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Pesticide Reregistration Rejection Rate Analysis

Occupational And Residential Exposure

REJECTION RATE ANALYSIS

OCCUPATIONAL AND RESIDENTIAL EXPOSURE

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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 acceptable quality studies. 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 first 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. While a rating of supplementary by a scientist could require substantial new work and add additional time delays to the process, this outcome is not very frequent in this discipline and has not been formally assessed.

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 completed Phase 4 last fiscal year (FY92), and List D chemicals will complete Phase 4 at the end of this 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 1984 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 occupational and residential exposure scientists 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: Ed Day (Dow Elanco), Monty Eberhart (Miles), and Paula Paul (NOR-AM). Industry and EPA scientists met on March 4, 1993 to discuss the problem areas in order to develop a better understanding of them.

The revised occupational and residential exposure chapter explicitly includes industry comments on each rejection factor and EPA's response to them.

III. OCCUPATIONAL AND RESIDENTIAL EXPOSURE CHAPTER

This chapter examines the results of the occupational and residential exposure rejection rate analysis. The following information is discussed: (1) a description of the discipline of occupational and residential exposure, (2) a list of the most common factors that have led to the rejection of these studies, and (3) conclusions.

IV. DESCRIPTION OF THE DISCIPLINE

Occupational and residential exposure data are used by EPA to estimate non-dietary, human exposure as a result of pesticide applications. With these data, EPA can determine a safe post-application/reentry interval for individuals entering pesticide treated areas and determine appropriate protective measures for individuals directly involved in pesticide application activities. Requirements for these data are delineated Subdivision K (Exposure: Reentry Protection) and Subdivision U (Applicator Exposure Monitoring) of the Pesticide Assessment Guidelines.

The Pesticide Assessment Guidelines Subdivision K, Exposure: Reentry Protection, present EPA requirements for the following studies (Post-application/reentry data are required under 40 CFR 158.390):

Post-application/Reentry Data

132-1A	Foliar Dislodgeable Residue Dissipation
132-1B	Soil Residue Dissipation
133-3	Dermal Passive Dosimetry Monitoring
133-4	Inhalation Exposure Monitoring

The Pesticide Assessment Guidelines Subdivision U, Applicator Exposure Monitoring present EPA requirements for the following studies (Subdivision U has yet to be published in the CFR although the guidelines were made available in 1987):

Mixer/Loader/Applicator Exposure Monitoring

231	Estimation of Dermal Exposure at Outdoor Sites
232	Estimation of Inhalation Exposure at Outdoor Sites
233	Estimation of Dermal Exposure at Indoor Sites
234	Estimation of Inhalation Exposure at Indoor Sites
235	Requirements for Exposure Monitoring at Outdoor and Indoor Sites by Biological Monitoring

The driving factors for determining data requirements are 1) the pesticide's toxicity, and 2) the human activities associated with the pesticide's use pattern that can lead to exposure. Before EPA requires a study, **both** the toxicity and exposure criteria must be met. OREB relies on HED's Toxicology Branches for the toxicology information. Often, the occupational and residential data requirements for a given pesticide are held in reserve until a complete toxicology database is established.

The initial toxicity criteria for determining these data requirements are acute toxicity studies using the Technical Grade Active Ingredient (TGAI). These studies must indicate that the pesticide is in either Toxicity Category I or II for acute dermal and/or inhalation toxicity to trigger the acute toxicity criteria

for post-application/reentry data requirements. In 40 CFR under 158.390, reentry data were originally required for pesticides in Toxicity Category I only. EPA now requires these data for pesticides in Toxicity Category I and II. Under Subdivision K, the acute toxicity criteria are met if the TGAI, or one of the pesticide metabolites meets one or more of the following (the corresponding toxicity guideline numbers are enclosed in parentheses):

Dermal LD_{50}: up to and including 2000 mg/kg (81-2);
Inhalation LC_{50}: up to and including 0.5 mg/l (81-3);
(4-hr exposure)

Other toxicity criteria that trigger post-application/reentry data requirements include:

neurotoxic, developmental (teratogenic), or carcinogenic effects identified in toxicity studies (81-7, 82-7, 83-2, and 83-3);

other adverse effects identified in subchronic, chronic, and reproduction studies (82-1, 82-2, 82-3, 82-4, and 83-4);

pesticide poisoning incident data or scientifically validated toxicological or epidemiological evidence showing that a pesticide, its residues, or its metabolites can cause adverse effects.

Mixer/loader/applicator data are required for pesticides in Toxicity Category I for dermal and/or inhalation toxicity. Under Subdivision U, the toxicity criteria are met if the TEP, TGAI, or one of the pesticide's metabolites meets one or more of the following (the corresponding toxicity guideline numbers are enclosed in parentheses):

Dermal LD_{50}: up to and including 200 mg/kg (81-2);
Inhalation LC_{50}: up to and including 0.05 mg/l (81-3);
(4-hr exposure)

Other toxicity criteria may include:

neurotoxic, developmental (teratogenic), or carcinogenic effects identified in toxicity studies (81-7, 82-7, 83-2, and 83-3);

other adverse effects identified in subchronic, chronic, and reproduction studies (82-1, 82-2, 82-3, 82-4, and 83-4);

pesticide poisoning incident data or scientifically validated toxicological or epidemiological evidence showing that a pesticide, its residues, or its metabolites can cause adverse

effects.

The following is a description of the occupational and residential exposure studies that are required by EPA to support the reregistration of pesticides that meet the exposure and toxicity criteria discussed above:

Post-application/Reentry

Foliar Dislodgeable Residue Dissipation (Subdivision K, guideline 132-1A). The purpose of conducting a foliar dislodgeable residue dissipation study is to measure pesticide residues that are deposited on and remain on plant surfaces following application. These are the residues likely to be touched and dislodged by people as they conduct post-application activities such as hand harvesting and pest scouting.

Soil Residue Dissipation (Subdivision K, guideline 132-1B). The purpose of this study is to measure pesticide residues that have been deposited on, incorporated into, or diffuse into the surface soil following application. This study is required when post-application activities involve substantial contact with the treated soil, such as hand harvesting of potatoes.

It should be noted that there is a difference between a soil residue dissipation study and a terrestrial field dissipation study (Subdivision N, guideline 164-1). Soil residue dissipation studies are designed to measure the dislodgeable residues on soil particles (less than 147 microns without grinding) situated on the soil surface to a depth of one centimeter (cm). These are the particles likely to be inhaled by or collected on the skin or clothing of individuals reentering fields treated with pesticides. Residues are to be expressed as ug or mg/cm^2. The residues to be measured are limited to the pesticide and or toxic metabolites of concern as determined by HED's Toxicology Branches. Soil residue dissipation studies must be conducted concurrently with dermal passive dosimetry and inhalation exposure monitoring to determine worker exposure.

Terrestrial field dissipation studies are designed to determine the overall fate of the pesticide and all its metabolites under field conditions. The metabolites to be studied are determined from previous hydrolysis, photolysis, and soil metabolism studies required by the Agency that have been conducted in the laboratory. Soil samples for this study are collected from the soil surface to a depth of 15 cm. Soil samples from this study would grossly underestimate residue levels likely to be encountered by a field worker. In addition, the units of measurement for the terrestrial field dissipation study are expressed as parts per million (ppm) or parts per billion (ppb).

Dermal Passive Dosimetry Monitoring (Subdivision K, guideline 133-3). Passive dosimetry monitoring is required when there is a potential for post-application pesticide residues to come into contact with the skin and clothing of workers and/or residents. Passive dosimetry is used to estimate the amount of pesticide that may impinge on the skin or clothing of workers. The residues are captured by placing dosimeters on study participants during reentry activities (i.e. a whole body dosimeter or cloth patches on various body parts such as arms, legs, chest etc.). The pesticides are then extracted from the dosimeters for analysis. EPA is currently requiring that passive dosimetry monitoring be conducted concurrently with foliar dislodgeable residue dissipation and soil residue dissipation where applicable. This guideline requirement is also applicable for dermal exposure concerns in residential situations for such pesticide applications as carpet treatments.

Inhalation Exposure Monitoring (Subdivision K, guideline 133-4). The purpose of this study is to measure the amount of pesticide that may be inhaled by individuals engaged in post-application activities having the highest potential for exposure. Various personal and stationary air monitors which draw known volumes of air over a given time period are used to measure the amount of a pesticide in the breathing zone. The exposure criteria for requirement of inhalation exposure monitoring includes both the use pattern and the volatility of the pesticide. Currently, data are required if the vapor pressure of the pesticide (TGAI) at standard temperature and pressure (mm Hg at 25C) is $\geq 10^{-3}$ for outdoor applications and $\geq 10^{-4}$ for indoor applications. When the new 158.390 regulations are published, inhalation exposure data will be required for outdoor applications if the vapor pressure is $\geq 10^{-4}$, and data will be required for any indoor application regardless of vapor pressure. Inhalation of airborne particles or dusts containing pesticide residues may also be of concern. This guideline requirement is also applicable for inhalation exposure concerns in indoor locations following total release fogger or aerosol applications.

<u>Some Key Terms</u>

Allowable Exposure Level (AEL) - The amount of pesticide residues at a given site that pose no reentry hazards. AEL's are derived using a no observed effect level (NOEL) from subchronic dermal or inhalation studies which are evaluated by HED's Toxicology Branches. AELs are expressed either as mg/kg/day or mg/m^3. Safety factors are applied to NOEL's for calculation of the AELs. OREB relies on the Toxicology Branches to provide the appropriate NOELs and safety factors.

Transfer Coefficient - transfer coefficients are used to predict the amount of pesticide residues that are transferred from the plant/soil surfaces to field workers. Although EPA now

requires that passive dosimetry monitoring be conducted concurrently with foliar dislodgeable residue dissipation and/or soil residue dissipation studies (and that a correlation be developed between the two), transfer coefficients selected from published literature were previously used to estimate dermal exposure to foliar residues. One such reference is "The Relationship Between Dermal Pesticide Exposure by Fruit Harvesters and Dislodgeable Foliar Residues," by G. Zweig, J. Leffingwell, and W. Popendorf.

Reentry Level - the "safe" level of a pesticide allowed on surfaces at the time of reentry. For field reentry, this level is expressed as $\mu g/cm^2$. The reentry level is calculated by dividing the AEL by the transfer coefficient.

Mixer/Loader/Applicator

Estimation of Dermal Exposure at Outdoor Sites (Subdivision U, guideline 231). The purpose of this study is to measure dermal exposure to appropriate body parts during mixing/loading and application activities conducted under field conditions. Passive dosimeters like those mentioned under guideline 133-3 are used in these studies. Separate measurements are made during mixing/loading, application, and clean-up activities. M/L/A dermal exposure studies are required to be conducted concurrently with inhalation exposure studies, discussed below.

Estimation of Inhalation Exposure at Outdoor Sites (Subdivision U, guideline 232). The purpose of this study is to measure inhalation exposure during mixing/loading and application activities conducted under field conditions. Various air monitors like those mentioned under guideline 133-4 are used in these studies. Separate measurements are made during mixing/loading, application, and clean-up activities. M/L/A inhalation exposure studies are required to be conducted concurrently with dermal exposure studies.

Estimation of Dermal Exposure at Indoor Sites (Subdivision U, guideline 233). This study is similar to the estimation of dermal exposure at outdoor sites. Besides the obvious difference inherent in the titles of the two studies, studies conducted under this guideline also include additional exposure monitoring during applicator reentry to the treated area.

Estimation of Inhalation Exposure at Indoor Sites (Subdivision U, guideline 234) This study is similar to the estimation of inhalation exposure at outdoor sites. Besides the obvious difference inherent in the titles of the two studies, studies conducted under this guideline also include additional exposure monitoring during applicator reentry to the treated area.

Requirements for Monitoring Exposure at Outdoor and Indoor Sites by Biological Monitoring (Subdivision U, guideline 235). This study is used to determine the internal dose of a pesticide that an individual may receive by: 1) measuring a body burden in selected tissues and/or fluids (blood), or 2) measuring the amount of the pesticide/metabolites in a person's excreted fluids (sweat, urine, saliva). This study is not typically required, but is an option available to registrants. Biological monitoring is required for those exposure scenarios where passive dosimetry is not practical (i.e. swimmers exposed to pesticides). The specific metabolism and pharmacokinetics of a pesticide must be well understood before a study of this nature can be conducted.

V. CURRENT REJECTION RATE

The small number of studies reviewed in this discipline limit the scope and meaningfulness of rejection rates. There were no rejected mixer/loader/applicator studies in the database that could be used in this rejection rate analysis. For post-application/reentry studies (132-1A, 132-1B, 133-3, and 133-4) our List A database indicates 18 out of 71 reviewed studies were coded as rejected (a 25% rejection rate). This number overestimates the number of studies that have to be repeated because an examination of some of these rejected studies indicated reasons for rejection that could be rectified without repeating the study (e.g. incorrect calculation of the transfer coefficient). Regardless, since all of the studies in this discipline are higher tier studies and are likely to be triggered late in the reregistration process, any rejected studies that have to be repeated will likely delay a RED and therefore is of concern to the Agency.

VI. REJECTION FACTORS

A total of 18 studies were evaluated to determine the most common reasons for rejecting occupational and residential exposure studies. By far, the most common cause for rejection is inadequate or, in some cases, a complete lack of Quality Assurance/Quality Control (QA/QC) data. Other reasons included: failure to provide meteorological data such as rainfall, wind speed, and temperature; not using appropriate toxicity end points to determine AELs; using the wrong transfer coefficient; and, poor study design. The majority of the studies evaluated for this report were post-application/reentry studies.

Admittedly, the Subdivision K guidelines for post-application/reentry exposure (published in October 1984) provided minimal guidance to the registrants regarding QA/QC. Nor were any Data Reporting Guidelines (DRG) or Standard Evaluation Procedures (SEP) established in the 1984 guidelines. The purpose of the guidelines at that time was to establish an acceptable scientific approach to these recently developed post-application/ reentry data requirements. However, a general discussion of Good Laboratory Practices (GLP) was provided. The Subdivision U guidelines for mixer/loader/applicator exposure (published in 1987) provide thorough QA/QC requirements acceptable to EPA. Since its publication, OREB has encouraged registrants to use the QA/QC criteria presented in the Subdivision U guidelines when conducting studies pursuant to Subdivision K. **Because Part 158 data requirements for mixer/loader/applicator exposure are not currently in the 40 CFR, the Subdivision U Guidelines were made available through the National Technical Information Service (NTIS), National Agricultural Chemicals Association (NACA), and the Federal Register.** To compensate for this and to minimize the submission of faulty data, OREB has requested that registrants submit a protocol for review by the Branch prior to the initiation of a study. Many basic flaws such as those discussed above are caught at this stage. Protocol submission and review is discussed further on page 19 of this document.

i. Four Major Rejection Factors

1. Rejection Factor: **Inadequate or complete lack of quality assurance/quality control data.**

EPA Guidance on this factor

- Subdivision K: 132-1A, 132-1B, 133-3, 133-4
- Subdivision U: 231, 232

Guidance on this topic appears in the Subdivision U-Applicator Exposure Monitoring Guidelines (Appendix A) and covers

laboratory recovery, field recovery, and storage stability data and are common causes of rejection. The absence of these types of data seriously compromise a study.

Industry Comment: Guidance is presented only as Quality Assurance Survey forms to be completed upon the submission of studies for inclusion in PHED (Pesticide Handlers Exposure Database). Such guidance should appear in the guidelines, not in an Appendix, and should clearly delineate the types of QA/QC data expected by the Agency.

EPA Response: QA/QC guidance is provided throughout the Subdivision U guidelines. However, the Subdivision K guidelines do not contain QA/QC requirements. The Agency is currently revising the Subdivision K Guidelines which are expected to be completed by the end of the calendar year. The revised Subdivision K guidelines will contain the Agency's requirements for QA/QC data.

EPA/Industry Comments and Responses Regarding Rejection Factor 1 - QA/QC Data Requirements

A. Laboratory recovery data verify the adequacy (accuracy, precision) of the analytical methods used to measure the residues in the collected samples. Without knowing the adequacy of the analytical method, the reviewer is left wondering whether the reported residue data are valid. Specific guidance regarding laboratory recovery is presented on pages 2-6, 2-18, and 2-36 of the Subdivision U Applicator Exposure Monitoring Guidelines. This is also referenced on page A-21 of a sample Quality Assurance form provided with the guidelines, and is identified in the Phase III Guidance Data Acceptability Criteria Checklist.

Industry Comment: It is agreed that the laboratory recovery of analytes from substrates must be tested prior to study initiation (page 2-6 of Subdivision U, Section c.3-dermal; and 2-18, Section h.2- airborne). It is also critical that lab recoveries be run with each set of experimental samples.

EPA Response: No comment necessary.

B. Field recovery data are generated using field spikes and provide a measure of the amount of the pesticide residue collected in the field that is found remaining in samples following transport to the lab and storage prior to analysis. Specific guidance regarding field recovery data is presented on pages 2-6 and 2-10 of the Subdivision U Applicator Exposure Monitoring Guidelines (Appendix A). This is referenced on page A-21 of a sample Quality Assurance form provided with the guidelines and identified in the Phase III Guidance Data

Acceptability Criteria Checklist.

Industry Comment: It is agreed that page 2-10, Section D.4 of Subdivision U adequately describes the requirement for conducting recoveries on dermal passive dosimeters, and page 2-23, Section K.4, for respiratory exposure measurements. However, the Agency needs to define the number of field spikes required for particular studies. Although Subdivision U Guidelines require one field spike per worker per day, the number of workers per day has nothing to do with the number of field QA samples necessary to validate an exposure sample replicate. The same number of field QA samples should be generated for an exposure replicate involving one worker as for a replicate involving 15 workers.

EPA Response: One concurrent set of field spike data per day should be sufficient in most cases to cover multiple exposure replicates on the same day. However, it should be noted that more field spikes are needed if field spike samples are also used to generate storage stability data.

C. Storage stability data provide a measure of the decay rate of pesticide residues in/on samples if they are stored prior to analysis. With increased pressure on laboratories for analytical services, this practice is becoming increasingly common. Specific guidance regarding storage stability data are presented on page 2-19 of the Subdivision U Applicator Exposure Monitoring Guidelines (Appendix A). This is also referenced on page A-21 of a sample Quality Assurance form provided with the guidelines and identified in the Phase III Guidance Data Acceptability Criteria Checklist. Also see pages 31, 37, and 44 of the Subdivision K Guidelines (Appendix A).

Industry Comment: Page 2-19 of Subdivision U addresses storage stability of pesticides on trapping materials from respiratory sampling. However, there is no corresponding section for dermal passive dosimeters. There is also no guidance on storage stability for biomonitoring samples, e.g., urine. Also, it is appropriate to test the storage stability before initiation of the study, but it is also useful to include storage stability samples with each day's experimental samples to verify stability during pre-shipment, shipment, and storage after receipt by the analytical laboratory. These storage stability samples should be prepared at the experimental site in order to closely simulate the conditions to which the experimental samples are exposed. However, if the field recovery data are adequate, the storage stability data are not used in any of the calculations of estimation of exposure. It does provide assurance that losses did not occur during shipping and storage.

EPA Response: As stated in Subdivision U, "At the current

stage of development, biological monitoring should be considered a chemical specific method. Consequently, only general guidance can be provided to assist in the selection of analytical methods, sampling collection schedule, and sample storage." There have been no major developments in this field of monitoring. The Agency will continue to evaluate studies employing biological monitoring on a case-by-case basis. Coordination with the appropriate toxicology branches is essential, particularly when considering the pharmacokinetics of the substances involved.

Guidance on dermal storage stability is provided on pages 2-6 and 2-7 of the Subdivision U guidelines. Additional information regarding QA/QC of passive dosimetry samples will be addressed in the appropriate section of the Subdivision K Guidelines currently undergoing revision.

D. Assessment of EPA Guidance on QA/QC Data Requirements: As previously mentioned (in the Rejection Rate Analysis document), Subdivision K provides minimal guidance on QA/QC data requirements. However, the new Subdivision K guidelines will address these requirements more effectively. Please note that the QA/QC data discussed here are used in all facets of data reporting to EPA (i.e. programs such as RCRA, CERCLA, and other FIFRA-related data reporting requirements).

Further guidance regarding QA/QC data is also provided in the Pesticide Handlers Exposure Database (PHED) which was developed by a task force composed of representatives of EPA, Health and Welfare Canada, and the National Agricultural Chemicals Association (NACA). The guidance provided in PHED delineates the criteria used for grading the various recovery data discussed above. The grades range from A to E with A being the best and E the worst.

Industry Comment: The EPA is correct in noting that QA/QC data are required under FIFRA. The guidance provided by PHED is helpful and the grading criteria emphasize the importance of adequate QA/QC data. However, until the Subdivision K revisions are completed, interim guidance is needed concerning the number of field spikes as well as additional QA/QC data that should be generated for worker exposure studies.

Good science practitioners understand the importance of laboratory recoveries to verify the adequacy of the analytical method and provide a correction factor for losses during the analytical procedure. Similarly, the generation of sound field recovery data is absolutely essential to adequately determining exposures to field workers. This indeed is of such importance that the Agency should consider giving additional guidance on how to do field recoveries. For example, it is recommended that diluted spray solution be used for fortification of sampling media. But what should be used when a granular product is being

tested? Also, what procedures should be considered when the active ingredient is volatile or photolabile and more likely to dissipate from the sampling medium during a full day of sampling?

EPA Response: The Agency continues to stress the importance of submitting protocols prior to study initiation as chemical specific problems are best addressed at that level. The Agency agrees that properly conducted field and laboratory recovery tests are both essential. Field recovery data should be used to correct the field residue data, while laboratory recovery data should only be used to verify the adequacy of the analytical method.

The Agency recognizes the need for interim guidance on QA/QC data requirements, particularly with respect to the following:

- o the definitions of field recovery and storage stability data;
- o additional guidance for generating field recovery and storage stability data;
- o guidance on how recovery data should be used;
- o guidance on what data are absolutely necessary and what data are optional;
- o guidance on QA/QC requirements for whole body dosimeters.

2. Rejection Factor: Not providing meteorological data.

EPA Guidance on this Factor

- Subdivision K: 132-1A, 132-1B, 133-3, 133-4

Guidance on this topic is presented on pages 11 and 30 of the Subdivision K guidelines. Since climate and weather conditions strongly influence the dissipation of pesticide residues, absence of these data are grounds for rejection of the study.

Industry Comment: Meteorological data are interesting and may permit an explanation for variations in data from one day to the next. However, the weather should have no effect on the validity of the study unless the study was conducted under conditions so adverse that the application or reentry operation was atypical. A limited amount of weather information is all that is needed, i.e., only temperature, wind speed and direction, humidity, and precipitation during the sampling period. Such data is not relevant when conducting studies indoors, though temperature and humidity should be recorded. The absence of complete meteorological data should not be cause of rejection as long as there is enough to provide evidence for the actual

conduct of the study as described. The specific types and the amount of meteorological data required needs to be clarified.

EPA Response: The Agency agrees that, at a minimum, meteorological data should include site specific rainfall data (not from the nearest airport), temperature, wind speed and direction, and humidity, as well as information on irrigation practices. Often, even the most basic meteorological data are not provided in study reports. If meteorological data were collected, but not reported, the study could be upgraded upon submission of these data.

If weather conditions are so adverse that they require lengthy discussions relative to the outcome of the study, the registrant should consider abandoning the study. The Agency is flexible in this regard when granting time extensions.

3. Rejection Factor: Using inappropriate toxicological end points and transfer coefficients when calculating reentry levels.

EPA Guidance on this Factor

- Subdivision K: 132-1A, 132-1B, 133-3, 133-4

Extensive discussion of the use of toxicity end points is presented on pages 24, 27, 28, and 29 of the Subdivision K guidelines. A discussion of transfer coefficients for use in the absence of real passive dosimetry data are provided in the abstract "The Relationship Between Dermal Pesticide Exposure By Fruit Harvesters and Dislodgeable Foliar Residues" by G. Zweig, J. Leffingwell, and W. Popendorf. OREB will provide registrants with the appropriate citations and we encourage registrants to solicit our input regarding transfer coefficients and toxicity end-points. Studies using unacceptable toxicity end points or transfer coefficients will be returned to the registrant for recalculation.

Industry Comment: It is not at all certain that the correlation between the transfer coefficient for a given task and dislodgeable residues is independent of the nature of the pesticide. Indeed, it is probable that the dislodgeability of a pesticide from foliage will vary from one chemical to another; hence, the use of published transfer coefficients for surrogate chemicals may not be appropriate for many chemicals. In any case, the registrant and the Agency should agree on the approach to be taken and the toxicity end points to be utilized before embarking on a Subdivision K study. However, the registrant's use of an inappropriate toxicological endpoint does not compromise the validity of the dislodgeable residue and worker exposure data and should not be a cause for the rejection of these data.

EPA Response: If an inappropriate toxicity end point or transfer coefficient is used, the study must be rejected initially, but could be upgraded accordingly after receiving the revised calculations. The Agency does not have the resources to devote time to recalculating data when reviewing a study. The Agency agrees that the transfer coefficient method may under or over estimate postapplication exposure. For this reason, we are currently requiring that foliar and soil dissipation studies be conducted concurrently with dermal and inhalation exposure studies. We suggest that registrants work together to identify areas where reentry exposure data and foliar dislodgeable residue data are needed to develop crop and work specific transfer coefficients in order to minimize the number of studies that need to be conducted. Most studies submitted to date have used published transfer coefficients to determine exposure from foliar dissipation data rather than conducting exposure studies to determine dermal transfer coefficients for the specific crops and work activities.

4. Rejection Factor: Insufficient sampling intervals.

EPA Guidance on this Factor

- Subdivision K: 132-1A, 132-1B, 133-3, 133-3

Guidance regarding standards for sample collection are provided on page 30 of the Subdivision K guidelines. An example of a typical sampling interval provided in the guidance indicates that samples should be taken as soon as the sprays have dried or the dusts have settled, and at 1, 2, 5, 7, 14, 21, 28, and 35 days after the final application.

Industry Comment: Indeed, these sampling intervals should be for guidance purposes only. There are many reasons for including alternative sampling intervals that are not on the specific days indicated in the guidelines. Also, if residues drop below certain levels, or plateau, registrants should be able to cease sampling for dislodgeable residues. While Subdivision K Guidelines recommend specific sampling intervals for foliar dissipation studies, the number of different sampling intervals for concurrent worker exposure studies are not specified in the guidelines. Fieldworker exposure on day 1 post-application should be considered worst case, and one sampling interval post-application for worker exposure studies should be considered adequate when the interval is the earliest possible (or anticipated) reentry time following application. However, conducting exposure studies at multiple intervals with the same workers in the same fields would provide valuable information concerning the exposure process and the validity of the generic transfer coefficient process.

EPA Response: The Agency agrees with Industry on these comments. A sufficient number of sampling intervals should be considered to establish a decline curve for dislodgeable residues. Typically, the intervals are frequent in the beginning of a study and less so near the end. The proposed sampling schedule should be included in the study protocol.

ii. Protocol Submission and Review

Submission and review of protocols prior to initiation of worker exposure studies is highly advisable for conducting acceptable studies. The design of worker exposure studies is open for suggestion and discussion, and many issues can be resolved at the protocol stage.

Industry Comment: Timely review by EPA of study protocols is essential; comments on the design of a study must be received before the study is scheduled to be initiated.

An issue that needs to be considered is whether a GLP protocol must be submitted or if a "study design report" is more appropriate for worker exposure studies. The nature of worker exposure studies makes it difficult to submit formal GLP protocols for review by the Agency prior to initiation of a study. The major parameters being considered in a field study such as application technique, type of crop and number of replicates are known in advance and can be provided for Agency review in a study design outline. In contrast, many of the minor details involved in a field study are not finalized until just prior to study initiation. The inclusion of these details in a GLP protocol for Agency review prior to study initiation would result in numerous protocol amendments and deviations to be signed and accounted for in the final report. In addition, guidance is needed on exactly what information the Agency would like included in the study design report or protocol.

EPA Response: Registrants should refer to the Reregistration Phase 3 Technical Guidance Document (dated Dec. 24, 1989), specifically the checklists for summarizing studies under Subdivision K and U, for a summary of what should be included in a study design report or protocol. Registrants should refer to Subdivision K and U for additional details of information and/or data to include in a protocol. The Agency does agree that additional guidance is needed concerning the minimum amount of information that should be included in these submissions.

Concerning GLP protocols, the Agency recognizes that, while all studies are required to be conducted according to GLP, the submission of a GLP protocol for review prior to initiation of a

study may not be feasible in most cases. The more informal requirement of a study design report is more practical and is recommended under Subdivision U. The Agency, therefore, recommends that registrants submit study design reports for review prior to initiation of studies rather than GLP protocols for Subdivision K and U studies. It should be noted that the study design report must include enough information to determine whether the proposed study will adequately address the worker exposure issue(s) of concern. A final GLP protocol must be signed by the appropriate study investigators prior to commencement of the study and this protocol should be included in the final study report submitted to the Agency.

iii. Examples of "Avoidable Rejection Factors" for Occupational and Residential Exposure Studies

Based on a review of the above factors, as well as other reasons, occupational and residential exposure studies may be rejected and hence OREB has generated the following list of avoidable rejection factors on the part of the registrants. Should these factors cause a future study submission to be rejected, EPA would likely consider taking appropriate regulatory actions. This assessment would only be applied to future studies submitted to EPA. This judgement would not be applied retroactively.

1) EPA Rejection Rate Study Comment: Complete lack of QA/QC data.

Industry Comment: Industry agrees with the Agency assessment.

EPA Response: No comment necessary.

2) EPA Rejection Rate Study Comment: Complete lack of weather data.

Industry Comment: Industry agrees with the Agency assessment, but data does not have to be extensive.

EPA Response: The weather data should, at a minimum, consist of rainfall (site specific), temperature, humidity, wind speed and wind direction.

3) EPA Rejection Rate Study Comment: Did not use the maximum application rate and frequencies of application as per EPA accepted labeling.

Industry Comment: This is dependent of the type of study. For foliar dislodgeable residues and associated reentry tasks, the requirement is probably appropriate. However, for monitoring reentry during activities such as incorporation, tillage, installing drainage tile, etc. the requirement should be for the maximum rate and frequency for the soil type, crop and locale, not simply the maximum use rate. For example, a fumigant may be used at one rate on potatoes in Washington, but at a much different rate on peanuts in North Carolina. The weather conditions, soil type, and equipment used may play more important roles than application rate. For measuring exposure to applicators, it should again be required that the maximum application rate (or anticipated maximum rate planned in the case of new products or label changes for existing products) be used for the crop and locale being studied, and not necessarily the maximum permissible rate on the label. For example, a fungicide may be used on apples in Virginia at the rate, X, but the same product may be used at only 1/2X in Washington on apples. Yet the conditions in the two states may be such that exposure under both sets of conditions should be studied. Additionally, it is the premise of PHED that exposure is due to physical parameters, and that exposure data is best normalized to the amount of product handled. Hence, it should be permissible to use less than maximum recommended rates as long as sampling is adequate to allow measurement of exposure. This should not automatically be a cause for rejection of an exposure study.

EPA Response: The important point is that the study, particularly for reentry, represent the worst case for exposure. The registrant must convince the Agency that the worst case has been evaluated. Industry's comment about PHED and the assumption that exposure data is best normalized for the amount of product handled is more appropriate for mixer/loader/applicator studies than for reentry studies.

4) EPA Rejection Rate Study Comment: Poorly organized, confusing reports.

Industry Comment: Industry agrees that the report should be sent back to the registrant.

EPA Response: No comment necessary.

5) EPA Rejection Rate Study Comment: Foliar dissipation and dermal exposure studies were not conducted concurrently to establish a transfer coefficient.

Industry Comment: Industry agrees that this needs to be done at minimally one time period after application in order to calculate a transfer coefficient.

EPA Response: The Agency currently believes it is desireable to include a minimum of two sampling intervals for dermal and/or inhalation passive dosimetry studies which are to be conducted concurrently with soil and/or foliar dissipation studies.

6) EPA Rejection Rate Study Comment: Inadequate statistical methods.

Industry Comment: It is not agreed that this should be an automatic reason for rejection. Often, data from field exposure studies are so variable that no statistical treatment at all is the appropriate method. Unless some specific guidance is provided by the Agency, this should not be reason for rejection.

EPA Response: The Agency recognizes that worker exposure data is often variable. However, the registrant must attempt to explain the variability. The Agency will address this topic in the revised Subdivision K guidelines.

7) EPA Rejection Rate Study Comment: Testing crops or reentry activities not representative of actual use situations (activities leading to the highest exposure should be studied).

Industry Comment: Industry agrees in principle with this, but there could be some disagreement between registrants and reviewers on what represents the highest exposure scenario. If there is disagreement, it should be resolved prior to initiation of a study. The Agency should also recognize that registrants and their employees are in the field frequently and through their experience have the better basis for selecting the scenarios that are likely to yield the highest exposures. In this regard, representatives from OREB should be provided more opportunity to observe the conduct of field exposure studies conducted by registrants.

EPA Response: It is the Agency's hope that the registrants know their chemical and its uses. The registrants should also recognize that the Agency's staff have seen many exposure studies

and may have some insight regarding particular exposure scenarios. The Agency encourages any discussion in this regard and welcomes the opportunity to witness "first-hand" field studies conducted by or on behalf of registrants.

8) EPA Rejection Rate Study Comment: Inadequate handling or storage of samples.

Industry Comment: Industry agrees with the Agency's assessment. Samples should be handled and stored according to GLPs.

EPA Response: No comment necessary.

9) EPA Rejection Rate Study Comment: Inadequate handling or maintenance of test substance or sample storage containers.

Industry Comment: The requirement under GLP to maintain all sample storage containers is only practical for lab studies. This requirement is not practical for worker exposure studies because of the large number of field samples generated and stored separately. EPA should consider a "blanket waiver" of the requirement to maintain sample storage containers for field studies.

EPA Response: EPA/OREB agrees that storage of numerous pesticide containers for the duration of field worker exposure studies is not practical. This is not an OREB criterion for study rejection. OREB has contacted the Office of Compliance Monitoring regarding this issue. OCM verbally affirmed that container storage is not practical for field studies and has provided a mechanism for obtaining waivers from that requirement in the case of field studies. An OCM Questions and Answers Document (Attachment 1) contains guidance to that end. OREB/HED will cooperate with Special Review and Reregistration Division and NACA regarding the possibility of obtaining a generic waiver from OCM relative to field studies.

The following factors may cause a study to be rejected but will not be a reason to initiate regulatory action:

1) Additional EPA Comment: Failure to propose a reentry interval.

Industry Comment: Industry agrees that it is in the registrant's best interest to propose a reentry interval for its product.

EPA Response: No comment necessary.

2) Additional EPA Comment: Failure to report data in terms of surface area for foliar dissipation studies (ie. reporting ppm instead of ug/cm^2).

Industry Comment: Industry agrees with the Agency's assessment.

EPA Response: No comment necessary.

3) Additional EPA Comment: Using personal protective equipment (PPE) or engineering controls in a study when these mitigating measures will not appear on accepted EPA labeling.

Industry Comment: The use of personal protective equipment by a worker during, for example, mixer/loader studies should be permitted by the worker providing the passive dosimetry measures potential exposure if the equipment was not worn. This should be at the worker's discretion, especially for new chemicals with which the worker has had no experience. Engineering controls should be permitted if it is the registrant's intent to require such controls on the label. In such cases, it should not be required that registrants conduct studies both with and without the controls.

EPA Response: The Agency agrees with Industry, as long as the exposure measured reflects the labeled use.

4) Additional EPA Comment: Did not use the TEP for which registration/reregistration is being requested.

Industry Comment: Some TEPs are such that the study of one

should suffice for others. For example, studying the exposure of applicators to an active formulated as a wettable powder (WP) will provide the same information as an aqueous suspension (AS), suspension concentrate (SC), or dry flowable (DF), because they are all in essentially the same physical form once they have been dispersed in water in the spray tank. The same could be said for determining foliar dislodgeable residues for such formulations.

EPA Response: The Agency agrees with Industry. However, with the growing list of formulation types, it would be helpful if the registrants informed the Agency which formulations would be represented in a given study prior to its initiation.

5) Additional EPA Comment: Sample contamination (in the field or laboratory).

Industry Comment: Industry agrees with the Agency assessment, such data should not be submitted.

EPA Response: No comment necessary.

6) Additional EPA Comment: Problems with the analytical method.

Industry Comment: Industry agrees with the Agency's assessment, only data based on validated analytical methodology should be submitted.

EPA Response: No comment necessary.

7) Additional EPA Comment: Although highly variable data may be unavoidable, the registrant should attempt to explain any variability.

Industry Comment: Industry agrees with the Agency assessment. If studies are conducted using good science, GLPs and proper record keeping, it is often possible to explain a highly aberrant result.

EPA Response: No comment necessary.

VII. SUMMARY TABLE OF REJECTION FACTORS

GUIDELINE	REJECTION FACTOR
132-1A, 132-1B, 133-3, 133-4:	-Inadequate or complete lack of quality assurance/quality control data. -Did not provide meteorological data. -Used inappropriate toxicological end points and transfer coefficients when calculating reentry levels. -Insufficient sampling intervals.

VIII. CONCLUSIONS

Despite a very limited sample size, several important points warrant emphasis here;

1) EPA Rejection Rate Study Comment:

All of the studies in this discipline are higher tier studies that are triggered by the results of animal toxicity studies (81-2,3,7; 82-1,2,3,4,7; 83-2,3,4). Since some of these toxicity studies are four year studies (83-2; 83-4), it is quite possible that any required occupational and residential exposure studies will be triggered late in the reregistration process. Consequently, even a low rejection rate will likely delay a RED and therefore is of great concern to the Agency;

2) EPA Rejection Rate Study Comment:

The most common rejection factor is inadequate quality assurance/quality control data. The guidelines for post-application/reentry exposure provide minimal guidance to registrants regarding QA/QC;

Industry Comment: It is agreed that guidance is minimal, so additional guidance is needed before more studies are rejected for this reason.

EPA Response: Every effort will be made to determine if the registrant made a "good faith effort" to follow accepted QA/QC procedures when conducting a study. If the Agency determines that the registrant has made such an effort, the study may be considered suitable for determining a reentry interval. However, if it is evident that QA/QC procedures were inadequate, the study must be rejected. If QA/QC data are not provided or discussed at all in the study report, the study must be initially rejected but the registrant will be given the opportunity to provide additional data to upgrade the study.

3) EPA Rejection Rate Study Comment:

Adequate QA/QC guidance does exist for the mixer/loader/applicator exposure studies and can be used for the post-application/reentry exposure studies.

Industry Comment: As indicated earlier, this guidance is only presented as the QA form for submission of data into PHED. A more detailed discussion of this topic in the body of the guidance documents is needed.

EPA Response: No comment necessary.

4) EPA Rejection Rate Study Comment:

The available studies evaluated for this report focus almost exclusively on the post-application/reentry exposure guidelines. At this time little is known about the rejection factors associated with the mixer/loader/applicator exposure guidelines.

Industry Comment: One reason for little being known about the rejection factors for M/L/A studies is that few thorough reviews have been conducted by Agency personnel and returned to registrants. Many registrants are simply not getting Agency reviews which would allow them to "fix" any problems with the studies. In addition, the review of protocols by Agency personnel has often been so slow that registrants have commenced studies and, in some cases, even completed the field monitoring portions of studies without having received formal comments or approval of the protocols. This puts registrants in tenable situations when studies are submitted in support of registrations or reregistrations.

EPA Response: The Agency has been open to holding meetings with registrants to discuss solutions to this situation. The Agency continues to encourage registrants to submit protocols as early as feasible, request meetings, or request time extensions until the protocols have been reviewed.

The Agency encourages registrants to revisit the Subdivision U guidelines as well as the Reregistration Criteria for Acceptability as these documents do provide guidance on QA/QC data. The Agency also encourages registrants to continue investigating the state-of-the-art of exposure methodology and ensure their protocols get to the Agency in a timely fashion.

IX. RECOMMENDATIONS

Solutions to many of the factors leading to the rejection of occupational and residential exposure studies were identified as a result of this rejection rate analysis and subsequent discussions with industry. The need for additional guidance on occupational and residential data requirements is evident. The Agency plans to issue revised Subdivision K Guidelines as well as Standard Evaluation Procedures (SEPs) for studies conducted under Subdivision K. Draft copies of these documents should be available by December, 1993.

In the interim, the Agency recommends that industry develop a proposal for Agency review that includes QA/QC requirements for particular studies and specific information that should be provided in protocols or study design reports that are submitted to the Agency prior to initiation of studies.

The development of the above documents should reduce the rejection rate for occupational and residential exposure studies.

With respect to protocol submission, the Agency recommends that registrants submit "study design reports" rather than formal GLP protocols prior to initiation of Subdivision K and U studies. The Agency recognizes that variations in study design for Subdivision K and U studies are necessary to ensure that the studies adequately address the worker exposure issue(s) of concern. Many issues that could potentially result in the rejection of a study, including requirements for meteorological data collection, number and timing of sampling intervals, and maximum vs. typical application rates, can be resolved at the protocol or study design stage.

Concerning Good Laboratory Practices (GLP) requirements, the Agency recognizes that the requirement under GLP to maintain all sample storage containers is not practical for field studies such as foliar and soil dissipation and worker exposure studies because of the large number of samples generated in these studies. A proposal to waive this GLP requirement for field studies should be drafted for consideration by the GLP Program/OCM.

The Agency continues to recommend that foliar and/or soil dissipation studies and postapplication worker exposure studies be conducted concurrently in order to calculate crop and task specific transfer coefficients; the Agency **does not** recommend the use of generic transfer coefficients. The Agency further recommends that industry, with the assistance of NACA, make a coordinated effort to determine crop groups based on the exposure data generated, i.e. crops should be grouped according to the postapplication worker exposure associated with each crop.

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 upgrade the study.

Finally, SRRD intends to continue tracking rejection rates for occupational and residential exposure guideline studies, particularly Subdivision K studies. If a significant reduction in the rejection rates for these studies is not observed, further regulatory action may be required.

X. APPENDIX A - EPA GUIDANCE DOCUMENTS

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

- **Subdivision K: Exposure: Reentry Protection (1984)**
- **Subdivision U: Applicator Exposure Monitoring (1986)**
- **"The Relationship Between Dermal Pesticide Exposure By Fruit Harvesters and Dislodgeable Foliar Residues", G. Zweig, J. Leffingwell, and W. Popendorf, 1985.**
- **FIFRA Accelerated Reregistration - Phase 3 Guidance (1989)**

APPENDIX B - Actions taken by OREB to reduce the rejection rate

To ensure that registrants develop and submit acceptable studies to the EPA, OREB has been carrying out the following actions for the last several years:

- sponsored and participated in American Chemical Society (ACS), American Society for Testing of Materials (ASTM), and the Society of Environmental Toxicology and Chemistry (SETAC) symposiums and conferences with National Agricultural Chemicals Association (NACA), federal agencies, and private industries on EPA reentry/worker exposure guideline requirements;

- participated with NACA, California Department of Food and Agriculture (CDFA), and Health and Welfare Canada on joint projects concerning indoor and turf reentry exposure methodology;

- created a task force with Health and Welfare Canada, CDFA, and NACA on the Pesticide Handlers Exposure Data Base (PHED) in regard to handler exposure data acceptability/availability (including a QA/QC grading criteria for data);

- presented talks to both national and international organizations outside EPA and published relevant reentry/worker exposure papers in ACS, American Industrial Hygiene Association (AIHA), ASTM, and other professional journals;

- published Federal Register notices as guidelines became available through the National Technical Information Service (NTIS);

- participated in updates of 40 CFR 158 Data Requirements for Registration;

- reviewed reentry study protocols submitted by the registrants before they were conducted;

- conducted face-to-face meetings and phone conferences with registrants regarding submitted study protocols;

- conducted meetings regarding data/protocol requirements with consultants and contractors that conduct reentry/exposure studies for registrants;

- provided Summaries of Guidance Data Acceptability Criteria in the Phase III Guidance Packages for Reregistration (it should be noted that it is our belief that registrants, in some cases, submit studies

knowing they are unacceptable, as demonstrated when they fill-out the Acceptability Criteria Summaries for Reregistration);

- o EPA funded exposure methodology research through university cooperative agreements and the Office of Research and Development/EPA-Pesticides Research Committee;

- o encouraged registrants to research new exposure methodologies as well as to pool their resources to do more comprehensive/acceptable studies.

Most recently, OREB has drafted an SEP for Subdivision K - Agricultural Crops and is currently revising the Subdivision K Guidelines.

ATTACHMENT 1

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

GOOD LABORATORY PRACTICE STANDARDS (GLPS)

QUESTIONS AND ANSWERS

Prepared by the
Pesticides Enforcement Policy Branch
Policy and Grants Division
Office of Compliance Monitoring
Office of Prevention, Pesticides, and Toxic Substances
U.S. Environmental Protection Agency

May 12, 1992

INTRODUCTION

On August 17, 1989, EPA published in the Federal Register revisions to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Good Laboratory Practice standards (GLPS) (54 FR 34052). This revision included changes that the Food and Drug Administration made to its GLPS (September 4, 1987; 52 FR 33768) and expanded the scope of the regulations to include data submissions which had previously not been under GLPS. The expansion of GLPS to include field studies has brought many facilities under GLPS for the first time while also making the standards applicable to entirely different types of testing environments than had previously been the case.

Since the publication of the revised rule in 1989, EPA has received many questions from persons who wish clarification regarding the applicability of the rule to their activities. These questions have ranged from simply asking whether the work they are doing is required to comply to technical questions regarding how the standards should be applied in the context of field as opposed to laboratory studies. Many written replies have been made to persons who have submitted specific questions in writing to EPA. Copies of specific correspondence have been provided upon request.

Notwithstanding, the correspondence file is of limited usefulness to other persons since the issues addressed are often specific to a particular situation. There have been requests for a general guidance document regarding EPA's FIFRA GLP policy. The following questions and answers have been prepared by the Policy and Grants Division of the Office of Compliance Monitoring to serve as official written policy for the regulated community.

QUESTIONS AND ANSWERS

APPLICABILITY

1. **What is the applicability of GLPS to work in progress at the time that the rule became effective?**

   The GLPS apply to all study-related work which is performed on or after the effective date of the rule. Studies in progress must be in compliance with GLPS from the effective date onward. A statement of compliance or non-compliance must accompany the final study report for such a study. This statement must either (1) state that the study was in compliance with GLPS, (2) describe in detail how it did not comply with GLPS, or (3) state that the submitter did not sponsor or conduct the study and does not know its compliance status. The statement must account for compliance or deviations with both the previous GLP rule (effective 1984), and the current rule (effective 1989), as applicable.

2. **If a study was in progress on October 16, 1989, must it have a protocol? What parts of the study would the protocol address?**

   All portions of the study performed on or after the effective date must be performed according to a written protocol as provided at 40 CFR 160.120. That protocol need only address those parts of the study performed on or after the effective date. Please note that if a study was subject to the 1984 GLPS, a protocol was required for all parts of the study conducted after the effective date of that rule. The compliance statement submitted with that study's report must specify in detail those study activities which were not performed in accordance with GLPS.

3. **Current reregistration procedures involve submission of data that resulted from studies performed prior to the effective date of GLPS. Do GLPS apply to such data, and if so, how?**

   Any data presently submitted in support of a pesticide research or marketing permit must be accompanied by a true and correct compliance statement as described at 40 CFR 160.12 regardless of when the study was performed. Therefore, data submitted to meet reregistration requirements are required to be accompanied with a true and correct compliance statement informing EPA in detail of all differences between the practices used in the study and those required by GLPS. It is not unlawful to truthfully admit that studies supporting such

submissions did not comply with GLPS, nor would such an admission necessarily lead to rejection of the data. The compliance statement will help the Agency to determine the reliability of the data based on current data requirements. Note that such an admission may nevertheless result in an enforcement action if they indicate that an unlawful act has occurred. For example, other regulations, i.e., books and records as stated at 40 CFR 169.2(k), require retention of raw data generated in support of registered pesticides prior to the effective date of GLPS. Admitting to destruction of records would not exclude the Agency from taking enforcement actions for the books and records violation.

4. **Do GLPS apply to data used to support tolerance petitions?**

Yes. The scope of the regulations as stated at 40 CFR 160.1 require that studies conducted to develop data pursuant to sections 408 and 409 of the Federal Food, Drug, and Cosmetic Act be performed in accordance with GLPS.

5. **Are studies conducted under the Interregional Research Project Number 4 (IR-4) program to support the registration of minor uses subject to the GLPS?**

Yes.

6. **Do GLPS apply to weather data and soil analysis data?**

Any data which are collected as part of a study listed in 40 CFR 160.1 must be collected according to GLPS. This includes weather data and soil analyses which are collected as part of a larger study which must comply with GLPS. If non-study data such as local weather data are cited in a study report, and the study report clearly indicates that such data were not gathered as part of the study, GLPS would not apply to such data.

7. **What applicability do GLPS have when State, Federal, or independent laboratories are used to provide soil or weather data for GLP studies?**

GLPS are applicable in such circumstances if such data are gathered as part of a FIFRA study. Only where such data are gathered independently of the study, and the study report clearly indicates that such data were not gathered as part of the study, would GLPS not apply.

DEFINITIONS

8. **Will EPA issue separate GLP standards for field testing as opposed to laboratory testing?**

The expansion of GLPS to cover field studies was based on the need to assure identical standards for all data submitted to EPA under FIFRA, and on the determination that the GLPS are technically general enough to cover virtually any type of research environment. EPA does not intend to issue separate standards.

9. **Can an experiment be divided into more than one study, based on where or when the work is performed, or the phase of the experimental work?**

Under GLPS, the term "study" refers to an experiment to determine or predict the effects or characteristics of a test substance. EPA considers a study to be composed of all of the necessary elements of research which are performed in order to obtain the reported results. If the elements of research consist of several phases of work which must be taken in the context of each other to get meaningful results, they are all considered to be elements of the same study. An example of this would be where one laboratory treats a test system with a test substance and sends the treated test system to another laboratory for analysis.

If the experiment involves treatment of test systems in several different locations, the experiment may be considered to be composed of either one study encompassing all locations or several studies each involving one or more locations. In the latter case, however, it would be necessary that each separate study stand entirely by itself, i.e., meet all of the criteria of a study. There would have to be separate compliance statements for each, separate tracking on master schedules, separate quality assurance inspections, etc. Each study would have to have a study director (and only one study director), although it may be possible for the same study director to oversee several of such studies at the same time. Finally, where several studies are compiled for submission, the submission must include true and correct compliance statements for each study involved in the submission.

10. **What is EPA's formal policy on certifying copies of raw data? Must each page be signed and dated?**

EPA stated in the preamble to the August 17, 1989 rule (54 FR 34066) that acceptable alternatives to signing and dating each page may be devised and incorporated into standard operating procedures. EPA did not further elaborate in order to allow each testing facility flexibility in implementing SOPs that would

provide adequate assurances within its facilities. Note that EPA may inspect the original records, which must be maintained by the registrant as provided at 40 CFR 169.2(k), to assure that they have been kept and that the copies are correct.

11. **Is it permissible to discard original raw data worksheets after exact copies have been made?**

Destruction of original raw data is prohibited. The registrant is responsible for maintaining all original raw data as specified at 40 CFR 169.2(k). Copies of data may be used to assure compliance with GLPS at the level of the testing facility, but EPA requires that the registrant maintain all original data that support a study.

12. **What type of sponsor-testing facility communication is considered to be raw data which must be archived at the end of the study?**

All records of sponsor-testing facility communication which occur as part of the activities of a study are considered to be raw data, as defined at 40 CFR 160.3. This includes memoranda, letters, and records of telephone conversations which occur during the course of the study. Communication conducted prior to the study (i.e., before the protocol is signed) or following the completion of the study (i.e., after the report is signed) would not normally be considered to be raw data. Note that certain records not specific to a particular study which are generated when the study is not in progress still need to be retained to prove that study's compliance with GLPS. Examples include records of a sponsor's notifying a facility of the need to comply with GLPS as required at 40 CFR 160.10, and records of facility documents such as standard operating procedures.

STUDY DIRECTOR

13. **Many field studies involve more than one technical phase, each involving different personnel and different methodologies, often by different contractors. Concern has been raised over the difficulty for a single individual to physically oversee all phases and to be expert in all techniques involved. Within the same study, is it acceptable to assign a different study director to different phases?**

No. Each study must have a single study director who represents the single source of study control. This is explicitly stated in the GLPS at 40 CFR 160.33. A single point of control is necessary to the integrity of the study and to avoid the potential for conflicting instructions and confusion in study implementation.

14. If there can only be one study director assigned to a study, is it acceptable to assign "field directors" and "analytical directors" to manage the work which involves different phases and/or locations?

The assignment of responsibility for the study to the study director need not interfere with ordinary delegation of authority necessary for the performance of study duties. Any authority accepted by persons other than the study director does not reduce the study director's overall responsibility for the study.

QUALITY ASSURANCE UNITS (QAUs)

15. Is it acceptable to inspect study-related procedures at a time other than when the study is ongoing?

The GLPS state at 40 CFR 160.35(a) that a testing facility shall have a Quality Assurance Unit (QAU) that shall monitor each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the GLPS. The GLPS further state at 40 CFR 160.35(b)(3) that the QAU shall inspect each study at intervals adequate to ensure the integrity of the study.

Clearly, the QAU must conduct inspections adequate to provide the assurances required at 40 CFR 160.35(a) and, in the course of so doing, must inspect each study at least once. All parameters must be verified adequate for each site, but it is acceptable to use inspections conducted during other studies to provide necessary assurances. It is also acceptable to use inspections conducted when no study is in progress to assure that methods, personnel, etc. at a particular site are in conformance with GLPS. However, acceptability of such inspections is contingent on assuring that the facilities, personnel, methods, etc., which are inspected are representative of those used in the study. Note that it is necessary to reinspect facilities periodically to account for changes in personnel, equipment, etc. Finally, no matter how complete QAU inspectional coverage is regarding the sites involved in a study, it is still necessary to conduct at least one inspection of study activities while the study is in progress.

16. What would constitute adequate inspection of the ongoing study? Would an audit of the protocol or of data records be adequate?

At least one inspection must be conducted while the study is in progress. Under GLPS, the QAU monitoring of protocols, data records, or other documentation phases of a study are important just as is directly observing the experimental phase of the study. However, the GLPS state at 40 CFR 160.35(b)(3) that inspections must be done at intervals adequate to ensure the integrity of the study, and further, at 40 CFR 160.35(b)(4), that periodic status reports noting problems and corrective actions be submitted to management.

An audit of a study protocol would be of very limited utility since the subsequent reporting would be to management which, in all likelihood, has already reviewed the protocol. Data record audits would also be of very limited utility since they may occur after all experimental work is completed--in short, too late for any corrective actions to be taken. This problem also applies to protocol audits conducted after the experimental phase is completed. Thus, reliance solely on such types of audits would not meet the GLP requirements as stated at 40 CFR 160.35.

FACILITIES

17. Is it permissible to store mixed feeds containing the test substance in the same room with the test system during feeding studies?

As discussed at 40 CFR 160.47(b) test substance mixture storage areas must be stored in separate areas from the areas where test systems are kept. However, working quantities of test substance mixtures need not be stored in separate rooms from test systems. Separate areas within the same room may be designated for test substance mixture storage and test systems as long as the separation is adequate to preserve the integrity of the study and the identity, strength, purity and stability of the mixture.

TEST, CONTROL, AND REFERENCE SUBSTANCE CHARACTERIZATION

18. **Do characterization requirements at 40 CFR 160.105 apply to analytical standards?**

Analytical standards are considered to be reference substances and are subject to all GLP standards that apply to reference substances, including characterization.

19. **Can data developed by the supplier of the standard be accepted? If not, can it be used on an "interim" basis until the standard is adequately characterized?**

Information developed by a supplier can be used to support characterization requirements, but the compliance statement for the overall study must state whether such data were developed under GLPS. Any data not developed under GLPS may be rejected by the Agency. Analyses must be performed to characterize the reference substance before it is used. In the case that a standard is used before it is analyzed, this is a violation of 40 CFR 160.105(a), which requires such determinations to be made before the standard is used in the study.

20. **What documentation would apply to standards?**

Full characterization information as stated at 40 CFR 160.105 is required of standards. This section requires that any information that is appropriate for defining the standard, including identity, strength, purity, or composition, shall be determined for each batch before it is used. In the case of an analytical standard, for example, it is necessary to obtain analysis data documenting the identity, strength, and purity, for each batch. A labeled assay value, in and of itself, is insufficient.

TEST SUBSTANCE STORAGE CONTAINERS

21. **Is it necessary to retain test substance storage containers for the duration of a field study?**

Yes, as provided at 40 CFR 160.105(c), storage containers for test substances shall be assigned for the duration of a study. This requirement is necessary to assure that test substances are stored in proper containers, and that the containers that are used can be accounted for during the study. At any time during the study, it must be possible to examine the containers to assure that this standard is met. However, requests for waivers involving large numbers of containers or safety

concerns may be made to the Director, Policy and Grants Division (see question #23).

22. **If a large number of containers are involved in a study and/or unusual safety problems are caused by the storage of such containers, is there any alternative to storage?**

Yes, but only if written permission is obtained from the Director, Policy and Grants Division (see question # 23). The written letter authorizing disposal of containers will impose certain requirements that will ensure that the intent of the GLP standards are met.

23. **How does one obtain such permission?**

A request for permission must be submitted in writing to the Director, Policy and Grants Division, Office of Compliance Monitoring (EN-342), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460. The request must identify the study for which permission is requested, the testing facility, the nature and quantity of containers involved, and the time and location(s) of the study. The request should also identify any special storage burdens or safety hazards which retention of the containers may pose.

24. **What types of conditions would be imposed by EPA in granting such permission?**

EPA will request that sufficient documentation be available to assure that any containers which have been used for test substance storage during the course of a study are thoroughly accounted for from the time of receipt to disposal. This documentation would generally include such items as bills of lading, inventory records, receipts, use logs, and any other supportive records. In addition, the letter will stipulate that the Director of the Laboratory Data Integrity Assurance Division of OCM be notified of the location of such records in order that they be available for inspection.

25. **Can "generic" permission be obtained to cover multiple studies and/or test substances?**

No. Each case will be evaluated individually. However, more than one study and/or test substance may be included in given request, as long as each study and test substance is specifically identified.

PROTOCOLS

26. **Can a "generic protocol" be used for obtaining sponsor approval?**

The GLPS require that the protocol be approved by the sponsor, and the date of approval must be included with the protocol; however the GLPS also provide flexibility in how this approval is obtained. A "generic protocol" approach may be acceptable for obtaining sponsor approval of certain protocol elements. In such a case, the testing facility which is drafting the protocol for a study would only need to obtain approval of those elements which were not included in the generic protocol. Please note that since the GLPS require protocols to include certain information that would not be included in a generic protocol, such as the test substance or the proposed start and termination dates, it would still be necessary to obtain sponsor approval for such information in addition to the approval of the generic protocol.

27. **What records of seeds or transplants of crops or plants used in field studies must be maintained?**

Where crops or plants are the test system or a component of the test system, all GLP standards relating to test system records are applicable. These include protocol provisions given at 40 CFR 160.120(a)(6) and (7), as applicable. Included, for example, would be the source of the test system supply, species, method of identification, etc. Lot numbers of seeds, brand names, and other information uniquely identifying the test system would be relevant.

REPORTING

28. **The GLPS at 40 CFR 160.185(a)(12) require that signed and dated reports of each scientist or other professional in the study be included in the final report. Can these reports be combined into one report, with all of the scientists and professionals dating and signing that report?**

This requirement is intended to ensure that all information related to the study is included in the final report. Specifically, when individual scientists findings are part of the study effort, they are required to be included separately. Combined reports may in effect be consensus documents, and that would defeat the purpose of this requirement. Note that this requirement is not intended to require separate reports of all scientists participating in a study if such scientists are not.

in fact, providing individual findings or opinions. For example, pathologist's reports are considered to be separate findings which must be reported separately.

ARCHIVES

29. **The GLPS state that the study director must assure that raw data are transferred to archives during or at the close of the study. Is there a "grace" period allowed after the end of the study to allow this to be done?**

Under GLPS, the study director is required to assure that all raw data, documentation, the protocol, specimens, and final reports are transferred to the archives during or at the close of the study (40 CFR 160.33(f)). Thus, there is no grace period. The study director must comply with this requirement prior to signing the compliance statement. This ensures that data are fully accounted for at the completion of the study.

30. **How does EPA define "close of study" in regard to archiving?**

The term "at the close of the study" is strictly interpreted to mean that point of time at which the study director signs the final study report. The act of signing the final report is one of assurance by the study director that the report is a true representation of the data that support the report. At or prior to the time that the study report is signed, the study director must pass control of the raw data to the archives where their integrity will be maintained. Any delay in the transfer of data beyond the close of the study creates a lapse between the time that the study director assures that the raw data support the study report and the time that the data are secured from damage, misuse, or loss.

31. **Given that data must be transferred to archives at the close of the study, is it possible to use temporary archives prior to transfer to a central archive?**

There is flexibility in the location of the archives of raw data and specimens. At 40 CFR 160.190(b), the GLPS state that retention of records at alternate locations is acceptable, provided that there is specific reference to those locations in the archives. Such off-location archives must still meet the full requirements of 40 CFR 160.190. Whether records are archived at the registrant's facility, at a contractor's central location, or at separate contractors' locations, the study director must assure that all raw data and specimens have been archived before the study report is signed. If the study director cannot assure that records at a particular location are archived correctly, he should not sign a compliance statement that indicates that this standard has been met. Note that, for the

purpose of complying with GLPS, true copies may be archived at the close of the study. The original records will have to be maintained as well but need not be archived at the end of the study if this is impractical, for example where the original data constitutes a facility record shared by other studies still in progress at the close of the study.

32. **Is it necessary to retain frozen tissue samples in archives, or may these be discarded after quality assurance verification?**

Under FIFRA GLPS, 40 CFR 160.195, frozen tissue samples are required to be retained in archives, and there are no specific allowances for their being discarded as there are for "specimens obtained from mutagenicity tests, specimens of soil, water, and plants, and wet specimens of blood, urine, feces, and biological fluids." The GLPS do not require specially prepared material to be retained beyond the period that it affords evaluation if such material is relatively fragile and differs markedly in stability or quality during storage. EPA does not believe that this is the case for many types of frozen tissues. The reason that tissues are frozen is to retain their utility for evaluation. Please note that, as provided at 40 CFR 160.195(h), non-documentary material such as samples and specimens may be discarded after EPA has notified the sponsor or testing facility in writing that retention is no longer required.

33. **Must field notebooks be archived during or at the close of a study?**

If a notebook contains raw data, the notebook or the raw data must be archived at the close of the study. Note that the registrant is responsible for the original records under 40 CFR 169.2(k) and section 8 of FIFRA, so it is inadvisable to enter raw data for studies related to different registrations in the same bound notebook.

34. **Must analytical preparations (e.g., scintillation vials and solutions) be archived?**

Such preparations need not be retained beyond the period that they afford evaluation, as stated at 40 CFR 160.195(c). Generally, samples prepared for analysis have limited utility beyond the time of analysis and can be discarded.

35. **How long must soil, water and plant specimens be retained?**

These need only be retained until the QAU has verified that their disposal will not jeopardize the integrity of the study, as provided at 40 CFR 160.190(a) and 160.195(c). Please note that there may be study-specific sample retention

requirements in addition to and independent of GLP requirements. Failure to retain such samples may result in rejection of data by EPA or enforcement actions independently of whether a GLP violation has occurred.

GLP VIOLATIONS

36. **Can EPA assess penalties for GLP violations?**

Yes. FIFRA section 14 states the EPA's authority to assess penalties for violations of the Act.

37. **What are the possible violations under the statute?**

Violations of GLPS may constitute unlawful acts under FIFRA. Under section 12(a)(2)(M) it is unlawful to knowingly falsify all or part of any application for registration, application for experimental use permit, any information submitted to the Administrator pursuant to section 7, any records required to be maintained pursuant to this Act, any report filed under this Act, or any information marked as confidential and submitted to the Administrator under any provision of this Act to be submitted to EPA or of records required to be maintained. Under section 12(a)(2)(Q) of FIFRA it is unlawful to falsify all or part of any information relating to the testing of any pesticide (or any ingredient, metabolite, or degradation product thereof), including the nature of any protocol, procedure, substance, organism, or equipment used, observation made, or conclusion or opinion formed, submitted to the Administrator, or that the person knows will be furnished to the Administrator, or will become a part of any records required to be maintained by this Act. Under section 12(a)(2)(R) of FIFRA it is unlawful to submit to the Administrator data known to be false in support of a registration. Finally, it is unlawful under FIFRA section 12(a)(2)(B)(i) of FIFRA to refuse to prepare, maintain or submit any records required by or under sections 5, 7, 8, 11, or 19.

38. **What are the maximum penalties that can be imposed?**

Section 14(a) of FIFRA provides for maximum civil penalties of not more than $5000 per offense for violations of the Act by registrants, commercial applicators, wholesalers, dealers, retailers, or other distributors, and of not more than $1000 per offense for other persons. For knowing violations of the Act, FIFRA section 14(b) provides for maximum criminal penalties of not more than $50,000 and/or 1

year imprisonment for producers, registrants, or applicants for registration and of not more than $25,000 and/or 1 year imprisonment for other knowing violators.

39. Will civil or criminal penalties be imposed for all GLP violations?

No. Section 9(c)(3) of FIFRA allows a written notice of warning to be issued for a minor violation, if such warning is determined to be adequate to serve the public interest. Section 14(a)(4) of the Act further provides that in determining the size of a penalty EPA may issue a warning in the case that a violation occurred despite exercise of due caution or did not cause significant harm to health or the environment. Finally, section 14(a)(2) of FIFRA provides that persons other than registrants, commercial applicators, wholesalers, dealers, retailers or other distributors who violate any provision of the Act may be assessed a civil penalty only subsequent to receiving a written warning for a prior violation. Thus, persons who only perform testing and are not engaged in the distribution and sale of pesticides will not be assessed civil penalties for their first offense. This does not extend to criminal penalties as described at section 14(b)(2) of FIFRA.

40. Can EPA reject studies not conducted in accordance with GLPS?

Yes. The regulations specifically provide for this at 40 CFR 160.17(a), which states that "EPA may refuse to consider reliable ... any data from a study which [is] not conducted in accordance with [GLPS]." GLP violations associated with a study submitted to EPA may also result in enforcement actions whether or not a study is rejected.