum registered rates -Need for confirmation of residue identities by second technique
LIVESTOCK METABOLISM STUDIES: 171-4B	-No characterization of residues -Dosing with a mixture of compounds -Partial characterization of residues -Animals dosed with wrong material such as an isomer of the pesticide or pesticide radiolabeled in a potentially labile site -Need for confirmation of residue identities by second technique
ANALYTICAL METHODS: 171-4C,D	-Method inadequately validated
STORAGE STABILITY: 171-4E	-Samples not fortified with all components of the total toxic residue -Fortification with a mixture -Use of an Analytical method which gives low and variable recoveries -Insufficient information regarding dates, storage conditions, and descriptions of analytical methods -Failure to include a sufficient range of commodities
CROP RESIDUE STUDIES: 171-4K	-Method inadequately validated or described -Insufficient geographical representation -No data for aerial/sprinkler application on label -Relevant formulation not tested -Registered use/minimum PHI not reflected -Inadequate storage stability data -Application number/rate too low -Untreated RAC contaminated -Summary data presented, not supported by raw data -No data on relevant metabolites -No data on relevant commodity
FOOD PROCESSING STUDIES: 171-4L	-No data on relevant commodity -Method - Inadequate description/validation data -Exaggerated application rate needed -No data on storage conditions/stability -Application rate less than maximum -Relevant metabolite not analyzed

VIII. IR-4 COMMENTS

As part of the review process for this analysis, IR-4 was asked to comment on this chapter. This section summarizes those comments.

IR-4 noted that it has similar problems as industry in developing data for the reregistration of specific uses. Even with the EPA's Minor Use Policy, the residue chemistry requirements are the same for IR-4 as they are for industry. To the extent possible, IR-4 relies upon the industry's generic core data packages that are submitted to EPA. The reregistration data gaps normally make up the bulk of the major turndowns for IR-4 petitions. However, IR-4 believes that once the reregistration process is completed, the generic core data base will be state-of-the-art. This fact alone will permit IR-4 to improve its success rate. Also, IR-4 believes that with positive results from EPA's Rejection Rate Analysis, IR-4, growers, and the public will all benefit.

To help minimize residue chemistry rejections for new and reregistration uses, some of the high priority points for IR-4 (minor crops/uses) are:

1. Improved listing of required crop sites for residue data development to include;

   -individual crops,
   -individual crop groups, and
   -individual crop subgroups.

2. List of concentration factors for crops that are processed.

3. Improved listing of crop fractions to be analyzed.

4. Consistent definitions (e.g. raw data and much) and record requirements that meet the regulatory end points of what EPA reviewers will require under residue chemistry and GLP's.

5. As appropriate, have EPA work with industry to develop generic core data bases for;

   -storage stability (adequate duration), and
   -metabolism (plant/animal)

   that will help IR-4 and the growers clear needed uses in a timely fashion.

EPA Response

With respect to IR-4's priority 1 spelled out above, EPA suggests that industry and IR-4 prepare a package for Agency

review that addresses the number of sites needed for various crops and the states in which the trials should be conducted. For more details see the EPA response (page 39) to Rejection Factor 2 under 171-4K.

The needs for concentration factors and an updated Table II of the Residue Chemistry Guidelines are discussed under the 171-4L portion of this chapter. As noted on pages 53 and 60 (Recommendations), the Agency plans to update Table II (crop parts, processed commodities, livestock feeds) by mid-1993 and issue a list of theoretical concentration factors by December 1992.

The need for guidance on "raw data" is discussed under Rejection Factor 9 for 171-4K (see page 42). By December 1992 the Agency plans to prepare a document outlining which raw data should be submitted with residue chemistry studies.

With respect to priority 5 of IR-4, a major goal of reregistration in the residue chemistry area is to ensure development of plant and animal metabolism data that clearly define the residues of concern for each active ingredient. Industry will also need to develop an adequate storage stability data base for each pesticide.

IX. INTERNAL EPA OBSTACLES

One outcome of this rejection rate study was an examination of the data review process in OPP, which handles reregistration. Two internal problems that were identified involve the timeliness of the review and intra-agency communication.

Sometimes the rejection rate is tied to what priority the review has. If the studies are reviewed early, the chance for upgrading them are better because the samples are fresh. The longer the wait, the more likely it is that new samples will have to be generated, i.e. redo the study.

Another internal EPA problem identified is inadequate communication between divisional personnel. In some cases, the science divisions that conduct the technical review of studies have concluded a particular study is "upgradable" or "acceptable," however, the review manager in the reregistration program has interpreted the review as "rejected." However, in compiling the statistics for this report, this problem was corrected. This problem is being addressed by the following modification being made to the science reviews. One problem is that multiple studies on different crops are required to satisfy plant metabolism requirements. The science reviews will begin to provide study (MRID) specific conclusions as well as guideline specific conclusions in their reviews. Secondly, where relevant, the science review will articulate whether the study deficiencies require:

(1) more additional information but no additional lab work,
(2) additional lab work on existing samples, or
(3) the generation of new samples.

Requirement (1) above, should be interpreted as an "upgradable" study. Requirement (2), should be also interpreted as an "upgradable" study as long as the probability is high that the deficiencies can be addressed by further analysis of existing samples. Requirement (3) should be interpreted as a "rejected" study.

X. CONCLUSIONS

Overall, the rejection rates for residue chemistry have shown dramatic improvement. The pre-1986 aggregate rejection rate for residue chemistry was 47 percent, and the post-1988 rejection rate is 12 percent. Two key guidelines, livestock metabolism (171-4B) and crop field trials (171-4K), have shown similar dramatic improvement. The rejection rate for livestock metabolism has dropped from 80 percent (pre-1986) to 9 percent (post-1988), and the rejection rate for crop field trials has dropped from 45 percent (pre-1986) to 16 percent (post-1988).

Two guidelines have not shown improvement, and their rejection rates remain at high levels. Plant metabolism (171-4A) has a post-1988 rejection rate of 27 percent, and processed food (171-4L) has a post-1988 rejection rate of 29 percent. Of the two, the plant metabolism rejection rate is the most problematic in terms of its potential for delaying REDs, because the other studies are contingent upon the adequacy of the characterization of the metabolites of the compound in the plant. Crop field trials (171-4K) also has a high rejection rate, at about 16 percent, inspite of improvements since pre-1986.

The Health Effects Division has provided a substantial amount of guidance to date for residue chemistry, starting with the Residue Chemistry Guidelines in 1982, two Data Reporting guidelines in 1986 and 1988, six Standard Evaluation Procedures between 1988 and 1990 and several miscellaneous items - a PR Notice, and position document and a policy letter - as recently as December 1991 (see Appendix A for a list of all guidance documents). Nevertheless, as a result of this assessment process, additional guidance needs have been identified, and the Agency is committed to addressing these needs (see Recommendations) in order to help reduce rejection rates.

The Agency's commitment to reducing rejection rates will not be limited merely to upgrading its guidance. For future studies rejected for factors where the Agency believes its guidance is adequate and the rejection factor is deemed "avoidable," regulatory action may be appropriate.

Two internal problems were identified. For a significant number of instances the chemical review manager misinterpreted the science reviews and concluded that the study was rejected when, in fact, the scientist's finding was that the study was upgradable and in some cases even acceptable. Secondly, it was learned that the timeliness of science reviews can affect the rejection rate. The longer the delay in reviewing the study, the less likely it is that stored samples can be used to upgrade a study and consequently the more likely it becomes that the study would have to be repeated.

Industry input provided substantial insight into (1) where

further Agency guidance would be most useful and (2) why certain rejection factors occur. Some of the rejection factors reflect very difficult technical problems. For example, inadequate characterization of the residue in plant metabolism studies is a frequently occurring rejection factor. It was pointed out that in situations where the application rate is very low, identification/characterization of portions of the residue in the plant becomes exceedingly difficult. Increasing the dose to facilitate identification is often not possible since it may kill the plant (especially for herbicides).

The tight time frames imposed by FIFRA 88 force industry to start studies before results from other pertinent studies have been reviewed and approved by the Agency. Consequently, rejection factors in the earlier studies can cascade down into the subsequent sequence of studies causing them to be rejected as well.

Industry also pointed out areas where the lack of clear guidance may have contributed to the occurrence of the rejection factor as well as having resulted in the application of different criteria by different reviewers. However, industry also acknowledged areas where there did appear to be adequate guidance.

XI. RECOMMENDATIONS

As a result of this rejection rate analysis and the ensuing discussions with industry, EPA realizes the need for additional guidance on various residue chemistry requirements. The Agency plans to issue the following documents:

Metabolism Guidance Document	July 1992
Acute Toxicity Guidelines	Fall 1992
Storage Stability Guidance	Dec. 1992
Theoretical Concentration Factors	Dec. 1992
Raw Data Guidance	Dec. 1992
Table II Revision	Mid. 1993

The Agency also recommends that industry develop a proposal with respect to the number of sites and geographic distribution of crop field trials for EPA review.

The development of the above documents should further reduce the rejection rate for residue chemistry studies.

With regard to the cascading effect of rejection of studies, EPA recommends that registrants consult with the Agency as soon as possible when questions arise regarding the need to regulate a recently discovered metabolite. EPA will continue to place metabolism studies in a high priority review status for reregistration.

The Agency also plans to modify its science reviews to make it clearer when a study is upgradable and what information or data are needed to accomplish that.

Finally, SRRD intends to continue tracking rejection rates for residue chemistry guideline studies in general and plant metabolism (171-4A), crop field trials (171-4K) and process foods (171-4L) in particular. If a significant reduction in the rejection rates for these studies is not observed, another analysis of causes for rejection may be conducted in the future.

XII. APPENDIX A - EPA GUIDANCE DOCUMENTS

EPA distributed the following documents to guide registrants on the correct procedures for conducting residue chemistry studies. Specific references to these materials are made under each of the rejection factors listed.

- **Subdivision O: Residue Chemistry Guidelines (1982)**

- **FIFRA Accelerated Reregistration - Phase 3 Guidance (1989)**

- **Data Reporting Guidelines:**
  Residue Chemistry - Addendum 2 (1986)

  Residue Chemistry - Addendum 4 (1988)

- **Standard Evaluation Procedures:**
  Analytical Methods/Residue Chemistry (1990)

  Qualitative Nature of the Residue:
  Metabolism in Food Animals (1990)

  Qualitative Nature of the Residue:
  Plant Metabolism (1989)

  Residues in Meat, Milk, Poultry and Eggs:
  Feeding Studies/Feed Troughs (1990)

  Storage Stability Study/Residue Chemistry (1990)

  Magnitude of the Residue:
  Processed Food/Feed Studies (1988)

- **PR Notice 88-5: Tolerance Enforcement Methods - Independent Laboratory Confirmation by Petitioner**

- **Position Document: Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data (1987)**

- **Letter dated December 6, 1991 from Robert S. Quick, Acting Chief, Chemistry Branch 1/HED to Dr. Richard F. Holt, Chairman, NACA Registration Committee Regarding Aerial Application Field Studies.**

- **Memorandum dated July 25, 1989: Guidance on When and How to Conduct Livestock Metabolism Studies, Richard Schmitt, PhD, Chief, Dietary Exposure Branch, Health Effects Division.**

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