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Pesticide Assessment Guidelines Subdivision K, Exposure: Reentry Protection

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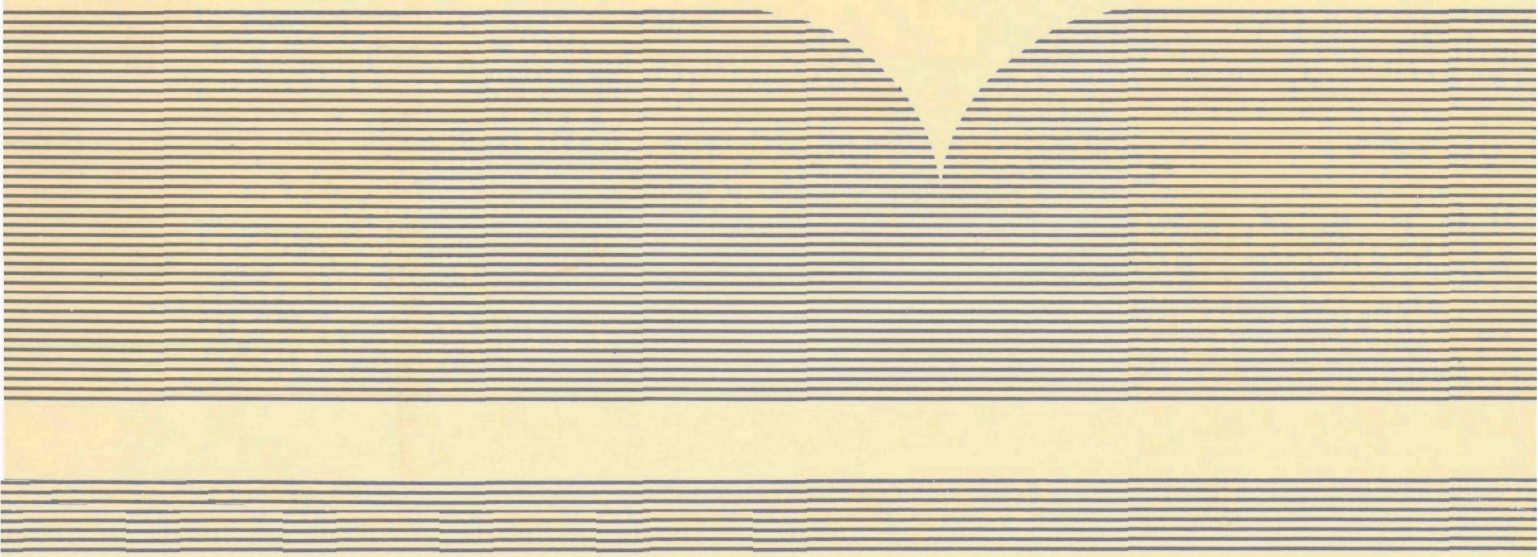

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This publication, Subdivision K of the Guidelines for Pesticide Registration, is intended to support 40 CFR 158 requirements for data for the registration of pesticides. Subdivision K, Exposure: Reentry Protection, addresses means for protecting agricultural workers from potential hazards of pesticide residues in previously treated fields. The primary goal is the establishment of reentry intervals for those pesticides whose toxicological properties and use-patterns indicate a high potential for field-worker hazard. Criteria for data requirements under 40 CFR 158.140 are listed, and alternatives to reentry intervals are provided.

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PESTICIDE ASSESSMENT GUIDELINES

SUBDIVISION K

EXPOSURE: REENTRY PROTECTION

by

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SUBDIVISION K -- EXPOSURE: REENTRY PROTECTION

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I. BACKGROUND: REENTRY PROTECTION CONSIDERATIONS

Soon after the uses of the highly toxic organic pesticides became widespread, the public expressed concern that people performing activities at the site of application could be poisoned by residues of these compounds (cf. Abrams and Leonard, 1950; and Ingram, 1951). In 1958, Quinby and Lemon reported a number of poisoning episodes in which groups of people had become ill during or soon after harvesting tree fruit crops. T.H. Milby (1971) also reported a number of worker poisonings. In all of these cases, the people had been exposed to residues of organophosphorus pesticides and exhibited symptoms of cholinesterase depression that are characteristic of organophosphorus poisoning. (For reviews on this subject, see Gunther et al., 1977; Kilgore et al., 1977; and Popendorf and Leffingwell, 1982).

In addition, the Agency has gathered similar information on reentry related poisonings. The information was gathered through the Agency's Pesticide Incident Monitoring System (PIMS) and from a series of reports put out by the California Department of Food and Agriculture. PIMS receives voluntary reports of incidents of pesticide poisoning. Over 20 percent of the reported incidents involved 2 or more people. Eighty-four of the reports recorded in PIMS are considered as reentry-related episodes, and most occurred in California. Thus, there is probably an overlap with the California Department of Food and Agriculture reports.

Restriction of reentry has received increasing attention from the public and the Agency because of the potential for poisoning of large groups of people. Unfortunately, national estimates of the number of field reentry poisonings do not exist. However, California, the Nation's largest agricultural producer, requires physicians to report worker injury to the State Government. In 1977, the most recent year for which data are available, a total of 1,518 cases of occupational illnesses or injuries related to pesticide exposure were reported. Of these 1,518 cases, 182 were in the field worker job category. The majority of the cases, 108, were classified as skin injuries, 50 were systemic illnesses, 21 were eye injuries, and 3 were eye and skin injuries. The actual number of cases is thought to be significantly higher because of incomplete reporting and diagnosing by physicians, and because workers often do not seek or are unable to obtain treatment from a physician for pesticide exposures.

Case reports of field reentry poisoning demonstrate that incidents can be very serious in terms of symptoms and number of individuals affected, as the following examples illustrate:

Example 1. The largest incident known to the Agency involved approximately 150 high school age workers who entered a corn

field in Indiana to detassel corn. The field had been treated the previous day by helicopter with Carbofuran and Dithane M-45. Seventy-four of the workers were affected and 29 were hospitalized. Major symptoms that occurred in this exposure episode were dizziness, nausea, blurred vision, and dermal irritation.

Example 2. Thirteen out of a group of 26 adult migratory workers in eastern Tennessee developed a hypersensitivity to Dyrene after prolonged work with tomato plants and fruit that had previously been treated with the pesticide. The tasks were planting and staking of plants and harvesting of fruit. Skin patch tests were positive for Dyrene sensitivity for six of the seven workers tested.

Example 3. A total of 118 workers from a 120-person grape-picking crew working in a vineyard near Madera, California, became ill in early September 1976. Of these (108 men and 10 women), 85 received medical attention and three of the 85 were admitted to the hospital. The symptoms were typical for organophosphate poisoning: average plasma and red cell cholinesterase values for the affected workers were depressed more than 60 percent. Most were treated with atropine and some were also treated with 2-PAM (pralidoxime). The workers were exposed to residues of the organophosphate pesticides dialifor (Torak) and phosalone (Zolone). It appeared that workers had been allowed into recently-treated areas before the expiration of the required 30-day safety interval for dialifor [required by the California Department of Food and Agriculture], and that excessive exposure to residues of this pesticide had resulted. (Details of this incident are reported in the Western Journal of Medicine 129: 273-277, 1978.)

Example 4. This incident occurred in North Carolina and involved parathion and maleic hydrazide on tobacco. A 15-year-old, 127-pound girl began topping three days after application. Label directions read "Wait 5 days before cutting or harvesting." The girl became ill shortly after leaving the field in midafternoon and was taken to an emergency room that evening where treatment began at 8:45 p.m. Her symptoms were chest tightness, confusion, difficult breathing, dilated pupils, fainting, headache, increased tearing, nausea, nervousness, and vomiting. Atropine (0.4 mg) was administered periodically. She also received intravenous support. Two laboratory tests indicated that cholinesterase activities were below normal.

From the episodes documented in the PIMS and California reports, the Agency concludes that:

- (1) Reentry into pesticide treated sites can present significant hazard;

(2) The problem exists throughout the country although it appears to be greatest in California; and

(3) Pesticides other than organophosphates can also pose reentry problems.

A number of factors affect the extent of the reentry hazard. The most important factors are: the surface and airborne residue levels of the parent compound and its toxic alteration products; the amount of these residues transferred to people; the absorbed dose; and the toxicological response to the absorbed residues. Many variables have direct impact on these key factors. Residue levels at a treated site are affected by climate, formulation, rate and frequency of application, conditions during application, type of crop, and the length of time since application. The transfer of residues to people, i.e., human exposure, may be influenced by the type of human activity (pruning, thinning, etc.), duration and frequency of activity, and the type of clothing worn. The toxicological response varies with susceptibility among people. For example, very old, very young, malnourished, or pregnant workers may be more sensitive to adverse effects.

Clearly, establishment of precise reentry intervals taking into account every possible exposure/risk situation in each geographic area is impractical. Human monitoring studies or scientific equations cannot reasonably be expected to handle all the significant variables outlined above. One practical solution would be to establish general reentry intervals, which then could be revised by new data or waived when certain protective mechanisms are used, as discussed below. The foliar residue dissipation study should be carried out at a site which is representative of the area where the pesticide is expected to be used. Criteria for site selection should include geographical and meterological considerations as well as crop type. Applicants may wish to consider carrying out additional such studies at other sites in order to propose separate reentry intervals for other geographical areas. Applicants should consider discussing site selection with the Agency before beginning such studies.

Certain pesticides have a potential to cause adverse effects on the environment or may cause injury to the applicator, even when applied in accordance with directions for use. Such pesticides are restricted to use only by certified applicators who have completed an approved training program. Training programs to certify applicators are designed to ensure that users have the competence to handle pesticides without endangering humans or the environment.

While Subdivisions F and H and the certified applicator program are designed in part to protect applicators of pesticides, Subdivision K and the reentry standards [40 CFR § 170.3(b)] are designed to protect those individuals reentering sites where pesticides have recently been applied. A new guidelines Subdivision U is being written to describe protocols to be used to establish methods for

the protection of mixers, loaders, applicators, etc. Subdivision K describes the data needed to develop appropriate label instructions regarding reentry. Certain of these reentry standards characterize measures which are not necessarily applicable to product labeling, but which are important practices designed to protect individuals returning to potentially hazardous treated sites. These practices include posted and/or verbal warnings and provision of protective equipment, washing facilities, and worker education or training, as well as reentry intervals and reentry levels. To prevent poisoning of human beings by residues of some of the most toxic pesticides, the Agency has established reentry intervals [in 40 CFR § 170.3(b)] for pesticide products containing any of twelve active ingredients. Eleven of these active ingredients are organophosphorus insecticides and the other active ingredient is an organochlorine insecticide. That section also contains other standards intended for the protection of farmworkers from the toxic effects of pesticides and pesticide residues.

In the past, the EPA has repeatedly indicated its interest in soliciting comments relevant to determination of reentry intervals using environmental chemistry and exposure data [see proposed Guidelines of June 25, 1975 (40 FR 26802) and July 10, 1978 (43 FR 29696]. Subpart F (43 FR 37336), proposed on August 22, 1978, contained a discussion of exposure data that would be useful for the establishment of reentry intervals, and invited comments. No response on this topic was received. In addition, during the past year the Agency has distributed prepublication drafts of this subdivision to the public in connection with a review of this subdivision by the FIFRA Scientific Advisory Panel. The EPA has received several comments on these drafts. The Agency has considered those comments and guidance received from the Scientific Advisory Panel in the development of this subdivision.

Certain states have also established reentry intervals and other measures for the protection of people from the toxic effects of pesticide residues. For example, the California Department of Food and Agriculture (CDFA) has established reentry intervals and data requirements for pesticide registration in that State. Under the CDFA regulations, foliar and soil residue data for a pesticide and any toxic alteration products must be submitted if any of several toxicology criteria are met. A more detailed discussion and comparison of the CDFA regulations with these Subdivision K guidelines is presented in part III(A) of this discussion.

II. ORGANIZATION AND PHILOSOPHY OF SUBDIVISION K

Proposed rule, 40 CFR 158, specifies the kinds of data and information that must be submitted to EPA to support the registration of each pesticide under the Federal Insecticide, Fungicide,

and Rodenticide Act. The Agency intends to promulgate Part 158 as a final rule during 1984. This subdivision provides information relating to the data requirements listed in 40 CFR § 158.140 including the conditions under which each data requirement is applicable, standards for acceptable testing, and the information that should be included in a test report. The purpose of this subdivision is to provide guidance so that an applicant can determine whether a reentry interval is required for his product and can develop the data necessary to make the calculations for the estimation of a reentry interval and reentry level.

This subdivision is organized into five series of sections. The first section series (130), General Provisions, sets forth definitions, basic requirements and guidance that apply to the other sections of this subdivision. The sections in this series describe the scope, purpose, and use of reentry intervals; define specific terms used in the subdivision; describe the criteria under which reentry intervals and supporting data are required by 40 CFR 158.140; and suggest standards for reporting the data.

The second section series (131), Toxicology Data, deals specifically with use of toxicity data in setting reentry intervals. Among other things, it states the assumptions concerning dermal and inhalation absorption of pesticide residues which should be used in determining an allowable exposure level, "AEL."

The third section series (132), Residue Dissipation Data, explains the § 158.140 requirements for data on the dissipation of dislodgeable and airborne residues; provides procedures for conduct of the studies; and suggests standards for reporting the data.

The fourth section series (133), Human Exposure Monitoring Data, describes needed use practice information; explains exposure data requirements of § 158.140; provides procedures for measurement of inhalation and dermal exposure; and suggests standards for reporting the data.

The last section series (134), Calculation of Reentry Levels and Intervals, discusses two methods for setting reentry intervals: the nondetectable residue method, and the allowable exposure level method. This section also contains provisions describing circumstances which may lead to revision of reentry intervals. Finally, this series discusses limitations for early reentry.

A. "When Required" Paragraphs.

The "When required" paragraphs in this subdivision discuss the circumstances under which 40 CFR § 158.140 requires specific data.

When data are required, that data is to support the registration of the end-use product and each manufacturing-use product used to formulate each end-use product. The data will normally be gathered by the manufacturer of the manufacturing-use product but using an end-use product for the tests. That end-use product need not be the end-use product submitted for registration.

B. References to Published Literature.

Many of the individual sections of this subdivision contain lists of references as an aid to applicants. These references contain test protocols or general information useful for the design, performance, or evaluation of test studies.

III. DISCUSSION OF INDIVIDUAL DATA REQUIREMENTS

A. General Provisions.

1. When Required. Reentry intervals are required by 40 CFR § 158.140 only for highly toxic pesticides which have use types likely to result in high dermal and inhalation exposure to persons entering pesticide treated fields. The various sections entitled "when required" discuss the conditions under which specific data are required by 40 CFR § 158.140, and explain that data are required only for those pesticides which meet both toxicity and use type criteria.

2. Toxicity criteria. The toxicity criteria, under which 40 CFR § 158.140 requires a reentry interval and supporting data, are listed and discussed in § 130-3 of this subdivision. The Agency requires that registration of pesticides with acute dermal, inhalation, and oral toxicity properties corresponding to Toxicity Category I as listed in Subdivision H at § 100-7 should be supported by the establishment of reentry intervals. These acute toxicity criteria are as follows:

- (1) LD_{50}: 200 mg/kg or less for dermal toxicity; - (2) LC_{50}: 200 mg/m^3 or less for inhalation toxicity; and - (3) LD_{50}: 50 mg/kg or less for oral toxicity.

The toxicity criteria in this subdivision are based on the toxicity of the technical pesticide and its toxic alteration products. This is necessary because persons reentering treated sites will normally not be exposed to the formulated product or to its diluted form as applied, but rather to a "weathered" or environmentally modified and dissipated residue, which no longer is composed of the same mixture or ratio of components present in the formulated product.

The selection of these acute toxicity criteria reflects the Agency's judgment that acutely hazardous exposure situations are likely only for the most acutely toxic pesticides. Experience with numerous episodes of pesticide reentry poisoning (see part I of this Discussion) substantiates this judgment. The Agency considered broadening these criteria to include pesticides with toxicological properties corresponding to Toxicity Category II of Subdivision H, but rejected this consideration for the above reason.

The Agency considers that reentry intervals should be required when an exposure or risk assessment procedure indicates the potential for adverse chronic effects upon persons entering a treated site. These adverse effects include neurotoxic, teratogenic, reproductive, and oncogenic effects, for which the Agency requires toxicology testing in Subdivision F of the guidelines.

The requirement for reentry intervals to minimize potential adverse chronic effects reflects the Agency's judgment that chronic exposures can result from repeated entry into treated sites. Adverse chronic effects resulting from such exposures are often subtle and delayed, and therefore not generally brought to the attention of medical personnel. Indeed, the exposed person may be unaware of the exposure. However, the Agency has a clear mandate to protect humans from unreasonable adverse chronic effects of pesticides. This requirement is also consistent with recent regulatory decisions on pesticides based on laboratory animal toxicology data.

As noted earlier in this Discussion, the California Department of Food and Agriculture has established registration requirements relating to reentry exposure considerations. The toxicology criteria specified by the CDFA regulations are broader than the criteria for requirement of reentry data specified in 40 CFR 158.140 and discussed in these guidelines. The CDFA criteria include the following:

- (1) LD_{50} less than 2000 mg/kg for dermal toxicity;
- (2) Highly irritating to the skin;
- (3) Is a sensitizer; and
- (4) Involves a potential risk of a chronic health effect.

3. Use type. The use type criteria for determining whether a reentry interval will be required are discussed in § 130-3. These use types are characterized by the high likelihood of dermal or inhalation exposure of persons who enter sites included in these classes. Dermal exposure will generally arise from contact with treated foliar, fruit, or soil surfaces; inhalation exposure will normally arise from respiration of volatilized pesticide residues and residues adhering to particulate matter which has became airborne.

The Agency believes that these use types constitute the most likely conditions for significant human exposure in reentry situations.

The Agency recognizes that other reentry exposure situations may occasionally occur that would not meet either the toxicity or use type criteria but which could potentially result in adverse acute or chronic effects to persons entering treated sites. In these cases, the Agency will consider the requirement for reentry intervals and supporting data on a case-by-case basis. Similarly, there are likely to be cases where the toxicity and use type criteria are met but exposure is not likely to occur. The Agency has included in 40 CFR 158 procedures for waiving the reentry interval requirement in such cases.

The Agency recognizes that all the many details of common agricultural practices involved in caring for crops combine to determine the magnitude of exposure to persons entering treated sites. There is wide geographical variability in these practices, caused largely by climatic factors which influence both pesticide application schedules and harvest times. Intermittent treatment of certain crops close to or during harvest time may occasionally result in difficulties for growers when long reentry intervals are established for the pesticides being used. The guidelines recognize this possibility, and attempt to provide a number of mechanisms for early reentry, that is, reentry before the established reentry interval has elapsed. These mechanisms represent, in essence, changes in specific agricultural practices, such as spraying the crop with water to reduce residues, using protective clothing when harvesting, reducing the hours per day that harvesting may take place, or performing analytical tests for pesticide residues at the site in order to demonstrate that such residues are below the reentry level. The Agency recognizes that in some cases the only solution may be to alter in some fashion the common practices used either to treat or to subsequently tend the crop, and solicits comments on these or other possible methods of reducing exposure during harvesting or other agricultural activities in treated sites.

In earlier drafts of these guidelines, the Agency had proposed that certain interior use types be included in the criteria of § 130-3. These included fumigations in storage facilities, greenhouses, and other buildings. At a recent public review of a prepublication draft of these guidelines, the FIFRA Scientific Advisory Panel expressed concern over whether these interior use types extended the original intent of the reentry interval concept beyond the basic goal of protecting fieldworkers harvesting or tending crops. (The Panel did, however, make it clear that the Agency should be concerned about limiting all exposure to pesticides, whether the exposure is to applicators, fieldworkers entering treated sites, or anyone else who may come in contact with

pesticides as a result of their use.) The discussion at the meeting centered on concerns that inclusion of these use types made the scope of the guidelines too broad, since exposure arising from interior uses of pesticides is a separate issue. Different routes and mechanisms of exposure are likely in interior settings, and the conceptual model proposed to establish reentry levels and intervals would not be applicable for these settings. The Agency has accordingly decided to limit the scope of the current guidelines to use types associated with growing crops, and has reserved the inclusion of criteria dealing with interior use types.

B. Toxicity Data.

No new toxicological studies are required by 40 CFR § 158.140. The toxicological data needed to estimate reentry intervals will be derived from studies required under 40 CFR § 158.135 and described in Subdivision F: Hazard Evaluation - Human and Domestic Animals.

Toxicity data obtained from studies described by Subdivision F should be used by the applicant for the purposes of this subdivision in the following ways:

- (1) The applicant should compare his toxicity data with the toxicity criteria listed in § 130-3. If the applicant's pesticide does not meet those criteria, no further data will generally be required under 40 CFR § 158.140. That is, neither reentry levels nor reentry intervals will generally be required for a pesticide if it is less toxic than specified in § 130-3.

- (2) If toxicity data and use types show that a reentry level and reentry interval are required by 40 CFR § 158.140, the applicant should use the toxicity data to estimate an allowable exposure level (AEL) unless the applicant elects to use the non-detectable residue approach.

  Estimation of an AEL from animal toxicity studies necessitates the use of appropriate safety factors and may necessitate the use of dermal absorption data. The Agency has in the past used safety factors ranging from 10 to 2000 for exposure and risk assessment, depending on the severity of the toxic effect and on the completeness of the data. The Agency considers that use of safety factors in the evaluation of reentry hazards is particularly useful and appropriate.

  The model for the estimation of an AEL contained in this document allows for the use of a dermal penetration factor. The applicant may assume 100 percent dermal absorption for estimation of the AEL. Alternatively and at the applicant's option, data

may be submitted to support the use of another dermal absorption factor. EPA has developed a suggested protocol, available on request, using rats for measurement of dermal absorption.

However, there are situations where dermal penetration data would not be appropriate for estimation of an AEL. These situations include direct estimation of the AEL from dermal toxicity data. Also, EPA recognizes that a model for calculation of reentry intervals proposed by the California State Department of Food and Agriculture uses an animal dermal toxicity protocol that may be appropriate for estimation of reentry intervals for organophosphorus pesticides. When that model is used, dermal absorption data would be superfluous. The Agency solicits comments on the use of dermal penetration data and on methodology for determination of such data.

- (3) The AEL should then be used to estimate and to propose a reentry level and a reentry interval.

The Agency has considered whether to include dermal irritation and dermal sensitization in the criteria for requiring reentry intervals and supporting data. Dermal irritation and/or dermal sensitization has often been reported to occur during reentry to treated fields. At a recent public review of a prepublication draft of the guidelines, the FIFRA Scientific Advisory Panel expressed a particular interest in protection from exposure to pesticides which can cause dermal irritation or dermal sensitization. However, since neither of these effects are characterized by a dose/response relationship, the Agency does not believe that the establishment of reentry intervals, which employs the concept of a dose/response relationship to determine an allowable exposure level, is an effective way to deal with health effects which may be manifested at very low exposure levels in certain sensitive individuals. Therefore, the Agency intends that in some cases reentry intervals be established using the criteria of § 130-3(a)(1)(v), which allows reentry intervals to be established on the basis of field experience with adverse effects such as dermal irritation or sensitization, rather than using results of animal testing to establish an AEL. The Agency solicits comments on methodology for the establishment of reentry intervals or other standards for the protection of workers with respect to dermal irritation or sensitization or to ocular irritation.

C. Residue Dissipation Data.

At one time, scientists theorized that the most significant mode for the transfer of pesticide residues to fieldworkers was volatilization with subsequent inhalation and perhaps dermal absorption of the vapors. Now, however, most scientists think that most fieldworker exposure to pesticides in field situations

is by dermal contact with residues sorbed to particulate matter. Inhalation exposure to vapor phase and particulate residues also occurs, but it has been reported to be less than one percent of the dermal exposure in field situations.

On the assumption that human exposure is almost entirely due to dermal contact with particulate matter, and to reduce the economic burden of testing, the requirement for a field dissipation study is limited to measurement with respect to time of the amount of pesticide residues adhering to particulate matter that could be transferred to people. Foliar dislodgeable residues adhering to particulates could cause human exposure during activities in tall crops such as tree fruits, grape vines, and corn. Tasks involving substantial soil contact may cause exposure to residues on particulates arising from a combination of foliage and soil. Such tasks include hand harvesting of potatoes, strawberries, or other low crops.

Data describing the dissipation of pesticide residues from fine soil material over a period of time will only be required when reentry activities include tasks involving substantial human contact with the soil.

The residues to be quantified in the dissipation study include any alteration product or impurity of the pesticide that meets the criteria listed in § 130-3. For example, in a dissipation study for parathion, residue levels of both paraoxon (a toxic alteration product) and S-ethyl O-ethyl 4-nitrophenyl phosphorothiolate (a toxic impurity) would have to be measured with respect to time.

Certain formulation types can increase the persistence of a pesticide's activity and, therefore, the toxic hazard to humans. Among these formulation types are encapsulated and wettable powder formulations. Formulation type may also affect the physical process of transfer of pesticide residues to humans. For example, residues adhering to a wettable powder would be more easily dislodged by human activity than residues sorbed directly to the plant surface from a formulation such as an emulsifiable concentrate. For these reasons, dissipation studies will be required for each formulation type that is proposed for registration. However, testing with only one formulation of an end-use product will be required within each formulation type (i.e., a "typical end-use product"; see 40 CFR 158.)

The fact that the majority of the reentry worker poisoning episodes have occurred in California has been attributed to the dry climate there. It has been suggested that rainfall reduces foliar residues by washing the residues from leaves. Also, rainfall, dew, and high humidity may contribute to dissipation of pesticide residues which are susceptible to hydrolysis. Other environmental factors, such as temperature and wind, are expected to be important in the dissipation process on the basis of established principles of chemical and physical processes. For example, the rate of a chemical reaction is approximately doubled for every 10°C increase

in temperature, and gaseous diffusion is strongly influenced by temperature and the speed and quantity of air movement. Since climate is expected to strongly influence the dissipation of pesticide residues, applicants should perform the dissipation study at a site representative of the climatic conditions expected in the intended use areas. The Agency will provide guidance on the choice of site upon request. At the applicant's option, reentry intervals could be established for other environmental conditions by conducting further dissipation studies at other sites, and it may be in the applicant's interest to propose multiple reentry intervals to deal with these environmental variations.

D. Human Exposure Monitoring Data.

The Allowable Exposure Level (AEL) method uses estimates of likely human exposure to determine a pesticide residue level at the treated site, called the reentry level, which can be expected to lead to human exposure at or less than the AEL. The reentry level is thus the basis of the allowable exposure level method. Reentry intervals will be established by determining the time necessary for pesticide residue levels at the site to decay to this level. These relationships are depicted graphically in § 134-2 of this subdivision.

An estimate of human exposure resulting from work activity in treated sites is thus a central facet of the AEL procedure. The Agency recognizes the extremely variable nature of human activities during reentry and the equally variable nature of the exposure process. In order to provide a reasonable limitation on the extent of exposure information needed to support the establishment of reentry intervals, the Agency will accept a "worst case" exposure assessment: that is, where the highest rate of pesticide transfer would occur. Since most known reentry poisoning episodes have occurred during the harvesting of tree fruit, the Agency will accept that as the worst case exposure situation.

It is thus possible to propose a reentry interval calculated by the AEL method of § 134-2 without the necessity of carrying out any field exposure monitoring studies for a new pesticide. This is because the exposure estimate can be derived from an existing correlation between pesticide residue levels at the work site and the resulting exposure levels. An example of such a correlation is the one published by Popendorf (1980) for workers harvesting citrus. The basis for that correlation is discussed in detail below.

The applicant or other interested parties may, at their option, propose shorter reentry intervals for previously registered pesticides, based on exposure data demonstrating that exposure during the performance of reentry tasks with the applicant's pesticide is in fact less than that predicted by the worst case correlation. Additional reentry intervals for a registered pesticide could also be

proposed based on lower site residue levels (as might result from lower pesticide use rates, more rapid dissipation in a different geographical area, etc.). In such cases, multiple reentry intervals could be established.

The Task Group on Occupational Exposure to Pesticides (1974) recommended the use of human exposure monitoring studies for setting safe reentry intervals. The Agency, however, feels that there is now sufficient information available to obviate the need for human exposure studies to set safe reentry intervals. However, under FIFRA, States are allowed to require studies for pesticides to be registered in that State. The State of California, which is a major use area for most registered pesticides, currently requires human exposure monitoring studies in some cases. A protocol developed by E. Kahn of the California State Department of Health (1980) outlines the factors that need to be included when monitoring studies are conducted. The Agency does not recommend or require these studies, but will accept data from such studies for review if conduct of the studies meets or exceeds the standards listed in §§ 133-3 and 133-4 of this guidelines subdivision.

The procedure used by the State of California for establishing reentry levels and intervals is conceptually similar to the allowable exposure level method proposed in these guidelines. That is, residue levels at a site, estimate of exposure of people working at a site, and toxicity of the residues to which they are exposed are used to establish reentry levels and intervals.

This subdivision proposes two procedures to obtain the exposure information necessary to support the establishment of reentry intervals. The first of these is to utilize existing exposure monitoring data obtained for other pesticides under similar use conditions. The second procedure is to carry out field monitoring studies of reentry exposure, using the procedures described in section 133 of this subdivision. The Agency's perception is that human dermal exposure in treated sites is predominantly a physical process as opposed to a chemical process. That is, transfer of pesticide residues to humans during reentry activities is governed more by the physical nature of the residues rather than their chemical properties. According to this concept, the form in which the pesticide was applied are of primary importance for the exposure process. For example, residues from application of formulations, such as wettable powders or encapsulations, that provide a physical vehicle for the transfer of residues to skin would present a greater hazard than those from a totally liquid formulation, such as a diluted emulsifiable concentrate, when the total foliar residue quantity was the same. That is, certain formulation types are expected to cause higher dislodgeable residue levels than other types. The amount of dermal exposure resulting from contact with foliar or soil residues is also a function of the extent and intimacy of that contact.

Thus, under the first procedure mentioned above, the Agency will accept human exposure monitoring data obtained from a previously

registered pesticide as a reasonable measure of the potential exposure to a new pesticide. The use of this "surrogate" data to establish a reentry interval removes the need for human exposure monitoring studies with new pesticides. This proposal is supported by recent studies [e.g. Popendorf (1980)] in which correlations are established between foliar dislodgeable residues and the resulting human dermal exposure.

The second procedure that might be used to obtain the human exposure information necessary to support the establishment of reentry intervals by the method of § 134-2 is to carry out new exposure studies. The Agency emphasizes that registration applicants should not undertake or authorize human exposure studies that could be expected to pose hazards to the study participants. Any studies conducted to obtain human exposure data must not violate FIFRA sec. 12(a)(2)(P), which provides that, "..it shall be unlawful for any person in any State to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purpose of the test..., and (ii) freely volunteer to participate in the test". Guidelines for Protection of Human Subjects [45 CFR 46], promulgated by the U. S. Department of Health, Education, and Welfare, contain information that should be considered for design of such studies.

The carrying out of exposure monitoring studies for previously unregistered pesticides may lead to exposure to unknown hazards. Applicants proposing registration of new pesticides should therefore utilize a surrogate correlation, such as that, described above to propose reentry intervals when they are required by § 158.140. In order to facilitate the identification and utilization of available correlations between residue levels and reentry exposure monitoring data, applicants are encouraged to inquire whether the Agency has identified any such monitoring data which could be used to estimate exposure to a new pesticide.

It appears unlikely that very many applications will arise for registration of new pesticides at new sites, for which reentry intervals will be required, and for which the applicant elects to use the method of § 134-2. In those cases that do occur, the Agency recommends that human exposure data be derived from an existing correlation rather than from further human exposure monitoring studies.

E. Calculation of Reentry Levels and Reentry Intervals.

If the toxicity criteria and the use type class (see § 130-3) indicate that a reentry interval is required by 40 CFR § 158.140, three methods for proposing the interval are provided:

- The non-detectable residue method;

- The allowable exposure level (AEL) method; and

- The adjusted reentry interval approach.

The reason for the three approaches is the need for practical, economic means of solving reentry problems that occur in a wide range of situations.

1. Non-Detectable Residue Method. The non-detectable residue method (§ 134-1) provides an alternative for the registrant whose pesticide does not persist on treated surfaces. Using this approach, the registrant would determine the elapsed time until pesticide residues decline to a nondetectable level at a proposed application site and application rate. This time interval then becomes the reentry interval, and the requirement for submission of human exposure monitoring data is waived.

2. Allowable Exposure Level (AEL). The basic method of establishing an interval is the allowable exposure level (AEL) method (§ 134-2). Use of this method makes collection of data on pesticide toxicology, residue dissipation, and human exposure from activities at the site necessary. The procedure involves establishment of the level of residues at a treated site, called the reentry level, to which humans can be exposed without unreasonable adverse effects. This in turn makes necessary the use or establishment of a correlation between human exposure and residue levels. The elapsed time (reentry interval) necessary to reach this level is determined from residue dissipation data at the site.

Thus, the steps necessary to propose a reentry interval by the allowable exposure level method are as follows:

- (1) An allowable exposure level is estimated from the toxicity data submitted in support of registration. Since the AEL is based only on the toxicity data, it is the same for all tasks and sites.

- (2) Then a reentry level is estimated for the task which is likely to lead to the highest exposure under common use and reentry practices. This is to be accomplished by use of a correlation between pesticide residue levels and expected human exposure; an example of such a correlation is shown in Figure 1 of § 134-2.

If no exposure data are available to establish such a correlation for the site and task of interest, the correlation may be established by carrying out human exposure monitoring studies with either the pesticide of interest or other pesticides which are registered for use at the site of interest.

- (3) The reentry level, in turn, will be used by the applicant to determine a reentry interval. This is to be accomplished by carrying out residue dissipation studies conducted on residues resulting from the end use product at the site. The reentry interval is determined from the residue decline curve as shown in Figure 2 of § 134-2.

The Agency thus assumes that the value of the reentry level is related primarily to the task and the AEL of the pesticide. Therefore, the applicant would not need to recalculate the reentry level in order to propose a reentry interval for the same task at another site.

Iwata et al. (1982) have used this method and the California Department of Food and Agriculture method for the calculation of a reentry interval and have reported that the two methods give the same reentry interval.

3. Adjustment to Reentry Intervals. The adjusted reentry interval is designed to provide the registrant with optional procedures that may be followed to develop reentry times that are consistent with the needs and factors associated with a particular site and use type.

Three procedures to develop adjusted reentry intervals (§ 134-3) are available at the applicant's option. With the first procedure, adjustments based on toxicity data may be possible, if, for example, original toxicity testing was conducted with solvents. Additional testing may indicate that the pesticide without solvents is less toxic than originally determined. Such new toxicity data may allow a new calculation of the AEL.

A second approach for adjusting reentry intervals may be possible, if the applicant or other interested parties demonstrates that different climatic conditions or other factors significantly affect the dissipation of a pesticide in different regions of the country. Using this procedure, a reentry level is determined, and then a residue dissipation study for a particular region is conducted to determine the interval for the pesticide residues to decline to the reentry level. This time period would become the reentry interval for that particular region.

With the third adjustment procedure, data from human exposure studies may indicate that exposure levels are significantly different because of widespread changes in agricultural practices or other

conditions. In such cases, that data may support an adjusted reentry level and interval.

4. Early Reentry. Certain activities, such as posting, scouting, crop sampling, etc., may require early reentry into treated sites before the reentry interval has elapsed. Several practices may be necessary to protect people who undertake early reentry.

The first practice available to allow early reentry is reduction of site residues by rainfall or equivalent spray washing of the crop before reentry of people. Data should be developed to show that a certain amount of rainfall or water spraying results in a decline of pesticide residues to the reentry level. This amount of water would then be stated on the pesticide label, allowing the user of the pesticide to spray treated surfaces to permit early reentry or allowing reentry immediately after sufficient rainfall.

A second practice that can allow early reentry involves demonstration that personal protective equipment will reduce worker exposure to allowable levels, even if pesticide residues are higher than the determined reentry level.

A third example of early reentry on a site-by-site basis would be based on the development of practical and dependable field tests that could be used to demonstrate that the reentry level of pesticides had been reached on treated surfaces, even if the reentry interval had not elapsed. This procedure envisions the use of simple chemical tests by qualified persons on samples of foliage or other treated surfaces to show that the reentry level had been reached.

IV. REFERENCES CITED IN DISCUSSION

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(12) Task Group on Occupational Exposure to Pesticides, Federal Working Group on Pest Management. 1974. Occupational Exposure to Pesticides. U.S. Environmental Protection Agency, Washington, D.C. 20460.

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SUBDIVISION K -- EXPOSURE: REENTRY PROTECTION

Series 130: GENERAL PROVISIONS

§ 130-1 Basic guidance.

(a) Purpose and scope. (1) This subdivision describes the requirements of 40 CFR § 158.140 for registration support data which the Agency will evaluate in order to determine what label restrictions, if any, are needed to protect people who enter a site which has been treated with a pesticide. Human protection through minimization of human exposure to pesticide residues is the purpose of 40 CFR § 158.140 and this subdivision. The Agency requirements for data required by 40 CFR § 158.140 will be based upon:

(i) Determination of the time necessary for pesticide residues at the treated site to decline to an allowable reentry level (a level which will not be hazardous to humans);

(ii) Placement of a reentry interval (interval during which no entry to the treated site should routinely be permitted) on a pesticide label; and/or

(iii) Judgment as to the utility, availability, and likelihood of use of personal protective equipment to be used by people entering a treated site.

(2) The reentry level is a level of pesticide residues in the environment which will not cause unreasonable adverse health effects in people entering a treated site without use of personal protective equipment. The reentry interval is the time it takes for the pesticide residues to dissipate to the reentry level. Use of personal protective equipment and other measures will be required, when it is necessary for people to enter a site before the pesticide residues have dissipated to the reentry level.

(3) Data necessary to determine reentry levels and reentry intervals include:

(i) Data on toxicity of the pesticide;

(ii) Data on expected human exposure to the pesticide residues from typical human activities that would take place at a site that has been treated with a pesticide; and

(iii) Data on the nature and amount of pesticide residues remaining at the treated site (on foliage, soil, or other surfaces and in the air).

(b) Use of reentry interval. The applicant should submit a label for the prospective product which will include a proposed reentry interval. This proposed interval is to be supported by data required by 40 CFR § 158.140 and described in § 130-3 of this subdivision. The Agency will review the data and accept or reject the proposed interval.

(c) Application status and compliance. The requirements of 40 CFR § 158.140 apply to products already registered, as well as those being proposed for registration. The Agency will notify registrants of products already registered, either (occasionally) through the data call-in program or (routinely) upon development of a registration standard, as to when they must satisfy the data requirements of this subdivision. Refer to 40 CFR 158 for details on application status in relation to submittal times.

(d) Formulators' exemption. As provided by 40 CFR § 158.50, an applicant for registration of an end-use product who purchases and legally uses a registered product to formulate the end-use product is not usually required to submit or cite data discussed in this subdivision. Such a purchased product must be registered and labeled for manufacturing use or for the same use as the end-use product being formulated by the applicant. This is consistent with the Congressional intent as set forth in sec. 3(c)(2)(D) of FIFRA, which provides that:

> "No applicant for registration of a pesticide who proposes to purchase a registered pesticide from another producer in order to formulate such purchase pesticide into an end-use product shall be required to--
>
> (i) submit or cite data pertaining to the safety of such purchased product; or
>
> (ii) offer to pay reasonable compensation otherwise required by [§ 3(c)(1)(D) of FIFRA] for the use of any such data."

Since studies required by 40 CFR § 158.140 and discussed in this guidelines subdivision would ordinarily be conducted by the basic manufacturer, pesticide formulators would not often be expected to conduct such tests themselves to develop data to support their individual products. They may do so if they wish, but they may merely rely on data developed by the manufacturing use producer.

(e) "When required" and "test substance" requirements. The registration applicant should be careful to distinguish between the "when required" and the "test substance" paragraph requirements of each section of this subdivision:

(1) The "when required" paragraphs pertain to the circumstances under which data are required by 40 CFR § 158.140 and specify the categories of products for which data must be generated to support registration applications. The test data are ordinarily required to support the registration of each end-use product with

the prescribed use type and each manufacturing-use product used to make such an end-use product.

(2) The "test substance" paragraphs refer to kinds of testing required to produce acceptable data and state the kind of pesticide material that must be used in each test. The test substance for studies described in this subdivision must be a typical end-use product, as required by 40 CFR § 158.140.

(f) General references. Information concerning the history of the reentry problem, the present state of the art, recent experimental activity, and suggested approaches to reentry assessment can be found in the following references:

(1) Task Group on Occupational Exposure to Pesticides, Federal Working Group on Pest Management. 1974. Occupational Exposure to Pesticides. U.S. Environmental Protection Agency, Washington, D.C. 20460. [This review contains a history and discussion of the problem of fieldworker poisonings with organophosphorus pesticide residues on crops up to 1974.]

(2) Gunther, F.A., Y. Iwata, G.E. Carman, and C.A. Smith. 1977. The citrus reentry problem: research on its causes and effects, and approaches to its minimization. Residue Reviews 67:1-139. [This review is recommended as a starting point for information on the reentry problem and for references to research on the subject up to 1977. The literature review is exhaustive and the index is useful.]

(3) Gunther, F.A., and J.D. Gunther (eds.). 1980. Minimizing occupational exposure to pesticides. Residue Reviews, Volume 75. [This entire volume constitutes the proceedings of a conference on reentry and contains a number of papers on various topics underlying the prevention of field worker poisonings.]

(4) Popendorf, W.J., and J.T. Leffingwell. 1982. Regulating OP pesticide residues for farm worker protection. Residue Reviews 82:125-201. [This paper contains a review of the literature as support for the authors' suggested model for the calculation of reentry intervals.]

§ 130-2 Definitions.

(a) Terms used in this subdivision have the meanings set forth at 40 CFR § 162.3 and at 40 CFR 158.

(b) In addition, for the purposes of this subdivision:

(1) The term "airborne residue" means residue of a pesticide, including vapors, aerosols, and airborne particulates, that remains suspended in the air after pesticide application or is caused to

become suspended in the air at a treated site during a normal human activity.

(2) The term "allowable exposure level" or "AEL" means the maximum amount of combined dermal and inhalation exposure which is considered not to cause unreasonable adverse effects to people entering a previously treated site. An AEL will generally be based on animal toxicity studies and adjusted by means of an appropriate safety factor.

(3) The term "dermal exposure" means the process by which pesticide residues are deposited on the skin of people entering a previously-treated site. The term also refers to a measure of the amount of residue deposited by such exposure. It is synonymous with the external dermal exposure, and it is not necessarily equivalent to the amount of residue which would be absorbed into the body through the skin.

(4) The term "direct exposure method" means a procedure for measuring the quantity of pesticide residue transferred to a person's skin or respiratory tract. This method would involve, but not be limited to, measuring residues on dermal patches or respirator filters. This method excludes indirect exposure methods, such as quantification of pesticide residues in blood, urine, or tissues, and excludes measurement of physiological changes, such as changes of blood enzyme activities.

(5) The term "dislodgeable residue" means that portion of pesticide residue on a surface that can be dislodged from that surface by human activities involving contact with the surface. The term also includes residue that can be dislodged by dissolving in moisture (dew, rain, perspiration) and which then can contaminate skin, respiratory tissues, hair, clothing, etc., of people entering the treated site. The surfaces involved include, but are not limited to, foliage, agricultural produce, and soils.

(6) The term "dissipation curve" means a plot of the logarithm of pesticide residue level against time of sampling, or the mathematical representation of such a plot.

(7) The term "early reentry" means the entry of people into a site previously treated with a pesticide prior to expiration of any established, pertinent reentry interval.

(8) The term "inhalation exposure" means the process by which pesticide residues are inhaled by a person in a treated site. The term also refers to the quantity of residue sorbed by respiratory tissues by such a process. This term is synonymous with pulmonary or respiratory exposure, and is not necessarily equivalent to the amount of residue which would be absorbed into the body through the pulmonary system.

(9) The term "personal protective equipment" means special clothing, hats, shoes, gloves, respirators, or other devices attached to or covering people and intended to reduce human exposure to pesticide residues. This term refers to items that normally would not be used in the absence of pesticide hazards and that would provide greater protection to people than normal attire.

(10) The term "proposed reentry interval" means a reentry interval proposed by an applicant as adequate for human protection.

(11) The term "reentry" means the entry of one or more people into a site subsequent to pesticide application.

(12) The term "reentry interval" means the length of time that must elapse after pesticide application before people who are not using personal protective equipment may enter the treated site without risk of any unreasonable adverse effects due to exposure to pesticide residues. This term is synonymous with "reentry time" [cf. 40 CFR § 170.2(a)].

(13) The term "reentry level" means the maximum level of pesticide residues at a treated site that is not likely to pose unreasonable adverse affects on people entering the site without personal protective equipment.

(14) The terms "residue(s), pesticide residue(s), and residue(s) of a pesticide" mean active ingredient(s), toxic impurities of the pesticide, and toxic alteration products of the active ingredient that remain at the site of application or that remain on items that are subsequently removed from the site.

(15) The term "site" means a specific agricultural area such as a field, grove, vineyard, or orchard.

(16) The terms "surrogate", "surrogate of a pesticide", or "pesticide surrogate" means a chemical compound or a mixture of compounds other than the pesticide being investigated which could be used to quantify human exposure. The surrogate could be an active ingredient of a pesticide previously registered for that use. See § 133-2 for further information.

(17) The term "task" means a human work activity performed according to current commonly-recognized practice or any other human activity that could cause exposure to pesticide residues at the site.

(18) The term "typical end-use product" means a pesticide product that is representative of a major formulation category (e.g., emulsifiable concentrate, granular product, wettable powder) and contains the active ingredient of the registration applicant's product.

(19) The term "use type" means a grouping of crops or plants with similar potential for exposure during reentry activities.

§ 130-3 Requirement for reentry interval and supporting data.

(a) When required. A reentry interval and the supporting data discussed in this subdivision are required by 40 CFR § 158.140 to support the registration of each end-use product that meets one or more of the toxicity criteria specified in paragraph (1) below, and that has a use type that could be included in the use classifications specified in paragraph (2) below.

(1) Toxicity criteria. If the pesticide toxicity data meet one or more of the following criteria based on toxicity studies required under 40 CFR § 158.135, then a reentry interval and supporting data are required:

(i) If the LD_{50} of the technical grade of any active ingredient in the end-use product is less than 200 mg/kg (body weight) as determined by acute dermal toxicity testing (§ 81-2); or

(ii) If the LC_{50} of the technical grade of any active ingredient in the end-use product is less than 200 mg/m^3 (for a one-hour exposure) as determined by acute inhalation toxicity testing (§ 81-3); or

(iii) If the LD_{50} of the technical grade of any active ingredient in the end-use product is less than 50 mg/kg (body weight) as determined by acute oral toxicity testing (§ 81-1); or

(iv) If neurotoxic, teratogenic, or oncogenic effects, as evidenced by studies conducted in accordance with §§ 81-7, 82-5, 83-2, or 83-3, or other adverse effects as evidenced by subchronic, chronic, and reproduction studies conducted in accordance with §§ 82-1, -2, -3, -4, 83-1, and -4, would be expected from entry of persons into treated sites, taking into account the pattern and frequency of pesticide use and the results of a risk analysis based on margins of safety or derived from mathematical models according to § 131-3; or

(v) If the Agency receives other scientifically validated toxicological or epidemiological evidence that a pesticide or residue of a pesticide could cause adverse effects to persons entering treated sites. In this situation, reentry intervals and supporting data may be required on a case-by-case basis.

(2) Use types. The following pesticide use types are subject to the requirement for submittal of proposed reentry intervals and the corresponding data;

(i) Applications to growing crops, such as typical applications of insecticides, fungicides, and herbicides made to or around all horticultural and agronomic crops that are field- or orchard-grown;

(ii) Uses of pesticides to all outdoor tree nursery and forestry operations;

(iii) Applications to turf crops and commercial applications to turf; and

(iv) Applications to parks and arboretums.

(b) Waivers. (1) General waiver. An applicant for registration may request a waiver from the requirement to submit some or all of the data required by 40 CFR § 158.140 and described in this subdivision provided that he submits written evidence that such data are inapplicable to the specific pesticide or product.

(2) Waiver for no substantial exposure. The applicant may provide a description of sites and human reentry activities (See § 133-1) revealing that no substantial human exposure to pesticide residues can be reasonably foreseen. If the applicant also requests a waiver from the requirement to provide a reentry interval on a particular product label, the Agency will review the request and the descriptions submitted. If the Agency agrees with the submitted rationale, it will grant a waiver.

(3) Waiver for other specific reasons. The applicant may request a waiver from submittal of certain data required by 40 CFR § 158.140 and discussed in this subdivision, if he submits evidence that specific properties or characteristics of his pesticide or product preclude the requirement for such data. Such properties or characteristics could include, but are not limited to, the composition, degradation rate, toxicity, and such other chemical and physical properties of a specific pesticide or product that are fundamentally different from the factors considered by the Agency in the establishment of the data requirements of 40 CFR § 158.140.

(c) Exposure only to airborne residues covered by other regulations. In the case of reentry to a site which is expected to involve only exposures to airborne residues which are covered by the Permissible Exposure Limits developed by the Occupational Safety and Health Administration (29 CFR § 1910.1000) or the Threshold Limit Values (TLV) developed by the American Conference of Governmental Industrial Hygienists (ACGIH), those limits may serve as reentry levels for airborne residues and can be used by a registrant for determination of a proposed reentry interval.

§ 130-4 General reporting requirements.

(a) General. Each test report submitted to meet the requirements of 40 CFR § 158.140 should include the following information specified in paragraphs (b), (c), and (d) of this section, unless a specific section elsewhere in this subdivision indicates otherwise. The registration applicant should remember that standardization of data reporting and submission of a complete report will expedite

the review process. Multipurpose data should be referenced to specific pages in other volumes or be duplicated and submitted in each appropriate volume.

(b) Test report. The test report should include all information necessary to provide a complete and accurate description of test procedures, materials, results, and analysis of the data, a statement of conclusions drawn from the analyses, and a tabular summary and abstract of results. Units of measurement should be in the metric system, but the English system may, in addition, be used. The two systems should not be mixed (e.g., g/ft^2). The statement of test method(s) used should include a full description of the experimental design, the site(s) or location(s), duration, and actual dates of the study.

(c) Deviation. The report should indicate all ways in which the test procedure failed to meet applicable standards for acceptable testing contained in this subdivision, and should state the reasons for such deviations.

(d) Test substance. (1) The test substance should be identified, including chemical name, molecular structure, and a quantitative and qualitative determination of its chemical composition (including names and quantities of known contaminants and impurities, so far as technically feasible). The determinations should also include quantities of unknown materials, if any, so that 100 percent of the sample tested is accounted for. This information would ordinarily be developed to meet the requirements of 40 CFR § 158.120 discussed in Subdivision D.

(2) Manufacturer and lot and sample numbers of the test substance should be reported.

§ 130-5 Coordination with other requirements in 40 CFR Part 158.

The applicant should determine whether studies conducted to meet the requirements of 40 CFR § 158.140 can be coordinated with studies required by other sections of 40 CFR Part 158, such as § 158.160 discussed in Subdivision G (Product Performance); § 158.150 discussed in Subdivision J (Hazard Evaluation: Nontarget target Plants); § 158.130 discussed in Subdivision N (Chemistry Requirements: Environmental Fate), and § 158.125 discussed in Subdivision O (Chemistry Requirements: Residue Chemistry). The studies should be coordinated with the data gathered to meet the requirements of 40 CFR § 158.135 discussed in Subdivision F (Hazard Evaluation: Humans and Domestic Animals) and with information from Subdivision I (Experimental Use Permits). The applicant should also be cognizant of the labeling implications of this subdivision in relation to Subdivision H (Label Development). In addition, some of the studies might be usefully coordinated with those required for supporting a tolerance or temporary tolerance petition under the Federal Food, Drug and Cosmetic Act.

Series 131: TOXICITY DATA

§ 131-1 Data required.

The toxicological data submitted by registration applicants to evaluate the toxicity of a pesticide to humans and domestic animals as required by 40 CFR §158.135 should be used to determine an allowable exposure level (AEL) for use in proposing reentry intervals. Those data are described in the following sections of Subdivision F.

Acute oral toxicity	§ 81-1
Acute dermal toxicity	§ 81-2
Acute inhalation toxicity	§ 81-3
Primary eye irritation	§ 81-4
Primary dermal irritation	§ 81-5
Dermal sensitization	§ 81-6
Acute delayed neurotoxicity	§ 81-7
Subchronic oral toxicity	§ 82-1
Subchronic dermal toxicity	§ 82-2,-3
Subchronic inhalation toxicity	§ 82-4
Subchronic neurotoxicity	§ 82-5
Chronic toxicity	§ 83-1
Oncogenicity	§ 83-2
Teratogenicity	§ 83-3
Repro. and fertility effects	§ 83-4
Combined chronic tox./oncogen.	§ 83-5
Mutagenicity	§ 84-2

§ 131-2 Exposure conversions and penetration assumptions.

(a) General procedure. (1) The allowable exposure level (AEL) should be determined by the applicant from either:

(i) Animal dermal and/or inhalation toxicity data from acute and subchronic studies conducted to meet the requirements of 40 CFR § 158.135, as described in subdivision F (§§ 81-2, -3, §§ 82-2, -3, and -4); or

(ii) The no observed effect levels (NOELs) from subchronic dermal and/or subchronic inhalation studies.

(2) The toxicity data used for this determination should be that which gives the lowest AEL.

(b) Use of data from other studies. When NOELs from studies such as subchronic neurotoxicity, teratogenicity, and reproduction are lower than NOELs from subchronic dermal and/or inhalation studies, the data from the studies yielding the lower NOELs should be used to determine the AEL.

(c) Conversion of toxicity data from oral routes to dermal routes. The following considerations may be helpful if it is necessary to convert toxicity data obtained from animals dosed by oral route to approximate absorbed dermal dose.

(1) Comparison of acute oral LD_{50} and acute dermal LD_{50} (see §§ 81-1 and -2);

(2) Physical state of the pesticide when exposure is expected (e.g., liquid, dust, granular, or encapsulated residues); and

(3) Actual dermal absorption data from experimental animal studies with the same or analogous chemicals [see also paragraph (d)(1) of this section].

(d) Absorption. For estimating penetration of pesticides through skin, the applicant may either assume 100 percent absorption or submit data including, but not limited to, that described in paragraph (c) above, to indicate that absorption is less than 100 percent. For penetration of pesticides through lung surfaces, the Agency will assume 100 percent penetration unless adequate data are submitted by the applicant to indicate otherwise.

§ 131-3 Determining allowable exposure level.

(a) When required. An allowable exposure level (AEL) for each active ingredient in an end-use product is required to support the registration of each end-use product for which a reentry interval is required by 40 CFR § 158.140 and discussed in § 130-3 of this subdivision.

(b) Determining the AEL. The procedure used to determine an AEL will depend on the kinds of toxic effects produced by the active ingredient and on the extent of absorption. If the active ingredient does not produce oncogenic effects, the AEL should be determined using the guidance and considerations in paragraph (b)(2) of this section. The applicant may determine an AEL using other means and submit supporting data for the approach.

(1) Non-oncogenic substances. The no observed effect levels (NOELs) discussed in § 131-(2) should be divided by an appropriate safety factor to determine the AEL. This safety factor should reflect the degree or amount of uncertainty to be considered when experimental data in animals are extrapolated to effects on man. Safety factors may vary from 10 to 2000 and should reflect the nature of the toxicity (severity and reversibility), the length of the exposure, and the comparability (if known) between the animal and humans for pesticide absorption, distribution, excretion, and metabolic transformations. The NOELs from subchronic dermal or subchronic inhalation studies should generally be used to determine

the allowable levels of human exposure. However, when a NOEL from studies such as subchronic neurotoxicity, teratology, and reproduction are lower, the NOEL derived from these studies should be used. If the animal studies are those which do not yield a NOEL, then appropriate levels of risk should be used to determine an allowable exposure level.

(2) Oncogenic substances. The AEL for oncogenic substances should be based on a risk assessment using appropriate mathematical models applied to data derived from life-time animal studies. The applicant may determine an AEL using other means but should submit data to support the approach. The Agency can provide instructions for risk assessment and for calculation of the AEL.

(c) Reporting of AEL. (1) If the end-use product contains more than one active ingredient, the lowest AEL should be reported.

(2) The AEL should be expressed in terms of daily dermal dose (such as mg/kg/day) or, in the case of airborne residues, in terms of airborne concentrations (such as mg/m^3).

(3) The report on the calculation of the AEL should indicate the data used, any safety factor used, the mathematical model (if any), and the reasons for selecting each.

Series 132: RESIDUE DISSIPATION DATA

§ 132-1 Requirements for residue dissipation data.

(a) When required. When a reentry interval is required under 40 CFR § 158.140 [see § 130-3(a)], that part also requires residue dissipation studies as described in § 132-2 for residues of the applicant's pesticide to support the proposed reentry interval.

(b) Selection of study. The type of residue dissipation study (or studies) that will be required will be based on the use type:

(1) Products intended for foliar application to agricultural crops should be supported by data from a study of the dissipation of foliar dislodgeable residues with respect to time;

(2) When a task will cause substantial human contact with soil, a study of dissipation of residues from soil surfaces with respect to time is needed.

§ 132-2 Dissipation of dislodgeable residues.

(a) Purpose. Requirements of 40 CFR § 158.140 and described in this section are confined to the measurements of pesticide residues which are deposited on and remain on surfaces after pesticide application. These surfaces are limited to those that can be touched or disturbed by people, and from which residues can be dislodged during the performance of various tasks and subsequently deposited on human skin and clothing or inhaled.

(b) When required. Data on residue dissipation are required for each manufacturing-use product whose use is likely to cause dislodgeable residues on surfaces and for which a reentry interval is required under 40 CFR § 158.140 [See § 130-3 of this subdivision].

(c) Test standards. (1) Test substance. A typical end-use product should be used for this study.

(2) Sites for conduct of tests. Since climate strongly influences the dissipation of pesticide residues, the applicant should perform dissipation study at a site representative of the climatic conditions expected in the intended use areas. The Agency will provide guidance on the choice of site upon request.

(3) Substitutions for sites. In certain cases, data from one site (when available) may be substituted for data from another site when surface characteristics are generally similar or nearly identical (e.g., orange and grapefruit orchard applications). For those cases, available residue data should demonstrate that dissipation rates at the two sites do not differ significantly for similar use patterns.

(4) Method of application. The test substance should be applied by application methods recommended for the end-use product. Application of the test substance to the site, area, or objects should be at the least dilution and highest rate permitted for that end-use product.

(5) Timing of application. The test substance should be applied at the time of year or season that would normally be recommended to achieve satisfactory pest control by the product.

(6) Meteorological conditions. Daily meteorological conditions at or near the site of application should be recorded as part of the data in this study. Such data would include, as appropriate, temperature, wind speed, daily rainfall, humidity, and similar information.

(7) Standards for sample collection. (i) Duplicate samples. Duplicate foliar samples should be collected periodically for the development of dissipation curves. The first samples should be

taken as soon as the spray has dried or the dust has settled. The intervals at the start of sampling should be relatively short and may increase with time. For example, samples taken as soon as the spray has dried or the dust has settled, and at 1, 2, 5, 7, 14, 21, 28, and 35 days after pesticide application would probably be appropriate for some pesticides. Comparable control or baseline samples should be collected immediately before the pesticide application. If analyses of samples reveal dislodgeable residues above the reentry level, sampling and analyses should continue until a level at or below the reentry level is reached.

(ii) Additional standards for soil samples. (A) Whenever the applied pesticide deposits on, is incorporated into, or diffuses into soil at the site of application and whenever tasks at the treated site will involve exposure of workers to large amounts of soil, duplicate soil samples for pesticide residue analysis should be collected from the soil surface or from not more than the upper one centimeter of soil in the test plot.

(B) The fine material should be isolated from the soil samples without grinding to give all of the material having particle sizes of 147 microns or less without particles larger than 147 microns. The fine material will be extracted for residue analysis.

(iii) Sample storage. Samples and sample extracts may be stored for later analysis only if fortified controls are included to permit evaluation of possible residue deterioration during storage. Such samples should be stored under conditions which will minimize deterioration.

(8) Procedures for chemical extraction and analysis. The dislodgeable pesticide residues should be extracted from the foliar material and soil, isolated from interfering materials by suitable cleanup procedures, and quantified.

(d) Reporting of test results. In addition to meeting the general reporting requirements of 40 CFR § 158.140 [See § 130-4], the test report should also meet the following requirements:

(1) For surface residues such as foliar residues, the analytical results should be expressed in terms of milligrams or micrograms of residues per square centimeter of surface (e.g., leaf surface). It will be necessary to estimate the surface area of extracted leaves that are too small for a standard leaf punch to be used.

(2) For residues on media such as soil, the analytical results should be expressed in terms of micrograms per gram of fine material. The fine material should be reported in milligrams or micrograms per square centimeter of surface of the soil area from which the sample was obtained.

(e) Evaluation and use of data. Data obtained from this study are for the development of dissipation curves which can be used in the calculation of reentry intervals according to the approaches described in section series 134 of this subdivision.

(f) References. (1) Experimental procedures for determination of dislodgeable foliar residues are given in the following publications:

(i) Gunther, F.A., W.E. Westlake, J.H. Barkley, W. Winterlin, and L. Langbehn. 1973. Establishing dislodgeable pesticide residues on leaf surfaces. Bull. Environ. Contam. Toxicol. 9:243-249. [Also included in this reference are discussions of sampling procedures and a description of leaf punches used in sample collection.]

(ii) Iwata, Y., J.B. Knaak, R.C. Spear, and R.J. Foster. 1977. Worker reentry into pesticide treated crops. I. Procedure for the determination of dislodgeable residues on foliage. Bull. Environ. Contam. Toxicol. 18:649-655. [This is a recent modification of the above procedure for quantification of dislodgeable residues and increases the applicability of the method. Although additional research may uncover other methods more predictive of the respiratory and dermal dose variable, at present these techniques are the most suitable for foliar residues.]

(2) Experimental procedures for the determination of pesticide residues on fine soil particles can be found in the following publications:

(i) Spencer, W.F., Y. Iwata, W.W. Kilgore, and J.B. Knaak. 1977. Worker reentry into pesticide treated crops. II. Procedures for the determination of pesticide residues on the soil surface. Bull. Environ. Contam. Toxicol. 18:656-662. [This paper contains a procedure for sampling of fine, dry particulate matter from the soil surface and a procedure for extraction of pesticide residues from soil.]

(ii) Berck, B., Y. Iwata, and F.A. Gunther. 1981. Worker environment research: Rapid field method for estimation of organophosphorus insecticide residues on citrus foliage and in grove soil. J. Agric. Food Chem. 29:209-216. [The procedure for sampling fine surface soil material in this paper may be appropriate for damp soils as well as wet soils.]

(iii) Smith, C.A., and F.A. Gunther. 1978. Rapid estimation of organophosphorus pesticide residues in citrus grove soil. Bull. Environ. Contam. Toxicol. 19:571-577. [This paper reports procedures for analysis in the field of pesticide residues sorbed to surface soil.]

Series 133: MEASUREMENT OF HUMAN EXPOSURE

§ 133-1 Descriptions of human activity.

(a) Purpose. The purpose of this section is to delineate the requirements for developing and submitting descriptions of human activities likely to occur at a site that has been treated with a specific pesticide.

(b) When required. The registration of a manufacturing-use product should be supported by a brief description of each of the human activities associated with each of the general use patterns for which a reentry interval is required by 40 CFR § 158.140 [See § 130-3].

(c) Description of activities. Each brief description prepared in accordance with the requirement of paragraph (b) of this section should include, but not necessarily be limited to:

(1) Nature of human activity (e.g., harvesting, thinning, scouting, etc.);

(2) Principal source(s) of exposure (e.g., foliage, soil, air, etc.);

(3) Usual environmental conditions for activity (e.g., hot, humid, cool, dry, wet, etc.);

(4) Level of physical exertion (e.g., mild, moderate, heavy); and

(5) Expected frequency and duration of activity (e.g., number of times per day or per week, number of hours per day, etc.).

(d) Designation of maximum exposure activity. In connection with the submittal of descriptions of human activities discussed in paragraph (b) of this section, the applicant should state which activity is the most likely to result in maximum human exposure to pesticide residues for each site. In some pesticide use situations, the most significant human exposure to pesticide residues occurs when harvested commodities are transferred from the application site and handled (e.g., sorting of fruits or vegetables). The applicant should include a brief rationale supporting his selection. The activity selected will represent the maximum expected exposure activity for that specific use, and may be employed as the exposure standard for future calculations under § 134-2 of this subdivision, if that section is used for calculating a reentry interval.

§ 133-2 Requirements for exposure data.

(a) Purpose and scope. (1) The purpose of this section is to delineate the requirements for developing and submitting data relating to human exposure for purposes of supporting reentry intervals proposed according to § 134-2. The registration applicant should understand that useful exposure studies using surrogate chemicals -- often other pesticides -- may already exist and may be cited to meet the requirements of 40 CFR § 158.140 discussed in this section; actual conduct of the study may be unnecessary if these data are cited. Therefore, the applicant should consult with the Agency before undertaking such studies. The submission and use of extant human exposure data on a surrogate pesticide is encouraged by the Agency and is acceptable if the registrant submits descriptions demonstrating that the sites and human activities for which the surrogate exposure data were obtained produce exposure which is greater than or substantially similar to those for which the reentry interval is being proposed.

(2) A registration applicant should not undertake or authorize development of information to meet the requirements of this section in such a manner as to pose a hazard to people assigned to perform activities in the study. The Guidelines for Protection of Human Subjects [45 CFR 46] promulgated by the U. S. Department of Health, Education, and Welfare contains information that should be considered for design of such studies. Before conducting any such studies, registration applicants should submit study protocols for approval by the appropriate institutional review board or public health department in states where the studies are to be performed.

(3) Any studies or monitoring conducted pursuant to this section must not violate FIFRA sec. 12(a)(2)(P) which provides that "....it shall be unlawful for any person in any State to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purpose of the test ....., and (ii) freely volunteer to participate in the test."

(b) When required. Data relating to human exposure are also required by 40 CFR § 158.140 when reentry intervals are required by § 158.140 as discussed in § 130-3 and when the applicant elects to propose reentry intervals using the method in § 134-2.

(c) General test standards. (1) The applicant should obtain data from one or more studies regarding the quantity of pesticide residues that would be expected:

(i) To be deposited on the skin and clothing of a person undertaking the maximum exposure activity upon reentry.

(ii) To be inhaled by a person undertaking the maximum exposure activity upon reentry.

(iii) To result in a dose to a person by any combined route of

intake that would be appropriate for the maximum exposure activity upon reentry.

(2) Different sites may result in very similar exposures to people engaged in the same general tasks (e.g., lettuce and cabbage harvesting). If data on other pesticides indicate that this is the case, data for one site may be used to estimate exposure at another site. A detailed explanation of any extrapolation processes used, such as from published studies to the study undertaken or from studies on exposure in one crop to their use on another crop, should be reported.

(d) Reporting requirements. The applicant should submit a complete description of the results of the exposure study, including all supporting data, extrapolations, estimates, and other relevant information. Such a description should include, but not be limited to:

(1) A complete description of the selected task (or tasks) used in the exposure study (See § 133-1).

(2) A complete description of the end-use product used for the study.

(3) A complete description of the statistical approaches and treatment of data for the study.

§ 133-3 Measurement of dermal exposure.

(a) Purpose. Use of data on dermal exposure to the pesticide or a surrogate by means of a direct exposure method is required by 40 CFR § 158.140 so that the amount of dermal exposure during the performance of an activity at a site can be estimated. The data will then be used for the calculation of reentry levels and the establishment of reentry intervals as described in section series 134.

(b) When required. (1) Use of data on the estimated dermal exposure of humans are required by 40 CFR § 158.140 to support the registration of an end-use product if:

(i) A reentry interval is required as discussed in § 130-3 of this subdivision; and

(ii) The reentry interval is determined by the method described in § 134-2.

(2) If the reentry interval for a use pattern is determined by the non-detectable residue method described in § 134-1, then the data requirements of this section do not apply.

(c) Combined studies. (1) Direct measurement of dermal exposure to a pesticide should be combined with measurement of inhalation exposure as described in § 133-4 when both types of data are required. The applicant should be certain that the standards for both types of studies are met.

(2) Measurement of dermal exposure to a pesticide during reentry into leafy crops should be combined with measurement of dislodgeable foliar residues. If significant exposure from soil-borne residues is expected, these measurements should be combined with quantification of soil residues. The measurement of dermal exposure may be combined with studies discussed in other sections of this subdivision and in other subdivisions of these guidelines, such as Subdivision G (Product Performance), Subdivision J (Hazard Evaluation: Nontarget Plants), Subdivision N (Chemistry Requirements: Environmental Fate), and Subdivision O (Chemistry Requirements: Residue Chemistry), and coordinated with Subdivision I (Experimental Use Permits).

(d) Test standards. In addition to meeting the general standards set forth in § 133-2(c), a direct dermal exposure study should also meet the following standards:

(1) Study substance. A typical end-use product should be used in these studies to support registration of the pesticide.

(2) Conduct of studies. (i) Attachment of exposure pads. Dermal exposure should be assessed by use of multilayered gauze pads. Pads should be attached to the subjects as specified in Table 1. Each pad should be numbered so that resulting data can be related to the subject and the location of the pad on the subject.

(ii) Assessment of hand exposure. Light cotton gloves should be used to trap residues of the pesticide or surrogate in order to develop data for assessing dermal exposure of human hands.

(iii) Handling of samples. Special care should be taken to protect the samples in the field. Glove and pad samples should be transported to the laboratory in sealed containers. The containers should be chilled or frozen to minimize residue losses in transit and storage.

(iv) Typical activities. All activities contributing to the exposure being studied should be carried out in a manner consistent with current agricultural practice.

(v) Pesticide application. (A) Application rates. Applications should be made at the maximum rate proposed for the end-use product, application method, and application situation being studied.

(B) Application method. Exposures should be determined after pesticide application by the method that experience has shown to cause the maximum residue levels.

(vi) Duration of exposure. The exposure period should be long enough for measurable residues to be collected if exposure is occurring, but short enough to avoid excessive losses. It is impossible to specify an exact duration of exposure that will give satisfactory results for a given activity, and this factor is left to the judgment of the investigator.

(vii) Number of replicates. The applicant should collect dermal exposure replicates sufficient for statistical validation of the exposure. It is suggested that ten workers be monitored in a test for dermal exposure. When small test plot size makes this impossible, the number of replicates could be increased by monitoring exposure for shorter periods.

(3) Residue extraction. The pesticide residues should be extracted from the pads and gloves, and the extracted residues should be separated from interfering substances (e.g. by liquid chromatography) before being quantified. A study should be conducted or cited that measures the efficiency of the method chosen to extract residues from exposure pads and gloves.

(4) Residue analysis. The residues should be quantified by a procedure capable of quantitative detection of residues on exposure pads or gloves at levels of 0.2 ug/cm^2 or less. A study should be conducted or cited demonstrating that the analytical procedure chosen is capable of detection at that level.

(5) Stability of compounds. (i) Stability of compounds on stored pads and gloves. If exposed pads or gloves are to be stored for longer than 24 hours, a study of the stability of the residue stored on moist exposure pads and on moist gloves should be conducted under the conditions to be used for storing the field samples. The storage times should be chosen so that the longest corresponds to the longest projected storage period for field samples and so that a decay curve can be constructed to allow extrapolation of residue levels found in field samples back to the time of collection. The pads and their protective containers should be extracted and analyzed by the methods to be employed in the field studies. Storage of field samples should not exceed periods that would result in loss of 50 percent or more of the original residue.

(ii) Stability of extracts. If extracts from pads or gloves are to be stored for longer than 24 hours before analysis, a study of stability should be conducted or cited for the solvent used. The storage times should be chosen so that the longest corresponds to the longest projected storage period for extracts from field samples and so that a decay curve can be constructed to allow extrapolation of residue levels found in stored extracts back to the time of extraction. Storage of extracts from field samples should not exceed periods that would result in loss of 50 percent or more of the residue originally extracted.

(e) Reporting of study results. (1) General site data. The following data should be reported for each treated site where exposure data are collected:

(i) Chemical name of pesticide or surrogate;

(ii) Type of formulation;

(iii) Method of application;

(iv) Application rate;

(v) Residue levels on pertinent surfaces as listed in § 132-1;

(vi) Dimensions of the treated site;

(vii) Environmental conditions during the exposure test;

(viii) Crop (if involved); and

(ix) Activity of study subjects at the site during the exposure.

(2) Data for individual subjects. Each study subject should be identified by name or number. A set of field data should be compiled for each subject in the study. These data sets should be indexed so that each subject and the intensity of that subject's activity can be related to the exposure levels found. The following data should be reported for each subject:

(i) Subject identification;

(ii) Some measure of intensity or productivity of the subject's activity during exposure (e.g., pounds of fruit picked/hour);

(iii) Pad number and pad location; and

(iv) Levels of toxic pesticide residues on each pad in $ug/cm^2/hr$.

(3) Analysis. Laboratory operations should be recorded on a sample history sheet which should include the sample number and dates of collection, extraction, and analysis for each sample. Paired pads may be combined for extraction and residue analysis.

(4) Calculations. For the calculation of dermal exposures of body areas expected to be exposed during reentry activities, the human body surface areas listed in Table 2 can be used as a guide. The dermal exposure for any body area should be expressed as the

product of the body surface area (see Table 2) and the appropriate residue level expressed as micrograms of residue per square centimeter of exposure pad per hour of exposure. In cases where more than one pad represents the area exposed, the mean of the residues found on the appropriate pads should be used. As an example of these calculations, assume that the residue levels for a person, are as follows (in micrograms per square centimeter per hour): right shoulder, 4; left shoulder, 2; back, 3; chest, 1; right forearm, 8; and left forearm, 6; total dermal exposure for right hand, 2,000 micrograms and for the left hand is 1,800 micrograms. These data multiplied by the adult body surface areas in Table 2 gave the results shown in Table 3.

(5) Evaluation. (i) The study results should be reported as the mean, plus or minus the standard deviation, of the exposure found for each body area for each individual in the exposure study.

(ii) Total dermal exposure should be reported in the same manner for each individual and for the study group as a whole.

(iii) For calculations, exposure below the limit of detection for the analytical method should be counted as 50 percent of that limit.

(iv) The number of individuals in the study and all assumptions used in the calculations should be specified.

(v) The results should be reported without regard to dermal absorption.

(f) References.

(1) Davis, J.E. 1980. Minimizing occupational exposure to pesticides: Personnel monitoring. Residue Reviews 75:34-50. [This review covers methodology for measurement of dermal exposure, conduct of the studies, and conversion of residue levels to total body dermal exposure.]

(2) Durham, W.F., and H.R. Wolfe. 1962. Measurement of the exposure of workers to pesticides. Bull. World. Health. Org. 26:75-91. [This paper discusses methodology for measurement of dermal exposure, conduct of the studies, and conversion of residue levels to total body exposure. The skin surface areas listed in Table 3 were taken from this paper.]

(3) Kahn, E. 1979. Outline guide for performance of field studies to establish safe reentry intervals for organophosphate pesticides. Residue Reviews 70:27-44. [This paper is primarily concerned with information for development of human-subject, field-study protocols for establishment of reentry intervals with organophosphorus pesticides.]

TABLE 1. PLACEMENT OF EXPOSURE PADS TO REPRESENT EXPOSED BODY AREAS.

Body area of concern	Exposure pads representative of the body area
Face	Right and left shoulder pads
Back of neck and back	Back pad (upper center of the back)
Front of neck and chest	Chest pad (upper center of the chest)
Upper arms	Right and left shoulder pads and right and left forearm pads
Forearms	Right and left forearm pads (upper surface near the midpoint of each forearm)
Thighs	Right and left thigh pads (front of each thigh)
Lower legs	Right and left ankle pads (front of each ankle)

TABLE 2. STANDARD BODY SURFACE AREAS

Body area	Body Surface area (cm^2)
Face	650
Back of neck	110
Front of neck plus "V" of chest	150
Chest and stomach	3,550
Back	3,500
Upper Arms	1,320
Forearms	1,210
Hands	820
Thighs	2,250
Lower Legs	2,380

TABLE 3. EXAMPLE OF DERMAL EXPOSURE CALCULATIONS USING DATA GIVEN IN § 133-3(e)(4)

Exposed area	Mean residue ($ug/cm^2/hr$)	Skin area 1/ (cm^2)	Dermal exposure (ug/hr)
Face	3	650	1,950
Back of neck	3	110	330
Front of neck	1	150	150
Forearms	7	1,210	8,470
Hands	-	-	3,800
Total dermal exposure			14,700

1/ Skin areas taken from Durham and Wolfe (1962).

§ 133-4 Measurement of inhalation exposure.

(a) Purpose. Data on inhalation exposure to airborne residues of a pesticide are required by 40 CFR § 158.140 to estimate the amount of respiratory exposure during performance of an activity at a site. The data will then be used for the calculation of reentry levels and reentry intervals as described in section series 134.

(b) When required. (1) Data on the estimated inhalation exposure of humans are required to support the registration of a product if:

(i) A reentry interval is required by 40 CFR § 158.140 [See § 130-3 of this subdivision]; and

(ii) The reentry interval is determined by the method described in § 134-2.

(2) If the reentry interval for a use pattern is determined by the non-detectable residue method described in § 134-1, then the data requirements of this section do not apply.

(c) Combined testing. (1) Measurement of inhalation exposure should be combined with measurement of dermal exposure, as described in § 133-3, when both types of data are required. The applicant should be certain that the standards for both types of testing are met in the combined study.

(2) Measurement of inhalation exposure to a pesticide during reentry into leafy crops should be combined with measurement of dislodgeable foliar residues. Measurement of inhalation exposure may be combined with tests discussed in this subdivision and other subdivisions of these guidelines, such as Subdivision G (Product Performance), Subdivision J (Hazard Evaluation: Nontarget Plants), Subdivision N (Chemistry Requirements: Environmental Fate), and Subdivision O (Chemistry Requirements: Residue Chemistry).

(d) Test standards. In addition to meeting the general test standards contained in § 133-2(c), an inhalation exposure study should also meet the following standards:

(1) Test substance. The applicant should use a typical end-use product for this data requirement.

(2) Preparations for tests. The specific sampling method, sampling medium, and analytical procedure to be used will depend on the material being studied, and are left to the discretion of the investigator, provided they meet the standards prescribed in this section.

(i) Sampling media. The specific sampling medium or media to be used will depend on the compound to be sampled. Polyurethane foam or a granular solid sorbent are generally recommended for vapors. Pore sizes and mesh sizes should be selected to permit appropriate airflow rates. Sorbents should be pre-extracted until the extract contains no material which will interfere with subsequent analysis. The sorbents should then be dried and placed in collection modules. If the sorbent does not adequately trap dust, dusts should be collected with glass fiber or PVC membrane filters placed in the collection module to follow the sorbent in the air stream.

(ii) Sampling unit. Whenever possible, battery-powered personal air samplers should be used. If the expected pesticide levels are below the limits of detectability by such low-volume air samplers, then stationary high-volume air samplers should be used instead.

(iii) Sampling efficiency. (A) Sampling efficiency of low volume air-sampling pumps. The sampling efficiency of the sampling unit and media should be demonstrated for the residues of interest and reported data should be adjusted accordingly.

(B) Sampling efficiency of high-volume air-sampling pumps. Both the retention and collection efficiencies for the combination of sampler and sorbent should be determined with the residue of interest. Whenever possible, tests should be performed outdoors with unaltered ambient air; if necessary, intake air should be filtered to remove interfering contaminants. At least one blank determination with unfortified filters should be made simultaneously to correct for airborne interferences, contamination, or losses through the analytical methodology.

(C) Standards for air-sampling collection efficiency. For each test, at least five determinations should be made and the mean and standard deviation for recovery of the original material determined. The mean recovery should be at least 75 percent.

(iv) Extraction method. The extraction efficiency of the method chosen to extract residues from the sorbents should be determined or cited. Sorbent traps should be charged with the same material and formulation to be studied and at approximately the level expected to be collected during a sampling period in the field study. At least five replicate samples should be extracted and the mean and standard deviation for recovery determined. The mean recovery should be at least 75 percent of the original material.

(v) Analytical procedure. A study should be conducted or cited to demonstrate that the analytical method chosen, coupled with the sorbent and extraction method to be used, is capable of quantitative detection of 0.5 ug/m^3 or less of the compound being studied, or of human exposure to 1 ug/hr or less of the compound when possible. For applications involving material of very high toxic hazard, a greater sensitivity may be required.

(vi) Stability of samples and extracts. (A) Stability of exposed media. If sampling media are to be stored for longer than 24 hours after exposure, a test of stability of the residues of interest while sorbed to the media should be conducted or cited. Media should be charged with pesticide by the same procedure used in paragraph (d)(3)(iii) of this section for sampling efficiency testing. Lots of five replicate samples should be stored for at least three different periods of time under the storage conditions for field samples. The samples should be extracted and analyzed by the methods to be used in field studies. The storage times should be chosen so that the longest corresponds to the longest projected storage period for field samples and so that a decay curve can be constructed to allow extrapolation of residue levels back to the time of collection. Storage of field samples should not exceed periods that would result in loss of 50 percent or more of the original residue.

(B) Stability of extracts. If extracts from field samples are to be stored for longer than 24 hours before analysis, a study should be conducted or cited that the demonstrates stability of the compound of interest in the solvent to be used. Storage times should be chosen so that the longest corresponds to the longest projected storage period for extracts from field samples and so that a decay curve can be constructed to allow extrapolation of residue levels back to the time of extraction. Storage of extracts from field samples should not exceed periods that would result in loss of 50 percent or more of the residue originally extracted.

(vii) Calibration of air-sampling equipment. Sampling pump airflow instruments should be calibrated for the particular sampling medium to be used.

(3) Conduct of tests. (i) Positioning of sampling units. If personal air samplers are used, the air intakes should be positioned to be at the height of the human breathing zone and should be oriented downward or horizontally to avoid collection of non-respirable particles or droplets. If stationary samplers are used, the air sampling inlet should be positioned at the height of the breathing zone of an average-sized person engaged in the designated task. Airflow through the sampling unit should be measured at the beginning and end of each exposure period. If airflow changes during the exposure period, the mean of these two measurements

should be used as the airflow rate for calculations of air volume sampled.

(ii) Handling of samples. Special care should be taken to avoid contamination of the samples in the field. To avoid further possible contamination, samples should be transported to the laboratory in sealed containers. The containers should be chilled or frozen to minimize residue losses in transit and storage.

(iii) Typical activities. The investigator should insure that all activities contributing to the exposure being studied are carried out in a manner consistent with typical use patterns of the end-use product.

(iv) Application of the test substance. (A) Application rates. Applications should be made at the maximum rate proposed on pesticide labeling for the application method and site.

(B) Application method. The application method that causes maximum residue levels should be used.

(v) Duration of exposure. The exposure period should be long enough for measurable residues to be collected. Air should be sampled throughout the period during which a person is expected to be exposed to the pesticide in the selected maximum exposure activity.

(e) Reporting of test results. Data should be compiled for each exposure sample. These data sets should be indexed so that the exposure data can be related to the residue levels. The types of exposure data required may vary with the activity being studied. An example of the types of data needed in particular exposure situations are presented below as a guide:

(1) Exposure data. The following data, as appropriate to the use type, should be reported:

(i) Test substance and formulation;

(ii) Description of test site, including crop, plot size, row spacing, and height of crop;

(iii) Selected maximum exposure activity;

(iv) Investigator's name;

(v) Application rate;

(vi) Weather data, including relative humidity, wind conditions (steady or gusty), speed and direction of wind, sun condition (clear, partly cloudy, or overcast) and temperature;

(vii) Height of sample unit intake;

(viii) Number of samples collected;

(ix) Length of exposure;

(x) Beginning and ending airflow rates; and

(xi) Any special situation observed that might alter normal exposure.

(2) Analysis. Laboratory operations should be recorded on a sample history sheet which includes:

(i) Storage methods and conditions for media and extracts;

(ii) The extraction and analytical procedures used; and

(iii) For each sample, the sample number and dates of collection, extraction, and analysis.

(3) Evaluation. (i) Estimates of inhalation exposure should be reported for each individual sampling unit and for the group of sampling units as a whole.

(ii) The mean and the standard deviation of the exposures found for the group should be reported.

(iii) For calculations, exposure below the limit of detection for the analytical method should be counted as 50 percent of that limit.

(iv) The number of sampling units in the study and all assumptions used in the calculations should be reported.

(f) References. (1) Inhalation exposure studies require procedures for the trapping, extraction, cleanup, separation, and quantification of pesticides. Methods of those types and associated information can be found in the following references:

(i) Adams, J.D., and J.H. Caro. 1980. Polyurethane foam as trapping agent for airborne pesticides. EPA-600/4-80-008. (Available from NTIS, Springfield, VA 22161.) [This report contains methodology for the evaluation of trapping media, for extraction of trapped residues from the media, for clean-up and separation of trapped residues by liquid chromatography, and for quantification by GLC.]

(ii) Lewis, R.G. 1976. Sampling and analysis of airborne pesticides. In: Air Pollution from Pesticides and Agricultural Process. R.E. Lee (ed.) CRC Press, Inc. Cleveland, Ohio. pp. 51-94. [Reported methods for laboratory and field investigations of pesticides in air can be found in this review.]

(2) The following references may be useful for the design and interpretation of inhalation exposure studies.

(i) Davis, J.E. 1980. Minimizing occupational exposure to pesticides: Personnel monitoring. Residue Reviews 75:34-50. [This review covers methodology for measurement of inhalation exposure, conduct of the studies, and conversion of airborne residue levels to total inhalation exposure.]

(ii) Kahn, E. 1979. Outline guide for performance of field studies to establish safe reentry intervals for organophosphate pesticides. Residue Reviews 70:27-44. [This paper is primarily concerned with information for development of human-subject, field-study protocols to be conducted for establishment of reentry intervals for organophosphorus pesticides.]

(iii) Lewis, R.G., M.D. Jackson, and K.E. Macleod. 1980. Protocol for Assessment of Human Exposure to Airborne Pesticides. Report EPA600/2-80-180. Available from the National Technical Information Service, Springfield, VA 22161. [This report contains discussions of methods for the quantification of airborne residues in the worker environment and the conversion of airborne residue levels to inhalation exposure levels.]

Series 134: CALCULATION OF REENTRY LEVELS AND REENTRY INTERVALS

§ 134-1 Non-detectable residue method.

(a) When used. For purposes of this section, a reentry interval is that time period beyond which there are no detectable dislodgeable residues of the pesticide on surfaces to which the pesticide was applied, as indicated by studies conducted as described in § 132-2 of this subdivision.

(b) Approach. Environmental samples may be collected periodically until no residues are detected in three consecutive samplings using suitably sensitive analytical techniques and equipment. Alternately, the applicant may be justified in extrapolating a dissipation curve to the minimum detectable levels. The interval for residue dissipation to the non-detectable level would then be proposed as the reentry interval. For reentry intervals determined according to this approach, exposure information described in §§ 133-2, -3, and -4 are not required.

§ 134-2 Allowable exposure level method.

(a) When used. For purposes of this section, a reentry interval is that time period beyond which dislodgeable residues on surfaces to which the pesticide was applied have dissipated to the allowable exposure level (or lower) as indicated by studies described in §§ 132-2, 133-3, and 134-1 of this subdivision.

(b) Approach. (1) Calculation of a reentry interval according to the criteria of paragraph (a) of this section involves evaluation of data to determine that level of residue in a reentry site which will result in an amount of human exposure under specified human activities that is at or less than an allowable exposure level. To make this evaluation, the applicant should use two kinds of data:

(i) Data on the relationship between pesticide residue levels and total human exposure during an eight-hour period; and

(ii) Data on the relationship between pesticide residue levels and time.

(2) Figures 1 and 2 represent, in graphic form, the relationships which will be evaluated.

(3) For the approach outlined in paragraphs (b)(1) and (2) of this section:

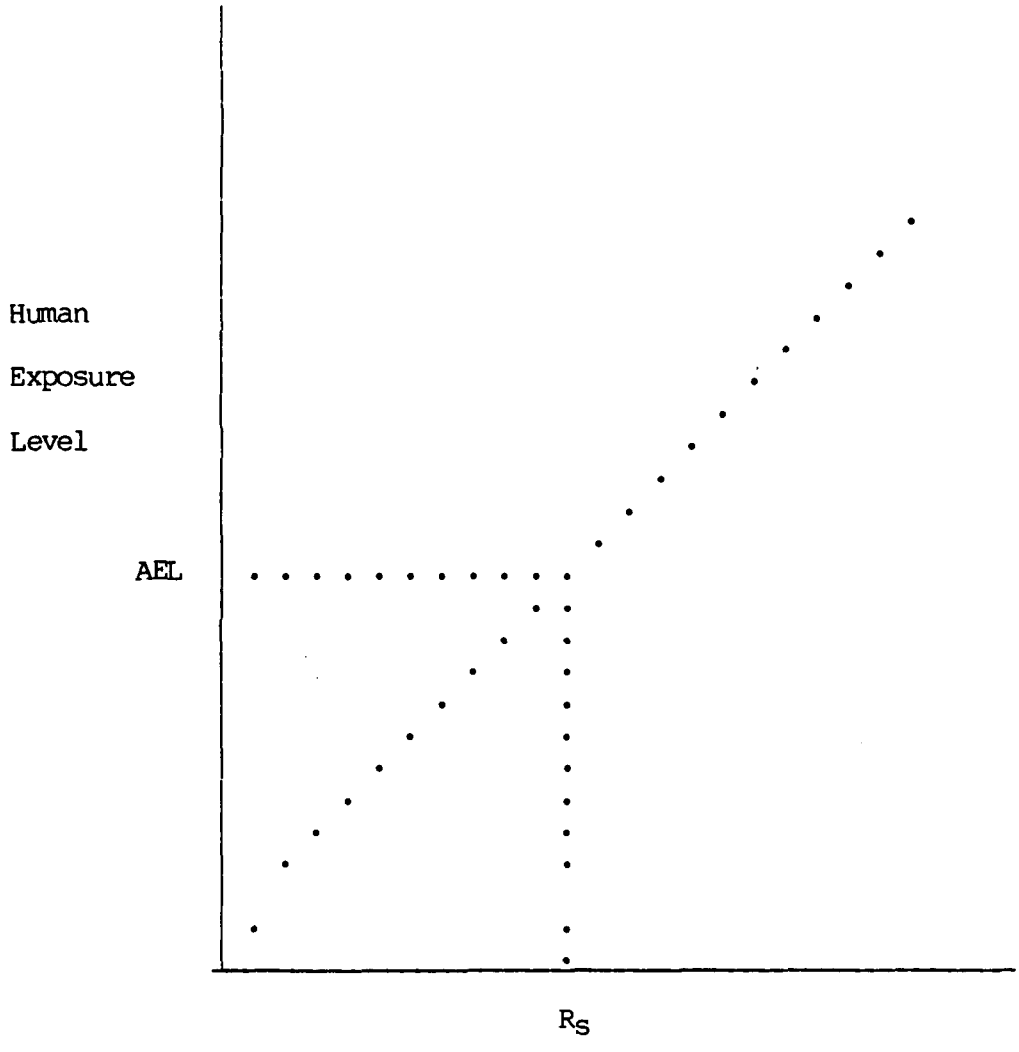
(i) The applicant will determine an allowable exposure level and described according to § 131-3, based on the toxicity data required by 40 CFR § 158.135 and described by Subdivision F of these guidelines.

(ii) The applicant will then examine human exposure data to determine how much exposure (or what dose) a person would receive when performing activities (specific to the proposed use) in a treated area with specified levels of residues. (See Figure 1.) These data will enable the applicant to determine a reentry level (R_S) for a particular combination of human activity, crop, pesticide formulation type, and site.

(iii) Finally, the applicant will review residue dissipation curves to determine how long after application it will take the residue levels to decline to the reentry level in the particular study location, thus estimating the reentry interval (T_S). (See Figure 2.)

(iv) The number of sampling units in the study and all assumptions used in the calculations should be specified.

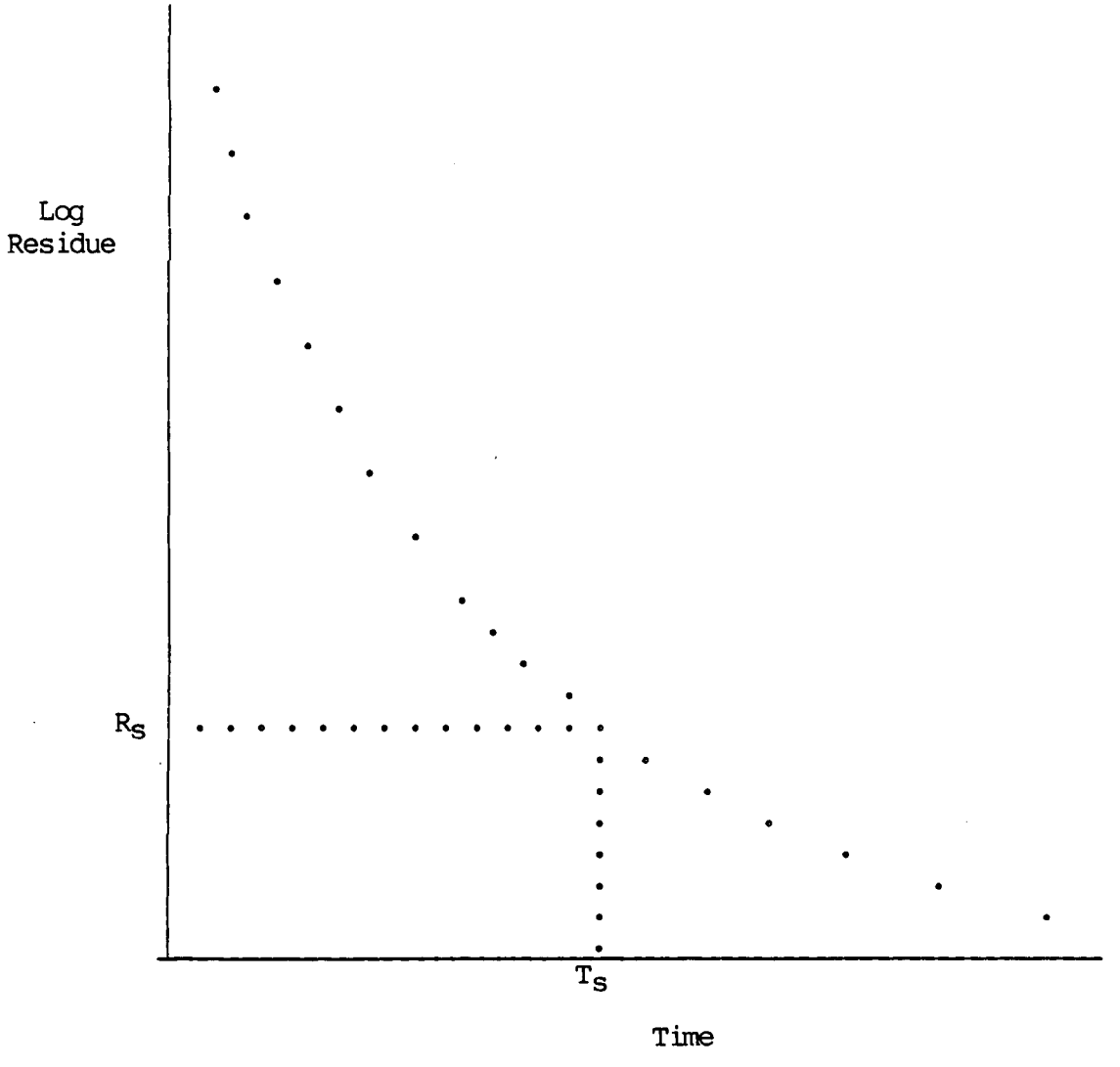
Figure 1. Estimation of exposure plotted against increasing levels of pesticide residue



R_S = The Reentry Level is that residue level which will impart the dose (AEL) during the course of a specified human activity in an eight-hour period.

AEL = The Allowable Exposure Level, which is the no observable effect level (NOEL) divided by an appropriate safety factor, appropriate safety factor, according to § 131-3.

Figure 2. Residue dissipation curve.



R_S = The Reentry Level, which is that residue level which will impart the dose (AEL) during the course of a specified human activity during an eight-hour period.

T_S = The Reentry Interval, which is the elapsed time after the completion of pesticide application at which the pesticide residues (determined according to the methods specified in section series 132) will have dissipated to the reentry residue level (R_S).

(c) References. The following paper used the AEL method for determining a reentry interval.

(1) Iwata, Y., J.B. Knaak, G.E. Carman, M.E. Düsch, and F.A. Gunther. 1982. Fruit residue data and worker reentry research for chlorthiophos applied to california citrus trees. J. Agric. Food Chem. 30:215-222. [This paper reports dissipation data for a pesticide and its five toxic alteration products and uses that data to estimate a reentry interval by the AEL and the CDFA methods. The authors report that both methods give the same reentry interval.]

§ 134-3 Adjustment to reentry intervals.

(a) When used. A registrant or registration applicant may provide information to support an adjustment of a reentry interval. Such information should be of one of the types described in paragraphs (b) through (d) of this section.

(b) Adjustments based on toxicity studies. The animal toxicity studies described in Subdivision F may have been performed using test substances of an end-use product or active ingredient in a solvent. Solvents may aid in dermal absorption of the pesticides and/or may increase their apparent toxicity. After application, such components of end-use products may dissipate from the application site more rapidly than the active ingredient. Testing of animals with the pesticide without solvents may show that it is not as toxic as the original product. If there are sufficient differences in toxicity or in residue retention after application, the applicant may wish to submit data to support adjustment of a reentry interval.

(c) Adjustments based on residue dissipation studies. In some cases, established reentry intervals are based on data developed from studies of a site that may not adequately characterize residue dissipation at another site because of regional and climatological differences, differences in application methods, or differences in post-treatment methods and exposure. These factors would likely affect the slope of the residue vs. time curve demonstrated in Figure 2 of § 134-2(b). In such cases, additional data may be submitted to the Agency to support an additional reentry interval.

(d) Adjustments based on human exposure studies. Data from human exposure studies may indicate significantly different human exposure levels because of widespread changes in agricultural practices or other conditions. Such data may be submitted to support adjustment of the reentry interval.

§ 134-4 Early reentry: practices and limitations.

(a) General. Local conditions and activities may necessitate early reentry by individuals into treated areas before the reentry period has completely elapsed. Such activities may include posting, scouting, crop sampling, and similar related activities, often of a brief and limited nature. Several practices may be necessary to protect individuals who must undertake early reentry. Some of these are described below. Consultation with local agricultural experts is generally recommended before early reentry is undertaken.

(b) Reduction of site residues. Site residues may be reduced to reentry level by rainfall or artificial means, such as spraying the site with water. Data on residue reduction by rainfall or equivalent spray washing (as in overhead irrigation) may be submitted to support early reentry. In those cases, early reentry may be granted to allow people to enter treated sites before expiration of the reentry interval.

(c) Use of personal protective equipment. Early reentry may be granted to allow people to enter treated sites before expiration of the reentry interval by use of personal protective equipment, such as protective clothing and appropriate respirators. The personal protective equipment should be appropriate for the pesticide residue levels at the site at the time of reentry and should conform to any existing protective standards (such as those established by OSHA). Data on the reduction of human exposure to residues by use of personal protective equipment should be submitted and support that the personal protective equipment would reduce human exposure to the allowable exposure level and would be likely to be used.

(d) Reduced exposure times. The reentry level is based on residue exposures representative of normal reentry activities for an 8-hour day. In circumstances where only respiratory exposure to airborne residue will occur, early reentry may be allowed for shorter periods at residue levels higher than the reentry level. The excursion factors described in the Threshold Limit Values (TLV) booklet of the American Conference of Governmental Industrial Hygienists (ACGIH) may be used. Excursion factors allow shorter exposures to chemicals at levels higher than the TLV or OSHA's Permissible Exposure Limit. This approach requires that the exposure level be within an acceptable excursion range and that the product of the concentration multiplied by the exposure time does not exceed the product of the TLV concentration multiplied by 8 hours. Such excursion factors are applied only to chemicals which do not have

established ACGIH "ceiling" designations. The ceiling designations indicate that the TLV should not be exceeded.

(e) Residue level test kits. Early reentry may be allowed if field test kits establish that residues have dissipated to reentry level prior to expiration of the reentry interval. Data should be submitted to support the use of field test kit systems for monitoring pesticide residue levels. Such systems could include any of several chemical residue detection devices or procedures that would readily indicate when residue levels of treated sites are greater or less than the allowable exposure level. (For this factor, the adjustment could either extend or shorten the reentry interval.)

(f) References. The following publications report procedures for the analysis of organophosphorus pesticide residues in the worker environment suitable for rapid tests in agricultural sites.

(1) Smith, C.A., F.A. Gunther, and J.D. Adams. 1976. Worker environment research. III. A rapid method for the semiquantitative determination of some dislodgeable pesticide residues on citrus foliage. Bull. Environ. Contam. Toxicol. 15:305-310. [This paper reported the use of a device for sampling foliar surface residues, and rapid methods for residue cleanup and quantification of organophosphorus pesticide residues. The method depends upon the generation of a color by reaction with 4(4-nitrobenzyl)pyridine.]

(2) Smith, C.A., and F.A. Gunther. 1978. Rapid estimation of organophosphorus pesticide residues in citrus grove soil. Bull. Environ. Contam. Toxicol. 19:571-577. [A procedure for field analysis of organophosphorus pesticide residues sorbed to surface soil is reported in this paper.]

(3) Berck, B., Y. Iwata, and F.A. Gunther. 1981. Worker environment research: Rapid field method for estimation of organophosphorus insecticide residues on citrus foliage and in grove soil. J. Agric. Food Chem. 29:209-216. [This paper is an elaboration of the studies in references (1) and (2) (above) using different sampling methodology and instrumentation. Procedures are reported for both foliar and soil residues.]