*H*AZARD *I*DENTIFICATION -

*T*OXICOLOGY *E*NDPOINT *S*ELECTION PROCESS

A GUIDANCE DOCUMENT

Prepared By:

Jess Rowland
Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division
Office of Pesticide Programs
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I. BACKGROUND

The Office of Pesticide Programs (OPP), has historically, focused on comprehensive risk assessment for chronic dietary [Reference Dose (RfD)] exposure, or for endpoints based on cancer, developmental or reproductive hazards. During the re-registration process, it became apparent that there were pesticide uses and exposures other than dietary which needed to be addressed. Therefore, the decision was made to perform comprehensive risk assessments for acute dietary as well as occupational and residential exposures. In order to accomplish this, based on the use pattern, several exposure scenarios have been developed and the toxicology data base is systematically evaluated for hazard identification for the various exposure scenarios. For hazard identification, the toxicology endpoint selection (TES)] entails identification of doses and endpoints from appropriate toxicological studies that most closely matched the route and duration of exposure for which a risk assessment is required. Hazard identification is accomplished at the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) meetings.

Exposure scenarios evaluated by the HIARC are divided into dietary and non-dietary, the latter of which is then subdivided by duration and route of exposure. **Acute Dietary** refers to **a one day** or 24 hour dietary exposure and **Chronic Dietary** refers to **life-time** dietary exposure. Non-dietary exposures include **Occupational or Residential Exposures** via the **dermal and inhalation** routes that are divided into three time periods: a **Short-Term** exposure period of **1 to 7 days**; an **Intermediate-Term** exposure period with a duration of **7-days to several months**; and a **Long-Term** exposure period covering a substantial portion of the life time (i.e., **several months to life-time**).

Occupational and residential exposure involves three categories of exposed individuals: 1) pesticide handlers, which includes those who mix, load and apply pesticides in their work; 2) reentry workers, which includes agricultural workers who reenter treated fields or greenhouses to harvest crops or undertake any other work in a treated area; and non-agricultural workers whose work area is treated with pesticides; and 3) individuals who are exposed at home or in the workplace to pesticides applied by themselves, family members, or professional applicators.

This guidance document describes the procedures used in toxicology endpoints selection for acute and chronic dietary, as well as occupational and residential risk assessments. For each exposure scenario, guidance is provided for: 1) evaluation of toxicity studies that are relevant for use (i.e., route and duration of the study being similar to the exposure duration of interest); 2) selection of appropriate endpoints for hazard identification (i.e., doses and endpoints that best define the potential hazard in association with the exposure scenario); 3) the process for hazard identification (i.e., use of a weight-of-evidence type approach in which all available studies are considered together as opposed to the results of a single study); 4) the influence of dermal absorption in hazard identification; 5) the criteria for the use of NOEL, LOEL, and the appropriate endpoints in the hazard identification process; and 6) the use of MOEs in risk assessments.

II. DIETARY RISK ASSESSMENT

A. ACUTE REFERENCE DOSE (ACUTE RFD)

1. Objective

The objective is to identify acute hazard (dose and endpoint) based on the toxic effects observed in a study following a single oral exposure (dose) of the pesticide to establish an Acute Reference Dose (Acute RfD).

2. Relevant Studies for Acute Hazard Identification

a. Acute Neurotoxicity Study in Rats

This study (§81-8) is pertinent because: 1) animals receive a single oral dose and therefore all toxicological effects can be attributed to that one dose and 2) the use of three dose levels yields a NOEL that can be used in risk assessments. This study, however, is not available in the existing database for most of the pesticides.

b. Prenatal Developmental Toxicity Studies

The use of the prenatal developmental toxicity studies (§83-3a,b) for acute hazard identification process *presumes* that the developmental effects could result from exposure to a single dose (US EPA, 1986b, 1991). The cells, tissues and organ systems are part of an ever-changing environment in a developing animal. An adverse effect is likely to occur when an exposure of sufficient magnitude occurrs during a critical period of fetal development and/or of a particular organ system. The nature of the critical period to a large extent defines the exposure conditions such as the dose, duration and frequency, necessary to result in an altered development. Consequently, decisions concerning the appropriateness of endpoints from these studies must be based on professional judgement. The prenatal developmental toxicity studies) are relevant because: 1) the treatment route is oral, 2) a single dose of a substance, administered at a critical point in the development of the organism, can elicit developmental effects and 3) frequently it is possible to ascertain the relationship between the day of dosing and the manifestation of the maternal or developmental effects. It is noted, however, that the treatment period consists of repeated dosing (9 days for rats and 15 for rabbits) to pregnant animals.

c. Other Studies

The subchronic, chronic, or reproductive toxicity, or carcinogenicity studies (conducted via the oral route) may be used ONLY if the acute hazards can be identified to have occurred during the first few days of the treatment and therefore are appropriate for extrapolation. Human data when there is information on the exposure levels associated with an appropriate endpoint. The human data, when available, are given first priority, with the animal toxicity studies serving to complement them.

3. **Hazard Identification Process for Acute Dietary Risk Assessment**

The critical element is the selection of toxicology endpoints observed after a single oral administration of a pesticide. When a potential acute endpoint is identified, a determination should be made as to **whether the toxicological effect is, in fact, very likely to be manifested as a result of a single or (at most) very few doses.**

If the acute hazard identified is from an acute neurotoxicity study, the following data are evaluated: 1) type and degree of neurotoxicological effects observed; 2) time of occurrence of these effects; 3) dose-response curves; 4)similarity and/or differences in toxicity between the sexes; and 5) the appropriateness of the NOEL/LOEL established.

If the acute endpoint identified is from a developmental toxicity study, (based on either maternal or developmental effects), a determination is made if these, are in fact potentially manifested after a single or (at most) after very few doses and when these effects are of the greatest concern. Also, results of the developmental toxicity studies are compared for any similarity or differences in the observed toxicity between pecies. Acute hazards may also be identified by extrapolating data from subchronic or chronic toxicity studies if the hazard is identified early in the study.

4. **Acute Hazard Identification For Various Population Subgroups**

The HED Dietary Risk Evaluation System (DRES) contains food consumption data for U.S populaiton and 22 subpopulaito and can provide acute dietary risk assessments for various subpopulations such as Females 13 + years, pregnant, Nursing infants, Non-nursing infants, Children 1-6 years old and 7-12 years old, Males, 13-19 years, Males 10 years and older, Females 13-19 years, and Females 20 years and older.

Therefore, for acute dietary risk assessments *only*, the population subgroups are divided into two main categories; **Females 13+** (i.e., child bearing age) and the **General Population** which includes infants and children and adult males (i.e, excluding Females 13+). **The hazard identification (i.e., endpoints selection), therefore, must be pertinent to these population subgroups in establishing the acute RfD..**

When the endpoint selected is from an acute neurotoxicity study (e.g., cholinergic signs, cholinesterase inhibition, behavioral alterations and/or neuropathology), or from subchronic or chronic toxicity studies (e.g.,, toxicity attributable early expsoure), it is appropriate for all population subgroups (i.e, Females 13+ as well as the General Population which includes infants and children) s.

On the other hand, **when a developmental endpoint is selected** from one of the developmental toxicity studies (rats/rabbits), **it is appropriate only for Females 13+** because: 1) the developmental effects are ***in utero*** effects (i.e., occurs only during pregnancy) and thus applicable only to females of childbearing age; 2) developmental effects are not relevant for adult males; and 3) the effects can not occur postnatally and therefore not applicable to infants and children. The acute RfD established on a developmental endpoint should be used for acute dietary risk assessment only for females of child bearing age (i.e, Females 13 +).

Therefore, when a developmental endpoint is selected, another endpoint (i.e., a "non-developmental)MUSTt be selected for the General Population (i.e, adult males, infants and children). This can be accomplished by evaluating the maternal toxicity observed in the developmental toxicity study that was used for Females 13+, or the acute neurotoxicity study, and/other oral toxicity studies. For example, if maternal toxicity (e.g., clinical signs, abortions, body weight loss in early dosing period, etc.) is attributable to a single exposure, it can be used for acute hazard identification for the General Population. Even though the endpoint identified is maternal toxicity and occurrs in pregnant animals, it is appropriate for use for the General Population because effects are seen in the most sensitive population (i.e., pregnant animals) and thus (the maternal NOEL) would be protective of potential adverse effects on the developing fetuses as well as the general population. This acute RfD should be used for acute dietary risk assessments for the General Population including infants and children.

When it is not possible to identify a dose and endpoint (i.e., a "non-developmental endpoint") attributable to a single exposure from any of the available oral toxicity studies, then a determination is made that no toxicological effects attributable to a single exposure (dose) were observed in oral toxicity studies. Thus an acute RfD can not be established and an acute dietary risk assessment will not be required for the General Population.

B. CHRONIC DIETARY RISK ASSESSMENT (CHRONIC RfD)

1. Objective

The objective is to identify chronic hazard (dose and endpoint) based on the toxic effects observed in a study following **repeated** oral exposure (dose) of the pesticide to establish an Chronic Reference Dose (Chronic RfD).

2. Relevant Studies for Chronic Hazard Identification

a. Chronic Toxicity Study in Dogs (§ 83-1b)

b. Chronic Toxicity/Carcinogenicity Study in Rats (§83-5)

c. Carcinogenicity Study in Mice (§83-2b)

d. Two-Generation Reproduction Study in Rats (§83-4)

e. Human Data

3. Hazard Identification Process for Chronic Dietary Risk Assessment

The quantification of toxicological effects of a pesticide consists of an assessment of noncarcinogenic and carcinogenic effects. Pesticides that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assume to act without a threshed. For chronic dietary risk assessment, a chronic Reference Dose (chronic RfD) is established based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity.

The Chronic RfD is an estimate (with an uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The critical element is the selection of toxicology endpoints observed following repeated oral exposure of a pesticide. Duration of exposure in the laboratory animal study selected for establishing the chronic RfD should be comparable to the expected human exposure. In general, a weight-of-the-evidence approach should be used in which appropriate endpoints from all available studies are considered together. Considerations would include the similarity of effects among species, the onset and development of effects (if this can be determined from the studies), and similarity or differences in effect levels among species.

When an animal study is selected for deriving the RfD, the principal (critical) study must be evaluated for the following factors: 1) adequacy of the study design (e.g., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups and sufficient magnitude of dose levels, the statistical tests used etc.); 2) appropriateness of the NOEL and LOELs established; 3) significance of the effect or endpoint identified for both humans and animals; 4) relationship of the study conclusions to the overall database (i.e., toxicity profile of the pesticide) and 5) the relevancy of the species (tested), dose (selected) and endpoint (identified) for human health risk assessments.

When human data, are available and there is information on the exposure levels associated with an appropriate endpoint, these data are given first priority with the animal toxicity studies serving to complement them. When a human study is selected for deriving the RfD, this study must be evaluated for the following: 1) adequacy of the study design; 2) reliable exposure and/or monitoring data; 3) sufficiently long period of exposure to account for health effects observed; 4) adequate control for confounding factors; and 5) appropriateness of the statistical tests used.

Once the critical study demonstrating the toxic effect of concern has been identified, the selection of the endpoint and dose (usually the NOEL but some times LOEL) results from an objective examination of the data available on the pesticide. The critical endpoint selected should be the effect exhibiting the lowest NOEL. The RfD is then derived by dividing the NOEL or the LOEL by an appropriate Uncertainty Factor (s). Selection of the Uncertainty Factor to be employed in the calculation of the RfD is based on professional judgement while considering the entire data base of toxicological effects for the pesticide.

III. OCCUPATIONAL OR RESIDENTIAL EXPOSURE RISK ASSESSMENTS

A. SHORT-TERM *DERMAL* RISK ASSESSMENT

1. Objective

The objective is to identify Short-Term hazard based on the toxic effects observed in studies where the treatment conditions in experimental animals are similar to the route (dermal) and duration (1-7 days) of human exposure.

2. Relevant Studies for Short-Term *Dermal* Hazard Identification Process

The guideline study that is most directly applicable to this route (dermal) and exposure period of concern (1-7days), is the 21-day dermal toxicity study. In the absence of a 21-day dermal toxicity study or other dermal studies, toxicity studies in which the route of administration is oral may be used for short-term hazard identification. If an oral study is used for dermal exposure risk assessment, the magnitude of dermal absorption must be ascertained and a dermal absorption factor must be identified for route-to-route extrapolation. The procedure for identifying the dermal absorption factor is discussed in detail in Section V.

In general, a Short-Term dermal exposure risk assessment will not be necessary if no systemic toxicity was seen at the Limit-dose (1000 mg/kg/day) in the 21-day dermal study. However, if the toxicity profile of the pesticide indicates serious concerns for toxicological effects not evaluated in the 21-day study (e.g., neurological or developmental effects), then a weight-of-evidence approach must be used in which all available studies (oral and dermal) are considered concomitantly for endpoint selection.

Studies that are considered to be most suitable for this risk assessment are:

a. 21-day Dermal Toxicity Study

This study in rats or rabbits (§82-2) is pertinent because: 1) the experimental conditions (dermal applications) simulate human dermal exposure depending on the intended pesticide formulation and use scenario, and 2) the treatment period (6 hours/day, 5 days/week for 3 weeks), although longer, does encompass the exposure period of concern (i.e., 1-7 days).

b. Prenatal Developmental Toxicity Studies (oral and/or dermal)

These studies (§83-3a,b) are considered to be appropriate when:

(1).A 21-day dermal toxicity study is not available;

(2).No systemic toxicity is seen in the available 21-day study but data from the developmental toxicity studies indicate a serious concern for developmental effects in the absence of maternal toxicity. Thus, the concern for the developmental effects outweighs the lack of adverse effects in the dermal study since the dermal studies do not evaluate parameters that characterize developmental toxicity endpoints;

(3) The relationship between the day of dosing and the manifestation of systemic toxicity can be ascertained in these studies since clinical observations are made throughout dosing period (9 days in rats and 15 in rabbits) making toxicity data available and comparable for the 1-7 day period;

(4) The nature and severity of the developmental effects observed across species are of concern or multiple observations of developmental toxicity (which constitute a syndrome) were observed in a single or multiple species; and/or

(5) Using the NOEL from the developmental toxicity study would increase the protection against potential adverse effects on the developing fetuses as well as the general population.

c. Acute Neurotoxicity Battery (oral)

This study (§81-8) is suitable when:

(1) There is a concern for neurotoxicological effects and/or

(2) The NOEL for acute neurotoxicity or other endpoints is lower than that for developmental toxicity or any other Short-Term endpoint

d. Other Studies

Range-finding (if available), subchronic (oral or dermal), chronic and/or reproductive toxicity (oral) studies may be used if treatment-related toxic effects appear early and are most appropriate to extrapolate for short-term exposures. Endpoints that can be used from these studies include effects that appear to occur early in the study (i.e., within 1-7 days). This extrapolation from long-term studies for short-term hazard identification is valid only if the endpoints are established early in the study and are thus most appropriate to extrapolate to short-term exposures. Early indications of effects in subchronic studies might include, but are not limited to, cage-side observations, hematology (e.g., anemia), clinical chemistry (indicate development of abnormal pathology) and histopathology (pre-neoplastic lesions) data. Body weight data from dietary studies are not appropriate due to palatability problems. Body weight data from oral (gavage), dermal and inhalation studies are appropriate as an indicators of early animal stress. Therefore, extrapolation from subchronic studies as opposed to chronic studies may yield a higher confidence in selecting an endpoint for this exposure period. On the other hand, cases in which effects appear late (i.e., after several months) are not appropriate for hazard identification for short-term risk assessment.

3. Hazard Identification Process for Short-Term *Dermal* Exposure Risk Assessment:

Toxicology endpoint selection should be made using toxicity data generated by the same route as the likely exposure (i.e., dermal). Therefore, in identifying the Short-Term enpdoints, the primary preference should be the 21-day dermal toxicity study,

When a 21-day dermal toxicity study is available and an appropriate endpoint is identified from this study, then a determination is made on the: 1) type and degree of toxicity observed; 2) relationship between the day of dosing and the manifestation of toxic effects during the first week of the study; 3) dose-and time-response curves; 4) toxicity between the sexes; 5) relationship between dermal and systemic toxicity; 6) significance of dermal absorption; and 7) the appropriateness of the NOEL/LOEL established.

When a 21-day dermal toxicity study is available and: 1) no systemic toxicity is seen; or 2) the effects seen are not appropriate for this exposure period (1-7 days)of concern (i.e., body weigh gain depression, alterations in hematological or clinical chemistry parameters measured only at termination, and/or histopathological lesions, etc.) and 3) the endpoint is not appropriate for making regulatory decisions (e.g., piloerection, etc), then this study should not be used in hazard identification.

When a 21-day dermal toxicity study is available but the toxicity profile of the pesticide indicates a potential for neurotoxicity concerns via the oral route, then the dermal study should be examined to determine wheather neurotoxicity parameters were evaluated. If they were not evaluated, then this study must be considered concomitantly with the acute neurotoxicity study. The toxicity observed in both these studies (oral and dermal) will be evaluated to ascertain the influence of dermal absorption as well as the relevancy of the effects based on the routes (oral vs. dermal) of administrations.

When a 21-day dermal study is available but 1) either no systemic toxicity is seen, or 2) the systemic toxicity seen does not reflect the toxicity profile of the pesticide (such as potential for developmental effects of concern), or 3) a developmental endpoint was used for establishing an acute RfD, then this study may not be appropriate for this risk assessment. Under these conditions, the 21-day dermal study is not appropriate for this risk assessment because: 1) of the concern for the fetal effects seen; 2) developmental effects are considered to be appropriate for this exposure period of concern; 3) fetal parameters are not evaluated in the dermal toxicity study (not a Guideline requirement) and these adverse effects can not be determined for the dermal route of exposure; and 4) the endpoint will provide adequate protection for pregnant workers. Under these conditions, the developmental endpoint should be selected for this (dermal) risk assessment along with a dermal absorption factor for route-to-route extrapolation.

When a 21-day dermal toxicity study is not available, endpoint selection is dependent on oral toxicity (prenatal developmental and/or acute neurotoxicity) studies. Under certain circumstances extrapolation from range-finding, subchronic, or chronic studies are acceptable if the treatment related effects appear early in the study (i.e., 1-7 days). Early expression of effects would include, but are not limited to, cage side observations and interim clinical pathology data. Endpoints observed during the early part of the study are also appropriate for extrapolation to Short-Term exposures. However, late appearing effects are not appropriate for extrapolation to short-term exposures.

When an oral NOEL is selected for short-term dermal risk assessment, a dermal absorption factor should be determined for appropriate route-to-route (oral to dermal) extrapolation. The dermal absorption factor can be obtained either from a dermal absorption study (if available) or estimated from the oral and dermal toxicity studies (See Section V)..

B. INTERMEDIATE-TERM DERMAL RISK ASSESSMENT.

1. Objective

The objective is to identify intermediate-term hazard based on the toxic effects observed in studies where the treatment conditions in experimental animals are similar to the route (dermal) and duration (1-week to several months) of human exposure.

2. Relevant Studies for Intermediate-Term *Dermal* Hazard Identification

The current toxicology data requirements contain a number of studies that are relevant for intermediate-term hazard identification. In these studies, the duration of treatment corresponds to the exposure period of concern (one week to several months). However, studies via the dermal route are limited to the 21-day (§82-2) and the 90-day studies in rats or rabbits (§82-3). Other studies that may be relevant for intermediate-term hazard identification conducted via the oral route include: 1) the subchronic neurotoxicity study in rats (§82-6); 2) the subchronic feeding studies in rats and dogs (§82-1a,b); 3) the prenatal developmental toxicity studies in rats and rabbits (§83-3a ,b); 4) the 2-generation reproduction study in rats (§83-4); and 5) interim data from chronic toxicity (§83-1 a,b) and carcinogenicity (§83-2 a,b) studies.

a. 21-day and 90-Day Dermal Toxicity Studies

These studies are considered to be directly applicable for the purpose of hazard identification since the experimental conditions (dermal applications) simulate the real-life exposure (dermal) depending on the intended pesticide formulation and use scenario. Also, the treatment period (6 hours/day, 5 days/week for 21-or 90-days) encompasses the exposure period of concern (1 week to several months). However, for most of the pesticides, the 21-day dermal toxicity study is conducted instead of the 90-day study based on the criteria specified in the 40 CFR. Part 158.

b. Other 90-Day Toxicity Studies (oral)

Studies of 90-days duration are conducted in multiple species (rats and dogs) by the oral route. In the absence of either a 21-day or 90-day dermal study, the 90-day oral or neurotoxicity studies may be used for intermediate-term hazard identification. However, since multiple species and routes are involved, selection of an appropriate dose and endpoint should include a comparison of results across these studies and the intended formulation and use scenario.

c. **Prenatal Developmental Toxicity Studies (oral)**

These studies are relevant ONLY when:

(1) Dermal toxicity studies are not available to ascertain toxicity via this route;

(2) No systemic or dermal toxicity is seen in the 21 or 90-day dermal toxicity studies but developmental toxicity studies indicate a concern for developmental toxicity in the absence of maternal toxicity (since developmental parameters are not examined in the dermal studies);.

(3) The nature and severity of the developmental toxicity observed across species are of concern or multiple observations of developmental toxicity (which constitute a syndrome) were observed in a single or multiple species; and/or

(4) Using the NOEL from the developmental toxicity studies would increase the protection against potential adverse effects on the developing fetuses as well as the general population.

d. **The 2-Generation Reproduction Study (dietary):**

The period of dosing (70 days prior to mating) represents exposure of intermediate duration; the route of exposure, however, is oral. Therefore, this study should be used only when the parental (systemic), reproductive or fetal toxicity are the major concerns and are the most appropriate endpoint for intermediate-term hazard identification.

e. **Long-Term Studies (oral):**

When a relevant study that is appropriate for the intermediate-term exposure period is unavailable, then the interim data from the long-term studies may be used. However, the interim data should be included as a part of the overall evaluation of subchronic effects when the weight-of-the-evidence evaluation is conducted. These data may provide a broader data base for evaluation of appropriate endpoints and hazard identification for intermediate-term exposure scenario.

3. **Hazard Identification Process for Intermediate-Term *Dermal* Exposure RiskAssessment:**

In identifying hazards for Intermediate-Term risk assessment, critical endpoints and considerations are similar to those that are currently used in establishing a NOEL/LOEL in any toxicity study. Generally, a weight-of-the-evidence approach should be used in which appropriate endpoints from all available 90-day studies are considered together. Considerations would include the similarity of effects among species, time course of development of effects (if this can be determined from the studies), and similarity or differences in effect levels among species. The dose identified for intermediate-term risk assessment should not be higher than the dose selected for short-term risk assessment. If the dose identified is from an oral study, then a dermal absorption factor (estimated, if not known) must be used.

When studies with appropriate duration, species and route are available, selection of dose and endpoint should include a comparison of results across studies. Points for considerations include, but are not limited to: 1) whether the effect occurs in multiple species, 2) if the effect is route specific, 3) time of onset (if it can be determined), and 4) the nature of the dose-response in different studies. Hazard identification from developmental or reproductive toxicity studies are relevant if the pesticide has shown the potential to be a developmental or reproductive toxicant and if the dose identified from these studies will increase the protection against potential developmental or reproductive effects on the developing fetus as well as the general population.

Comparison should be made to other subchronic studies or to interim data from long-term studies to evaluate any potential discrepancy between the various data sets. Interim data should be included as a part of the overall evaluation of subchronic effects when the weight-of-the-evidence evaluation is conducted. These data may provide a broader data base for evaluation of the appropriate endpoints. Increase in severity of a toxic response can be evaluated by comparing the NOELs/LOELs from the chronic and subchronic studies. If the NOELs/LOELs are similar, greater latitude can be given in extrapolating from long-term data to intermediate-term situations. Where NOELs/LOELs differ greatly, the effects may be cumulative in nature, and direct extrapolation from a long-term study to an intermediate-term time frame may be an overly conservative estimate of hazard.

3. LONG-TERM DERMAL RISK ASSESSMENT.

1. Objective

The objective is to identify long-term hazard based on the toxic effects observed in studies where the treatment conditions in experimental animals are similar to the route (dermal) and duration (several months to life time) of human exposure.

2. Relevant Studies for Long-Term *Dermal* Hazard Identification

If a long-term dermal study is available, that study is considered first. The current toxicology data requirements, however, do not contain long-term dermal studies for long-term hazard identification and risk assessment. Long-term studies are usually available by the oral route, in which the duration of treatment (major portion of the animals life span) corresponds to the exposure period (several months to life time). Due to this limitation, the Committee must rely on long-term oral studies for long-term hazard identification and risk assessment and take dermal absorption into account. These studies include the chronic toxicity studies in rodents and non-rodents (§83-1); the carcinogenicity study in mice and rats (§83-2); and the 2-generation reproduction study in rats (§83-4).

3. Hazard Identification Process for Long-Term *Dermal* Exposure Risk Assessment

For most pesticides, a Reference Dose (RfD) is used for chronic dietary risk assessment. Since long-term dermal toxicity studies are rarely available, the Committee has to depend on the long-term oral studies for identification of long-term hazards. In doing so, the Committee will evaluate the appropriateness of the dose and hazard identified for establishing the RfD in relation

to long-term hazard for occupational or residential exposure requirements. The Committee will recommend the use of the same dose and endpoint, used for deriving the RfD, for long-term dermal rrisk assessment. However, if the use pattern and exposure scenario indicates special concerns, if the toxicity of the pesticide warrants a hazard identification different from that of the RfD, or if the effects seen by the oral route are not expected by the dermal route (i.e., route-specific effects), then the Committee will identify a dose different from that used for deriving the RfD. If an oral NOEL (i.e., the same NOEL used to derive the chronic RfD) are selected for Long-Term dermal risk assessments, the Committee will select a dermal absorption factor for use in risk assessments. At times the 21- day or 90-day dermal (when available) study may be used if the Committee determines that the endpoints observed in this study is appropriate for Long-Term risk assessments and/or if it believes (based on other studies) that toxicity would not be expected to increase over time.

IV. OCCUPATIONAL OR RESIDENTIAL INHALATION EXPOSURE RISK ASSESSMENTS.

A. Objective

The objective is to identify inhalation hazards based on the toxic effects observed in inhalation studies where the treatment conditions in experimental animals is similar to the duration of human exposure; 1-7 days for short-term, one week to several months for intermediate-term and several months to life time for long-term.

B. Need for Risk Assessment

In general, the dermal route of exposure for occupational or residential uses is the most significant. For certain pesticides (and use patterns), such as the fumigants, the inhalation route is the most significant. Inhalation exposure is also a concern when the dermal exposure has been successfully mitigated or when dermal exposure has a very small impact (based on extremely low dermal absorption) on the total exposure scenario. Therefore, the need for risk assessment via this route is contingent on: 1) the type of pesticide formulation, 2) use-pattern (e.g., use in confined spaces such as termite treatment and fogging use), 3) the inherent toxicity of the pesticide (i.e., Toxicity Category based on LC_{50}), and/or the degree of exposure potential (i.e, greater than 1%).

C. Relevant Studies for Inhalation Hazard Identification

The current toxicology data requirements, are limited to the acute (§81-3) and subchronic (§82-4) toxicity studies. The acute study is not recommended for use in risk assessments since this study is conducted primarily to determine the inhalation LC_{50} values from which a Toxicity Category is assigned to provide information necessary for determining appropriate language for precautionary labeling. Therefore, the choice of study for this exposure assessment is limited to a subchronic toxicity study of any duration (14, 21 or 90-days). Also this study then can be used for inhalation exposure risk assessments for any time period (Short-, Intermediate-, or Long-Term).

When there is a concern for potential inhalation exposure (based on the use pattern) and there are no

inhalation toxicity studies (except for the acute LC_{50} study) available in the database, the Committee is left with no option but to resort to the use of an oral NOEL for inhalation risk assessments (i.e., route-to-route extrapolation). While it is generally recognized that route-to-route extrapolations should be avoided, in the absence of appropriate inhalation toxicity studies, route-to-route extrapolation overcomes the obstacle of inadequate data by allowing one route to substitute for another and provides a way to combine risk for multiple routes.

D. <u>Hazard Identification Process for Inhalation Exposure Risk Assessment:</u>

When a subchronic inhalation toxicity study (14, 21 day or a 90-day) is available, the results should be carefully evaluated to ascertain if the toxicity observed is in concordance with the overall toxicity profile of the pesticide. If the toxicity observed via the inhalation route is similar to those seen in other studies via the oral route (e.g., cholinesterase inhibition, neurotoxicity, hepatotoxicity, etc.), then the endpoint can be used for risk assessments. Since this is the only study that is available in the database, it can be used for risk assessments for any time period (i.e., Short-, Intermediate-, and Long-Term).

In contrast, if the toxicity observed in that study are clinical signs (such as alopecia and piloerection), decreases in body weight gain, and/or gross or histopathology of the respiratory tract but the toxicity profile of the pesticide indicate a concern for developmental, neurotoxicity, or hepatotoxicity, then this study is not appropriate for use in risk assessments since the endpoints observed in that study did not correspond to the toxicity profile of thepesticide. Similarly, the endpoints of concern selected for oral and dermal exposure risk assessments should be compared with the endpoints observed in the inhalation study. If the endpoints for oral and/or dermal risk assessments are based on developmental toxicity, alterations in hematological parameters or neuropathology, then the inhalation toxicity study is not suitable for risk assessments because these parameters (i.e, developmental, hematological or neurological) are not measure in this study. Under these conditions, route-to-route extrapolations should be used.

In order to conduct route-to-route extrapolations, one must convert exposure levels to mg/kg/day since the oral NOELs are usually reported in mg/kg/day. In route-to-route extrapolations, the step that allows the conversion from one route to the other is the dosage expressed in mg/kg/day. In order to convert the exposure (dermal and inhalation) levels to an oral equivalent dose (i.e., mg/kg/day, the following steps are recommended: 1) **convert** the inhalation exposure (µg/lb a.i) and the dermal exposure (mg/lb a.i) to oral equivalent doses (mg/kg/day); 2) **combine** the converted oral equivalent doses to get a combined dose for total (dermal + inhalation) exposure; and 3) the combined dose (mg/kg/day) should then be **compared** with the oral NOEL (mg/kg/day) to calculate the Margins of Exposure. (The procedure for the **"Three C's"** are as follows:

Step I: **Convert** the inhalation and dermal exposures to oral equivalent doses (mg/kg) as follows:

a. unit inhalation exposure (µg/lb ai) x absorption rate (100% default) x application rate (lb ai/acre) x acres treated x 1 mg/1000 µg/kg ÷ body weight (70 kg or 60 kg for developmental endpoints)

b. unit dermal exposure (mg/lb ai) x absorption rate (% recommended or 100% default) x application rate (lb ai/acre) x acres treated ÷ body weight (70 kg or 60 kg for developmental endpoints)

Step II: **Combine** the converted oral equivalent doses to obtain total exposure via these routes (inhalation and dermal).

Step III: **Compare** the combined dose to the oral NOELs for the appropriate exposure period (i.e., Short-, Intermediate-, or Long-Term).

V. THE INFLUENCE OF DERMAL ABSORPTION IN RISK ASSESSMENT.

Dermal absorption is a significant factor in occupational or residential exposure risk assessments since these exposures occur most frequently via the dermal route. Under the current toxicology data requirements, often data are not available to perform the route-specific risk assessment due to the lack of either dermal absorption data or appropriate dermal studies. One of the greatest difficulties encountered by the Committee is the task of estimating the proportion of the pesticide that is absorbed through the skin. Dermal absorption is critical especially when the hazard identified is from an oral study in which the experimental conditions (oral dosing) do not simulate the real-life exposure (dermal) scenario. Therefore, a correction must be made for this difference in absorption rates (i.e., oral vs. dermal). This can be accomplished by the use of a dermal absorption factor to adjust (correct) oral (systemic) absorption to potential dermal absorption. This correction should be described as an additional uncertainty in the final risk assessment. In determining dermal absorption, the Committee considers the weight-of-evidence approach including dermal absorption studies as well as comparison of the dermal and oral studies as discussed below.

When dermal absorption data are available, caution must be exercised as to what dermal absorption value to use. Some factors that effect percent dermal absorption include: application site; the type and amount of vehicle used; total time of application; total dose applied; and the distribution of the administered dose (e.g., quantity in skin wash and on the protective cover, material remaining in or on the washed skin, material in selected organs, if collected, and the residue in the carcass). When dermal absorption studies are available, the Committee reviews the data and selects the dermal absorption value (percent) reported for a 8-10 hour period, the time period that reflects an average work day for the pesticide handlers (mixer/loader/applicator).

When dermal absorption data are not available, the Committee estimates dermal absorption by: 1) comparing the LOELs established in the oral and dermal studies in the same species; 2) evaluating (on a case by case basis) the physical nature of the pesticide (i.e., granular, powder etc); and 3) examining the similarity of the concerned pesticide to other chemicals or classes of chemical compounds. When neither the appropriate LOELs and/or data on the pesticide nor structurally related chemicals are available (i.e., as a default), the Committee will assume 100% dermal absorption (a likely overestimate).

When a dermal absorption factor is estimated by comparing the appropriate LOELs, the Committee relies on oral and dermal studies conducted in the same species. When such data are available, the Committee will compare: 1) the LOEL from a 90- feeding study in rats to that of the LOEL established in the 90-day dermal study in rats, 2) the maternal or developmental LOEL (as the case may be) from a developmental study in rabbits to the LOEL in a 21-day or 90-day dermal toxicity study in rabbits, 3) the LOEL from the acute neurotoxicity study in rats to the LOEL in the 21-day or 90-day dermal toxicity study in rats, or 4) the LOEL from a reproductive study to the LOEL established in the 21-day or 90-day dermal toxicity study, and so on.

When oral and dermal studies are not available in the same species (i.e., appropriate LOELs), the Committee will make a comparison of the acute oral and dermal LD_{50} values to gain some "knowledge" on dermal absorption. This comparison, however, is less reliable because of the ambiguous nature of the measurement. If an attempt is made to use the LD_{50} values, the nature of toxic response (other than death) must be evaluated, and more than one dose level should be available. In other words, single dose studies or Limit-Dose studies are not used in such comparisons.

When data are available on the physical-chemical properties of the pesticide or on structurally related compounds, the Committee will use these data in estimating dermal absorption. For example, for one of the pyrethroids, the Committee estimated a dermal absorption value of 50% based on the physical and chemical nature as well as the similarity of the dermal absorption data for this class of chemical compounds.

The Committee, in estimating a dermal absorption factor, will routinely use the weight-of-evidence approach which considers all of the options discussed above. However, the Committee will assume 100% dermal absorption as a default when: 1) there is a concern for high occupational or residential dermal exposure; 2) an oral study was used for hazard identification; and 3) there is low confidence in the studies as well as the data available for estimating a dermal absorption factor or in the estimation itself. Although the 100% default is in most cases an overestimation of exposure, no better default has been identified.

VI. THE USE OF NOELs, LOELs AND ENDPOINTS IN TES PROCESS.

The dose identified for calculating the Margins of Exposure (MOE) for the various exposure scenarios is usually the NOEL (sometime LOEL) established in the appropriate study. Identification of the dose is based, not on the results of a single isolated study, but upon the entire data base using a weight-of-the-evidence approach. The criteria for use of the NOEL or the LOEL are discussed below.

A. No Observed Effect Level (NOEL)

A dose should not be selected routinely by default simply because it is the NOEL. The entire dose response curve should be reviewed to determine how the NOEL relates to the dose at which effects actually begin to appear (i.e., the LOEL). Similarly, the toxicology endpoint with the lowest NOEL should not be automatically selected because that endpoint may not be relevant to the exposure scenario under consideration. In some cases, data from two studies may be considered together to determine the most appropriate NOEL.

B. Lowest Observed Effect Level (LOEL)

The LOEL is not routinely used in risk assessments because it is identified as the lowest dose in the study where treatment related effects actually begin to appear. However, a LOEL may be used if a NOEL is not established in the critical study, when severity of the effects observed at this dose is of negligible concern for human risk, or when there is a data gap. Therefore, when a LOEL is identified for risk assessment, additional modifying factors (range of 3 to 10) may be used in addition to the total Uncertainty Factor of 100 (i.e., 10 for intra- and 10 for inter-species variation).

C. Toxicology Endpoints used in Hazard Identification Process

Toxicology endpoint selection is based on the NOELs and LOELs established in the Data Evaluation Records (DERs) prepared for each study. Examples of appropriate endpoints used for establishing the NOELs/LOELs may include the following:

1. Acute Neurotoxicity Battery

- Mortality
- Clinical signs indicative of neurotoxicity including cholinergic signs either in the presence or absence of cholinesterase inhibition
- Cholinesterase inhibition
- FOB and/or motor activity measurements evaluated at the estimated time of peak effect (i.e., within 8 hours of dosing).
- Histopathological findings
- Other non-neurotoxic but biologically significant findings (i.e., systemic and/or biochemical effects)

2. Developmental Toxicity Studies - The use of developmental studies in the TES process often assumes that toxic effects could result from exposure to a single dose. Consequently, decisions concerning the appropriateness of endpoints for acute hazard identification from these studies must be based on professional judgement.

- Maternal toxicity, characterized as deaths, clinical signs (e.g., cholinesterase inhibition, neurotoxic/cholinergic clinical signs) are appropriate if the possibility that these effects occurred after a single dose can not be discounted.
- Developmental toxicity, characterized as deaths (embryonic/ fetal resorptions, fetal/ pup deaths, post implantation loss), fetal/pup body weight decrements, and permanent alterations (malformations or visceral and skeletal variations), are appropriate if the possibility that these effects occurred after a single dose can not be discounted.

Other factors considered in the selection of developmental toxicity endpoints include:

- Developmental toxicity observed at maternally toxic or excessive doses generally lessens concern that effects could result from a single dose
- Developmental toxicity observed in the absence of maternal toxicity generally increases concern that effects could result from a single dose
- Slope of the dose-response curve

- Developmental toxicity observed across species or the effects are clearly dose-related
- Multiple observations of developmental toxicity (which constitute a syndrome) observed in a single or multiple species
- Developmental endpoints are not appropriate if equivocal or marginal developmental toxicity occurred only at the highest dose tested, were seen only in one species and were not accompanied by any other developmental effects.

3. 21-Day Dermal Toxicity Study

- Mortality
- Decreases in body weight gain and/or food consumption
- Clinical and/or cholinergic signs indicative of neurotoxicity
- Cholinesterase inhibition
- Systemic toxicity

4. 90-Day Studies

- Neurotoxicity (e.g., clinical/cholinergic signs, ChEI, FOB, motor activity)
- Systemic toxicity (e.g., mortality, body weight changes, alterations in clinical pathology parameters, changes in organ weights)
- Gross and/or histopathological lesions

5. 2-Generation Reproduction Study:

- Reproductive and fertility parameters of both sexes
- Systemic toxicity (e.g., mortality, clinical signs, body weight and food consumption, and organ weight changes) of parental animals of either generation
- Alternations in reproductive parameters (conception rate, number of corpora lutea etc.)
- Offspring data (e.g., number of pups born, pup viability, body weight changes, gross abnormalities)
- Reproductive organ toxicity (e.g., changes in the weights of the testis, prostate, seminal vesicle and epididymis, and ovaries
- Histopathological lesions of the testis, prostate, seminal vesicle, vas deferens, epididymis,

vagina, cervix, uterus, fallopian tubes and ovaries as well as the adrenal and pituitary glands (both sexes)

- Other data, such as semen analysis, accessory cell function (testosterone levels secreted by Leydig cells), and hormonal status [follicle-stimulating hormone (FSH) and luteinizing hormone (LH)], when available.

6. Long-Term Toxicity Studies

- The selection of appropriate endpoints for long-term hazard identification are essentially identical to those currently used in establishing the RfD such as neurotoxicity (e.g., cholinergic signs, ChEI, FOB and motor activity, histopathology), systemic toxicity (e.g., changes in body weight and body weight gains, food consumption, clinical pathology parameters, organ weights, and gross as well as histopathological lesions), and evidence of chronic toxicity or carcinogenicity or other significant toxic effects (e.g., target organ toxicity).

VI. APPLICATION OF THE TOXICOLOGY ENDPOINT SELECTION IN IN RISK ASSESSMENTS

The dose and endpoints selected in the TES process for the various exposure scenarios are used to characterize risks. Risk characterization is the discussion of the strengths, weaknesses, uncertainties and assumptions that are part of risk assessment. Risk assessment generally involves the integration of data on hazard identification, dose response evaluations and exposure assessment to determine the likelihood that humans will experience any of the various forms of toxicity associated with a pesticide. The results of risk characterization and risk assessment are used by the Agency to support regulatory actions.

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