3/14/00

TECHNICAL PROGRESS REPORT: IMPLEMENTATION PLAN FOR PROBABILISTIC ECOLOGICAL ASSESSMENTS

TERRESTRIAL SYSTEMS

I OVERVIEW

The Environmental Fate and Effects Division (EFED) is proposing a basic outline of an approach to implementing probabilistic risk assessments for terrestrial ecosystems. The implementation plan is based, in large part, on the Ecological Committee on FIFRA Risk Assessment Methods (ECOFRAM) Terrestrial Draft Report (1999) and the ECOFRAM Peer Input Workshop (1999). (A summary of the Terrestrial ECOFRAM Report is presented in Appendix 1, and a summary of the major comments from the Peer Input Workshop is presented in Appendix 2). EFED's overarching goal is to establish a consistent, predictable and transparent process for refining terrestrial risk assessments. We are seeking the input of the Scientific Advisory Panel at this stage in the development of the implementation plan in order to obtain the opinion and advice of the SAP on the most feasible and useful approaches and direction to take in moving forward to implement probabilistic ecological assessments in the Office of Pesticide Programs (OPP).

In addition to identifying the models and basic process of refining assessments, this report:

1. Defines the minimum data needed to reduce uncertainty as assessments are refined,
2. Identifies the additional models or data that need to be developed in the near term to implement the proposed process, and
3. Identifies the long term developmental work and research that are needed to fully implement probabilistic assessments.

EFED proposes a fluid four level assessment process (Table 1.) , referred to as the levels of

refinement, based on the suggestions made by ECOFRAM. However, one of EFED's initial concerns, which was also raised at the Peer Input Workshop, is the applicability of an assessment process that is fluid and adaptive to a regulatory process that strives to be consistent, predictable and transparent. While not mutually exclusive, we believe at a minimum the assessment process needs to: (1) define the questions that need to be answered at each level and the basic models that will be used to generate answers (as new models and assessment methods are developed, they too would be evaluated for their ability to provide necessary information); (2) provide a conceptual framework for how the basic models will be employed; and (3) establish, to the extent possible, the minimum data required at each level of refinement so as to avoid unnecessary iteration in the process, which can lead to inefficient use of resources by all parties involved. This is not to preclude the development of additional data which could further reduce uncertainties in the assessment, but to establish the minimum necessary to address the level of sophistication necessary in the assessment to support a regulatory decision. It also should be noted that this dictates the involvement of risk managers in the developmental process, which is an integral part of the implementation plan. The following presents an outline of the proposed models, data, and assessment process (levels of refinement).

1. Conceptualization of Agency Approach to Terrestrial Assessment

This paper describes EFED's initial efforts to define the models and processes to be adopted by the Agency for terrestrial systems and identifies a number of challenges that need to be met to reach the overall goal of improving ecological assessments of pesticides. This is a work in progress and not all potential challenges have been identified and many questions remain. However, EFED believes it is important to have an open process and have input from all interested parties during all phases of the development of these new tools. We believe Scientific Advisory Panel review at an early stage of development of the implementation plan is critical to help identify the most feasible and useful approaches and directions to take, as well as help avoid less productive options. A great deal of work remains, but our initial direction for terrestrial systems is outlined in this document.

II RISK ASSESSMENT CONCEPTUAL DESIGN

Subsequent sections of this document: (1) identify the initial scope of the terrestrial assessment as a generalized problem formulation, (2) outline the basic structure of the exposure and effects characterization and models that EFED is considering for adoption, (3) define a general process for the integration of these tools into the FIFRA regulatory framework , including minimum data needed to support the implementation of these models, and (4) identify some of the additional steps which are necessary to develop working models suitable for implementation.

For the purposes of this SAP consultation document, EFED elected to present the critical components of the conceptual design for terrestrial risk assessment in a progression from problem formulation, to discussion of generalized approaches for exposure and effects characterization, to a description of the refinement aspects of exposure and effects characterization and integration and ultimately to a discussion of the next technical steps in the implementation effort. Such an organization of concepts first imbues an understanding of the basic targets and tools available for the risk assessment and then builds upon this understanding with specific refinement options for those tools.

A. Problem Formulation

EFED's proposed initial implementation plan and model development for terrestrial systems is limited to a consideration of direct effects on avian species. Direct toxicity drives the current pesticide assessment process and is more manageable for assessment (given the current state of science) than other more complex interactions. The focus on birds does not imply they are the most important taxonomic groups. The larger databases of toxicity and life history information on these species are believed to make them more amenable for developing a new process for pesticide risk assessment. Therefore the proposed initial implementation plan and supporting model development are limited to a consideration of direct effects on avian species. However, EFED wants to emphasizes that focusing on direct effects of pesticides to avian individuals does

not imply an inflated importance of these effects or taxa, but rather provides a starting point. Once these methods are developed significantly to be employed, subsequent refinement of the assessment process will consider other taxa and effects. The subsequent refinements to the initial assessment of direct effects on birds are likely to include (but not necessarily be limited to) indirect effects on avian populations and communities as well as direct and indirect effects on mammals, reptiles, non-target terrestrial invertebrates, and non-target plant species and vegetative communities. This approach is consistent with the direction taken by the ECOFRAM Terrestrial Workgroup and recommendations by the Peer Input Panel.

B. Basic Model Concept

EFED is proposing to follow the same basic model proposed by the Terrestrial ECOFRAM Workgroup, with some minor modifications. This model will be retained through all levels of refinement of the risk assessment process. It is divided into estimates of the distribution of exposure (dose), effects (toxicity), and the integration of these distributions to estimate magnitude and probability of pesticide effects to non-target species.

The general approach to refinement will begin with conservative assumptions and point estimates for input variables at the earliest level. As refinement progresses, additional information (from new data requirements as well as from open literature sources) is applied to define distributions for input variables. The goals of the model refinement process are to focus additional resource expenditures on input variables that contribute significantly to overall assessment uncertainty and provide for an assessment that, in later stages, approaches physical, biological, and chemical conditions associated with proposed actual pesticide use sites.

1. Exposure Modeling

The operational definition of exposure for the purposes of the assessment process is the dose or the amount of pesticide introduced or taken up by the organism. The estimate of the distribution of exposure is separated into two components, the chemical/physical component and the

biological component. The chemical/physical components of estimating the dose are the environmental and chemical variables that influence the distribution of residue levels in time and space in the environmental media (e.g., air, water, soil, and food). The biological component addresses the animal behavior attributes that affect the frequency and intensity of the contact with the various environmental media.

For the estimate of the distribution of total exposure, three major routes of intake of the chemical are addressed: oral, dermal, and inhalation. The major chemical/physical variables that influence exposure (dose) for each exposure route are the chemical/fate properties of the pesticide, plant/crop characteristics and agricultural properties, meteorological conditions, soil properties, and wildlife water source properties.

For the biological component, the major variables that influence doses for each route of exposure are species dependent and include: (1) food, water and soil ingestion rates, (2) inhalation rate, (3) dietary diversity, (4) habitat requirements and spatial movement, (5) direct ingestion rates (granular and seed treatment formulation), and (6) dermal and inhalation absorption rates. These variables are combined into the following equation to estimate the distribution of total dose[1]:

$$Dose_{total} = Dose_{oral} + Dose_{dermal} + Dose_{inhal} \quad (1)$$

The Terrestrial ECOFRAM Workgroup's major emphasis was on oral dietary exposure and direct ingestion of granular pesticides. They explored the other routes of exposure to some extent, providing model outlines for water and soil oral ingestion and exposure through inhalation. Dermal exposure was given less attention and exposure through preening was omitted, as pointed out at the Peer Input Workshop. The Workgroup suggested that major routes of exposure

[1]It should be noted that EFED has not included a pesticide avoidance variable in the initial models and has deferred it until the final level of assessment. The principle difficulty in assessing the effect of avoidance is that the avoidance response is highly variable, and is influenced by many factors and quantifying this variation is even a more difficult task than most, if not all, the other variables that need attention in the model. The Terrestrial Workgroup provided an excellent overview on determining whether avoidance is a factor that is worth detailed investigation at the higher levels of refinement. However, a detailed assessment of avoidance requires nonstandard data and only a few chemicals and species have been evaluated.

(exposure through the diet and direct ingestion of granules) should be considered at each level of refinement of the assessment, and omitting minor routes of exposure (unclear which routes were minor) in the initial phases. However, available literature (Driver et al. 1991) suggest that exposure routes in addition to diet (e.g., inhalation, preening and dermal contact) can be significant contributors to overall exposure for some chemicals. Therefore, EFED believes that exposure models should address each of these exposure routes to the extent possible, recognizing that methods need to be developed to establish the effects associated with exposure from multiple pathways.

EFED proposes the following outline of the components of the basic exposure model. While it is relatively straightforward to identify the input variables for the model components, ascribing point estimates or distributional characteristics to them is a challenge. At this point in the implementation process, characterization of the inputs is described in the Levels of Refinement Section of this document. Exposure model inputs for which characterization is undefined are discussed in the Implementation Issues Section.

a. Model for Oral Dose (D_{oral})

EFED proposes the following general equation for the estimate of total oral exposure, which is separated into multiple sources (food, water, soil, granules, and preening) and is the sum of exposure from all five sources:

$$Dose_{oral} = Dose_{food} + Dose_{water} + Dose_{soil} + Dose_{preening} + Dose_{granular} \quad (2)$$

For each of these sources of oral exposure the following outlines the equations which can be used to estimate the dose from each source.

i Dose from Food (D_{food})

The distribution of dose from food can be estimated from the equation:

$$D_{food} = \sum_{i=1}^{i=N_i} \sum_{k=1}^{k=N_k} \sum_{j=1}^{j=N_j} (pf_{ij} \times pd_{ijk} \times TFIR_i \times C_{ijk}) / W \quad (3)$$

where:

D_{food} = total dietary exposure from multiple food types and areas (mg/kg/time),

N_i = total foraging period of interest,

i = index for different foraging days

N_k = total number of food types consumed by species (grass, fruits, insects, seeds, etc.)

k = index for food type

N_j = total number of areas food obtained from (fields, edges, non-sprayed areas)

j = index for number of foraging areas

pf_{ji} = proportion of total food or diet obtained from area j on day i (unitless)

pd_{ijk} = proportion of food or diet obtained from area j on day i that was derived from food type k

$TFIR_i$ = ingestion rate for food on day i (g/kg body wt/time,) and in general TFIR is estimated from allometric equations,

C_{ijk} = initial or average concentration of pesticide on/in food type k in area j on day i (mg/kg).

W = body weight

ii Dose from Water (D_{water})

The equation proposed for estimating the distribution of dose from drinking water is basically an extension of that for dietary exposure, in which water ingestion rate replaces a food ingestion rate and the concentration in water replaces the concentration in food in the dose equation.

$$D_{water} = \sum_{i=1}^{i=N_i} \sum_{k=1}^{k=N_k} \sum_{j=1}^{j=N_j} (ptw_{ij} \times pw_{ijk} \times TWIR_i \times C_{ijk}) / W \quad (4)$$

where:

D_{water} = total oral water exposure from multiple water sources and areas (mg/kg/time),

N_i = total period of interest,

i = index for different days

N_k = total number of water sources used by species (puddles, ponds, streams, dew, ect)

k = index for water source

N_j = total number of areas water is obtained from (field, edge, non-sprayed areas)

j = index for number of areas

ptw_{ji} = proportion of total water obtained from area j on day i (unitless)

pw_{ijk} = proportion of water obtained from area j on day i that was derived from water source k

$TWIR_i$ = total water ingestion rate day i (l/kg body wt/time,) and in general TWIR is estimated from allometric equations,

C_{ijk} = initial or average concentration of pesticide in water source k in area j on day i (mg/kg).

W = body weight

iii Dose From Soil (D_{soil})

The equation proposed for estimating the distribution of dose from soil is, as for water, basically an extension of the equation for dietary exposure. Soil ingestion rate replaces food ingestion rate and the concentration in soil replaces the concentration in food in the dose equation.

$$D_{soil} = \sum_{i=1}^{i=N_i} \sum_{j=1}^{j=N_i} (ps_{ij} \times TSIR_i \times C_{ij}) / W \qquad (5)$$

where:

D_{soil} = total exposure from soil ingestion from multiple areas (mg/kg/time),

N_i = total period of interest,

i = index for different days

N_j = total number of areas soil is obtained from (fields, edges, non-sprayed areas)

j = index for number of areas

ps_{ij} = proportion of soil obtained from area j on day i (unitless)

$TSIR_i$ = total ingestion rate for soil on day i (g/kg body wt/time,) and in general TSIR is estimated from data on soil ingestion as a percent of total food intake by wildlife species.

C_{ij} = initial or average concentration of pesticide in soil in area j on day i (mg/kg)

W = body weight

iv Dose from Granular ($D_{granular}$)

The distribution of dose from direct ingestion of granular products can be estimated from the equation:

$$D_{granular} = \sum_{i=1}^{i=N_i} \sum_{j=1}^{j=N_j} \frac{pg_{ij} \times TGIR_{ij} \times GnlWt \times C_{ij}}{W} \qquad (6)$$

where:

$D_{granular}$ = total exposure from granular ingestion from multiple areas (mg/kg/time)

N_i = total period of interest

i = index for different days

N_J = total number of areas granules are obtained from (field, edge, non-sprayed areas)

j = index for number of areas

pg_{ij} = proportion of granules ingested from area j on day i

$TGIR_{ij}$ = ingestion rate for granules in area j on day i (g/kg body wt/time,),

GnlWt = weight of a granule

C_{ij} = initial or average concentration of pesticide in/on granule area j on day i (mg/kg)

W = body weight

A critical aspect to this model is the ingestion rate of granules (TGIR). In the model developed by the Terrestrial Workgroup, TGIR is the number of granules an individual bird ingests over a specified period of time. TGIR is calculated from (1) the estimate of the number of grit particles a bird ingests that are in the same size range as granules, and (2) the estimated probability that bird selected particle in this ingested size range will be a granule as opposed to a natural grit particle. Grit ingestion is modeled as a series of binomial trials, with each particle being ingested representing one trial. In each trial, the bird may ingest either a granule or a natural grit particle. The total number of granules ingested by an individual during a given period becomes a function of the probability of ingesting a granule (p), the probability of ingesting a natural grit particle (q), and the number of trials occurring in that time period (N). The parameters p, q, and N define a binomial distribution from which a random sample is drawn to estimate TGIR for an individual bird, and the process may be repeated over many iterations to obtain a distribution for TGIR. The pesticide concentration in the granules is degraded over time and the uniformity of the application, i.e., broadcast vs. band, is addressed.

From this basic structure, the Workgroup developed the Granule Exposure Model (GEM). GEM simulates grit consumption behavior of replicated individual birds for a given species living in the vicinity of an agricultural field where a granular pesticide has been applied. The number of pesticides and resulting quantity of pesticide ingested each day over a ten-day period following application is calculated for each individual in the simulation. This is performed probabilistically through the use of Monte Carlo software programs. Assumed or actual distributions of data are used as inputs for the following model parameters:

number of grit particles ingested by birds on a daily basis, field use factors by birds, soil texture type, fraction of soil particles at a field with a given soil type that are in the size range of granules, and the fraction of granules remaining on the soil surface after application. Separate analysis may be performed for 29 bird species and 10 different geographical regions on the U.S. The model output is a probabilistic distribution of peak-day pesticide exposure levels expressed in mg pesticide per kg body weight per day for birds of a particular species within a particular region.

In summation, EFED believes that GEM is a significant step forward and deserves careful consideration for use in the assessment process. However, further evaluation, development, and research are warranted prior to its use. As we continue to gain experience with this model, EFED will be consulting with the SAP in the future on the results obtained and its usefulness in avian risk assessments.

v Dose From Preening ($D_{preening}$)

In the past, preening has not been considered as a route of pesticide exposure in birds inhabiting chemically treated fields. However, EFED believes that for birds in the field or field edges during application, direct feather contamination (interception of applied material) can constitute a potentially large dose of pesticide if preened. Besides direct contamination of feathers from application, avian species could contaminate feathers while moving through contaminated vegetation or dusting in contaminated soil. Driver et al. (1991) demonstrated that concentrations of pesticides on feathers of avian species following direct application of a pesticide at 1.2 kg a.i./ha ranged from 0.013 to 2.83 mg/g, the mean being approximately equal to the LD_{50} for the chemical being studied. In birds exposed to an organophosphate pesticide, significant inhibition of cholinesterase (ChE) was observed 4 and 24 hours after application, and the contribution from exposure through preening, ranged from 8 to 17 percent of total inhibition for all exposure routes studied.

EFED believes that further development of methods to estimate this exposure route appear warranted and should be pursued as model development continues.

b. Model for Inhalation Dose ($D_{inhalation}$)

The dose distribution from inhalation exposure can be estimated from the equation:

$$D_{inhalation} = \sum_{i=1}^{i=N_i} \sum_{j=1}^{j=N_j} pf_{ij} \times AIR_{ij} \times C_{ij} / W \qquad (7)$$

where:

$D_{inhalation}$ = total dose from inhalation

N_i = total period of interest

i = index for different days

N_J = total number of areas visited (field, edge, non-sprayed areas)

j = index for number of areas

pt_{ij} = proportion of time on area j on day i

AIR_{ij} = inhalation rate for species j (l/time or m^3 /time,), estimated using allometric equations

C_{ij} = initial or average concentration of pesticide in air on area j on day i (mg/kg)

W = body weight

The allometric equation listed in Table 2 is from Lasiewski and Calder (1971) for 6 species of non-passerine birds. There are two important limitations to the use of this inhalation rate relationship. First, the allometric relationship did not include passerines, which have somewhat higher metabolic rates than non-passerines. Second, the inhalation rates were derived from basal metabolic rates. Free-living metabolism is likely to be higher by a factor of at least 2 or 3 . Therefore, inhalation rates (AIR's) estimated from these equations must be adjusted to reflect this 2 to 3 fold increase in metabolism (USEPA 1993).

c. Dermal Dose (D_{dermal})

Dermal exposure to non-target wildlife has received limited attention and, as pointed out by the ECOFRAM Workgroup, has not been well characterized. EFED believes that this exposure route warrants more detailed consideration, though the presently available models may be unsuitable for regulatory purposes because of critical data limitations.

Dermal exposure has been shown, at least in one study of one chemical class, to be a major route of exposure. Driver et al.(1991) reported that dermal exposure to an organophosphate pesticide contributed 16% of the overall reduction of brain ChE activities in exposed birds as early as one hour post-spray. By 48 hours, the dermal exposure resulted in 42% inhibition of brain ChE activity.

The ECOFRAM report presents some simple models for passive rates of chemical mass flux across dermal membranes for each of the major environmental media that are based on Fick's law of diffusion. For each media the general equation presented is:

$$D_{dermal(k)ij} = pt_{ij} \times f_k \times D_m \times A_{ck} \times (C_{kij} - C_{bloodi}) / Wz \,, \qquad (8)$$

where:

$D_{dermal(k)ij}$ =	dermal dose from media k in area j on day i
pt_{ij} =	exposure period in area j on day i (time)
f_k =	fraction of exposure period the organism is in media k
D_m =	diffusion of the chemical across the membrane(skin)
A_{ck} =	dermal area in contact with media (cm^2)
C_{kij} =	initial or average pesticide concentration in media k in field j on day i
C_{bloodi} =	initial or average pesticide concentration in the organism on day i (mg/l)
W =	body weight
z =	width of the membrane

and total dermal dose estimated by summing the dose for multiple media (i.e., contaminated soil, vegetation and water).

While this basic model appears to provide a means to estimate this route of exposure, the practicality for implementation is not readily apparent. The Implementation Issues section of this document discusses the practical application of this model in more detail.

2. Effects Modeling (Toxicity)

The toxicity element of the basic risk model structure is defined as the estimate of the distribution of specific effects to non-target terrestrial species at a given distribution of exposure, the dose-response relationship. The major toxicity variables that influence the response of individuals animals include: intra- and inter-species variability, age and sex, nutritional status, breeding status, environmental conditions, and duration and extent of exposure.

ECOFRAM concentrated on the intra- and inter-species variation in sensitivity to a toxicant and methods to estimate or account for the variability and uncertainty in these distributions. They believed the models and methods developed for these aspects of effects characterization would provide a basis for development of the other parts of the model. However, they questioned, the adequacy of data to quantify the uncertainty associated with the majority of other variables that influence sensitivity.

EFED proposes the adoption of the basic conceptual model proposed by the Terrestrial Workgroup for estimating the dose response relationship for a species of concern. This model can be expressed as follows:

$$DRR_j = DRR_{tested} \times Intra_F \times Inter_{Fj} \times SubIF \qquad (9)$$

where,

DRR_j = dose-response relation for species j,

DRR_{tested} = dose-response relationship for one or more tested species,

$Intra_F$ = intra-species variability factor index (accounts for variation among studies, among age groups, etc.),

$InterF_j$ = inter-species variability factor for species j based on body size (index = 1 if species j is the test species),

SublF = sub-lethal factor (index to account for observations of sub-lethal effects in laboratory toxicity tests that may have implications in the field.

This conceptual model provides a starting point to develop an effects model. Inter-species variability was explored in-depth by the Workgroup and methods were proposed to account for the uncertainty in variability in the sensitivity of species to toxic chemicals ($InterF_j$). These methods, as outlined below, are being proposed for implementation in the models that EFED is developing. Also, methods were advanced by ECOFRAM to address intra-species variability ($IntraF_F$) with a number of parameters identified that need further consideration.

A. Accounting for Inter-Species Variability

One of the largest sources of uncertainty associated with predicting effects of pesticides to non-target species comes from the large variability in the sensitivity of species to toxic chemicals. The range has been found to extend up to three orders of magnitude for aquatic species (Mayer and Ellersieck 1986). The Terrestrial Workgroup reported that, for 53 carbamate and organophosphate insecticides, the LD_{50}'s among birds range from five to more than one hundred. For 70% of the products, this range extends between ten and one hundred (similar comparisons have not been performed for other pesticide classes). Given this large amount of variability among species, inter-species differences in sensitivity contribute large amounts of uncertainty in the risk assessments of pesticides that rely on a few laboratory derived toxicity values on one or two species. To account for this uncertainty in the models that are being developed, EFED proposes the adoption of the distribution-based extrapolation models derived from historical test data presented by the Terrestrial Workgroup.

The Terrestrial Workgroup explored two approaches for distribution-based interspecies

extrapolation (accounting for interspecies variability). The first approach consists of methods to extrapolate, from test species data, to a specified percentile of a random distribution of species sensitivity regardless of taxonomy (Luttik and Aldenberg1995). The second approach generated a predicted distribution of species sensitivity again from one or more test species studied, but considering phylogenetic patterns (Baril and Mineau 1996).

EFED believes that the second method appears to be more applicable to the Agency's process because the Agency requires specific species to be tested. In this approach, Baril and Mineau (1996) developed extrapolation factors (EF) from a historical data base of cholinesterase inhibiting insecticides tested on at least six species. This method predicts the 5^{th} percentile of the species sensitivity distribution from small data sets. Two procedures evolve depending on the number of species for which an LD_{50} value is available. When the number (N) of species is less than four, extrapolation factors specific to the number and species available are used. The EF appropriate to the species tested are used to determine the median estimate of the 5^{th} percentile. When used in combination with the standard deviation associated with the estimate of the EF, the 5^{th} percentile can be estimated with a specific level of confidence. Alternately, a distribution of predicted values of the 5^{th} percentile can be generated using a distribution of factors with EF as the mean and standard deviation of the EF. When the number of species tested is equal to four or greater, the parameters of the distribution are calculated directly without the use of extrapolation factors. Two outputs are obtained: the median estimates of the 5^{th} percentile and the 95% confidence limits of the 5^{th} percentile. (See Figure 1.)

The above method developed for inter-species extrapolation factors is based on the avian acute oral test. Inter-species extrapolations of the other principle toxicity test, the avian dietary LC_{50} unfortunately have not been developed. Unlike the LD_{50} test that has been applied to a wide variety of test species in many test compounds, there are few distributions of multi-species data available for the standard LC_{50} test. In order to develop interspecies extrapolation factors for the LC_{50}, more must be known about the comparative responses of a variety of avian species in order to predict sensitivity of wild birds. Also, with the proposed changes in the dietary test (discussed later) the data base becomes nonexistent. However, to reduce the uncertainty in assessments,

research needs to be initiated that will develop the needed data base.

In the interim, the factors developed for the LD_{50} are proposed for the LC_{50} test. As suggested by the Terrestrial Workgroup, these factors developed for the LD_{50} test may be relatively conservative for the LC_{50} test in that the LC_{50} test deals with issues beyond the sensitivity of birds to a toxicant, such as the onset of illness, food avoidance, metabolism and excretion. At the moment, given how little is known, it can be assumed that the inter-species variability seen with the LD_{50} test is applicable to the LC_{50} test.

There is also need for accounting for interspecies sensitivity differences for reproduction effects. The most straight forward approach for developing such an uncertainty factor would seem to be through a systematic investigation of the available avian reproduction data in EFED's Ecotoxicology Database. Because of the existing data requirements and testing protocols, the vast majority of avian reproduction studies conducted are for only two species (northern bobwhite quail and mallard ducks). This limitation to two species greatly hinders the ability to develop interspecies sensitivity uncertainty factors that can be applied across the myriad of bird species that are currently untested. EFED believes that a search and review of published avian reproduction data not currently in EFED's database will not greatly improve the situation. However, it is anticipated that the new refinements to the avian reproduction risk assessment approach, at higher levels of refinement, will ultimately generate information applicable to addressing these current data limitations. It is therefore likely that, as the database increases to include previously untested bird species, analysis of these data will enable EFED to modify its approach from the interim outlined below.

An interim approach to accounting for interspecies variability could be based on the interspecies uncertainty factors proposed for acute lethal effects. The interspecies factors of Baril and Mineau (1996) that are applied when only two species (bobwhite quail and mallard) have been tested are on the order of 5 to be applied to the geometric mean of LD_{50}s. In the case of reproduction effects with the same two species, a similar factor could be applied to the geometric mean of NOECs. However, there is a paucity of empirical data to support such a extrapolation factor and

EFED proposes a factor of at least 10 be applied for interspecies uncertainty.

B. Accounting for Intra-Species Variability

The dose-response curve generated from the basic toxicity tests required to support registration provides an estimate of intra-species variability. However, use of laboratory dose-response information in a risk assessment is subject to diverse uncertainties including statistical error associated with estimates (as represented by standard errors or confidence bounds) and an array of extrapolation uncertainties. Intra-specific factors that contribute to variability surrounding toxicity estimates for a test population include laboratory environmental conditions and the toxicity measurement process itself. Other important factors that may influence the shape of the dose response relationship and are not accounted for in laboratory testing include life stage sensitivity, animal health, nutritional status, metabolic status, different exposure durations, different environmental conditions and the occurrence of genetic polymorphisms. The Terrestrial Workgroup provided limited guidance (i.e., the application of a laboratory to field correction factor) on how to address these factors in a probabilistic assessment. The specifics of estimating the factor(s) need to be developed.

To account for intra-specific variability, EFED is evaluating the Terrestrial Workgroup approach to define the distribution of individual tolerances in a population, accounting for the variability introduced by the various factors. From the distribution of tolerances, the variability and uncertainty in the field response can be estimated. The equation that defines the distribution is:

$$RT = \left(LD50 \times UF \right) \times 10^{(z/slope)} \qquad (10)$$

The LD_{50} (or the LC_{50}) and the slope are represented by normal distributions defined by a review of historical data or the confidence limits reported for the supporting studies. The random value z is selected from the standard normal distribution. The uncertainty factor (UF) is estimated from available data that defines the uncertainty for extrapolating to field conditions. It could take on the form that there is an X% probability that the field LD_{50} is within an estimated factor of the laboratory LD_{50}.

C. Integration of Exposure and Effects Models

The ECOFRAM Terrestrial Workgroup discussed six different methods that could be used to estimate risk depending on the data available and the questions being addressed in the assessment. These methods included:

- **Method 1. Point Estimated Quotients**

  Exposure: Point estimate of exposure

  Effects: Point estimation of toxicity

  Output: A ratio of exposure/toxicity

- **Method 2. Comparison of Exposure Distribution With Point Estimation for Effects**

  Exposure: Distribution of exposure

  Effects: Point estimation of toxicity

  Output: Probability of exposure exceeding the effects levels

- **Method 3. Comparison of Exposure and Effects Distribution**

  Exposure: Cumulative frequency distribution of exposure

  Effects: Distribution of toxicity for i. Various species, or ii. Single species

  Output: Probability of certain effects occurring when a fixed exposure level is exceeded

- **Method 4. Distribution-based Quotients**

  Exposure: Distribution of exposure. (Use of Monte Carlo simulation)

  Effects: Distribution of toxicity for i. Various species, or ii. Single species

  Output: Probability distribution of quotients (probability that exposure exceeds toxicity).

- **Method 5. Integrated Exposure and Effects Distributions. (Use of Monte Carlo simulation)**

  Exposure: Distribution of exposure.

  Effects: Distribution of toxicity.

  Output: Probability and magnitude of effect occurring.

- **Method 6. Mechanistic/Process Models. Stage/age structured, meta-population, individual-based, or spatially explicit models.**

While each of these methods have value, EFED believes that Method 5 appears to show the most applicability to address risk management questions on magnitude and probability of effects. The other methods are based either on the probability of exceeding a threshold point or are risk quotients or distribution of risk quotients and are limited in their ability to predict how often and how extensive an effect will be, important considerations for risk managers. As indicated by the ECOFRAM Workgroup, limitations with current avian chronic studies make it difficult to apply method 5 to reproductive effects due to the lack of a dose-response distributions. Some of the suggestions at the Peer Input Workshop, as discussed later, may provide an interim solution. Method two, comparison of exposure distribution with point estimates for effects also has merit for addressing reproductive impairment, at least in the interim. None of these options have been ruled out. However, EFED's efforts to further development of probabilistic tools will focus on Method 5: Integration of Exposure and Effects Distribution using Monte Carlo techniques or other appropriate methods. Also as outlined later, the use of modified deterministic quotients (Method 1) for screening level assessments is proposed, as well. With development of the initial relatively simple probabilistic models and experience with their use, the additional resources required, if any, to run these models may prove to be insignificant in comparison to the increase in understanding of risk the probabilistic tool provides. Therefore, the utility of quotients may be of limited value in the future, except as explained in ECOFRAM, to provide a framework for risk managers understanding and a benchmark for Probabilistic Risk Assessment (PRA) results.

The integration of the exposure distribution with the effect's distribution to estimate a risk distribution is relatively straightforward using Monte Carlo or other appropriate techniques. For Monte Carlo simulations the exposure distribution is assumed to represent the range and frequency of doses to an individual that can occur in a population, and the effect's distribution (the probability density function of the dose-response curve) represents the range and frequency of individual tolerances to a pesticide dose in a population. For each run of a Monte Carlo simulation, a dose is randomly selected from the distribution of doses and compared to a randomly selected sensitivity from the tolerance distribution. Based on the probit model, the distributions of tolerances can be represented by:

$$RT = LD_{50} \times 10^{(z/slope)} \qquad (11)$$

where,

RT = random tolerance

LD_{50} = median lethal dose (mg/kg)

z = random selected value from the standard normal distribution, mean = 0, standard deviation = 1,

slope = slope of the dose-response curve

(Uncertainty Factor, UF, can be added as discussed previously)

If the randomly selected dose is greater than the randomly selected sensitivity, the individual is classified as being affected. If the dose is less than the sensitivity, the individual is classified as not affected. This sampling procedure is repeated for a set of individuals to generate a percent affected estimate. With multiple runs of sets of individuals, a probability density function (PDF) of percent affected is generated or a probability density function of risk. With available software calculations of average or mean effects, range, standard deviation, confidence limits and cumulative density functions (CDF's) can easily be made.

Risk distributions can also be estimated by combining the CDF's of the exposure and effects distributions. This is done by calculating effects doses which can include confidence or fiducial limits from the dose-response curve for responses ranging from 1 to 99%, and by comparing these effect doses with the CDF for exposure. For example, the estimated effects dose for a given

percent response x is $D_{x.}$ The occurrence or probability of this dose D_x is determined from the exposure CDF providing an estimate of the percent of exposures that exceed the effects dose D_x or the percent of exposures that do not exceed the effects dose D_x. Based on this method an estimate of the probability that a species is experiencing an x level of effect or greater (or less) can be made. This method can also be used to estimate the confidence limits on each probability estimate if confidence or fiducial limits for the dose-response curve are available following a similar procedure. Means and standard deviations can also be estimated from this method by generating the risk PDF from the risk CDF and sampling or using other techniques to estimate the distributions statistical parameters of interest.

Both of these methods appear to show promise for implementation in the assessment of ecological effects of pesticides and their use will depend on their applicability and efficiency in relation to the models that are developed.

D. The Levels of Refinement Process

EFEDs's proposed process for risk assessment refinement, adopted from the Workgroup's recommendations, presents a logical progression of methods for refining assessments and appears to be compatible with the FIFRA regulatory framework. As mentioned previously, the Terrestrial Workgroup recommended a four level process that moves from an initial screening assessment with limited data and conservative assumptions to more complex assessments which integrate additional data and probabilistic tools and methods.

One of EFED's initial concerns is the recommendation that the process be fluid and adaptive and still meet the needs of the regulatory process. So long as the proposed process defines the basic models that will be used at each level, how they will be employed, and the minimum data which are needed at each level of refinement, it can meet its goals and still be somewhat fluid and adaptive. To meet these requirements, an important component of the process is defining, to the extent possible under the risk/benefit determination required by FIFRA , the criteria or guidance that will be used to signal the need for further refinements of the assessment. The development of

these criteria requires substantial input from risk managers and is beyond the scope of this technical progress report. However, it should be noted that this is a fundamental part of the Agency's implementation plan and a workgroup with risk managers has recently been formed.

For the purposes of this SAP consultation document, EFED has outlined four levels of assessment refinement for both acute and reproduction risks. The presentation of refinement levels is segregated by the type of direct effects being evaluated, mortality or reproduction impairment. While the structure of basic exposure and effect models are the same for either mortality or reproduction impairment, the data requirements, the uncertainties and the developmental work that are needed are significantly different. As mentioned previously, this is a work in progress and the presentation reflects the current level of analysis of the options for data and methods. Not all potential challenges have been identified and many questions remain.

1. Levels of Refinement for Lethal Effects Risk Assessment

a. Level 1: A Refined Screening Lethal Effects Risk Assessment

Level 1 is designed as a simple screening level assessment. The majority of the major input variables are assumed to take on the upper bound of the distribution with some being derived from the tail (5^{th} or 95^{th} percentile) of the distributions where supporting data are adequate. The purpose of the Level 1 assessment is to identify those chemicals that pose limited direct risk to non-target species and for which further assessment is not required. Table 2 presents the major variables of the model and outlines proposed methods to estimate values or identifies the proposed default values as well as the minimum data that is proposed to support this initial level of assessment. In cases where additional developmental work is needed this is identified.

i Level 1 Exposure Assessment

At this initial level, generic bird species are being considered. Three weights of birds (15, 50 and 1000g) are proposed for evaluation for each of three dietary strategies, herbivore,

granivore, and insectivore. For each, oral, dermal, and inhalation exposures would be estimated using conservative assumptions, the upper 95% C.L. or upper bound of the exposure distributions. For each weight and food strategy, it would be assumed that 100 percent of its habitat is contaminated from direct application of the pesticide. Conservative (95%CL or an upper bound) average residue concentrations over the estimated exposure duration based on environmental half lives of the various environmental media would be used. For each route of exposure, oral, dermal and inhalation, distributions would be used to generate a distribution of total dose correcting for difference in sensitivity using toxicity equivalency factors TEF's (see Implementation Issues Section).

ii Level 1 Effects Assessment

At Level 1 EFED proposes that toxicity estimates would be based on the standard laboratory toxicity currently required to support registration and possibly an additional acute oral test. Results of LD_{50} studies will serve as the basis for assessing the risks of short term (single day or less) exposures. LC_{50} results will be used for longer term exposures, the duration of which is addressed in the Implementation Issues section of this document. The sensitivity of the generic species being considered would be estimated using the extrapolation methods proposed by the Terrestrial ECOFRAM Workgroup to calculate the 5th percentile of the sensitivity distribution for species. See Figure 1 for an outline of the method.

iii Level 1 Data Requirements

The Terrestrial ECOFRAM Workgroup provided an outline of the minimum data that would be needed at each level of refinement. For the environmental fate data, they concluded that the current suite of tests is adequate. However for the effects data at Level 1, they suggest for both short-term exposure (defined as minutes to hours) and medium-term exposure (define as a period of days) a single acute oral study is adequate to define the dose response for avian species. This is a reduction from the current three tests

required, (one acute oral and two dietary tests).

EFED is not comfortable with this recommendation. Variation among species in sensitivity to pesticides has been demonstrated to be substantial and may be the greatest source of variation for integrating effects estimates of untested species into probabilistic assessments. Both in terrestrial and aquatic environments, the range of sensitivities can extend up to three orders of magnitude. For 53 carbamate and organophosphate insecticides the LD_{50}'s among bird species ranged from five to more than one hundred. For 70% of the products, this range extends between 10 and 100 (ECOFRAM Draft Report 1999). At the initial screening level assessment, the process outlined by the ECOFRAM Terrestrial Workgroup, applied Extrapolation Factors to account for this large variability. However, and acknowledged by the Workgroup, the process needs to be evaluated through case studies. Even prior to case studies, EFED believes sensitivity analysis to evaluate the consequences of limiting initial data to only one LD_{50} test is needed. For chemicals with 10 to100 fold differences in toxicity (70% of 53 compounds) what different conclusions would be reached if only one test is available for a chemical with a 10 to 100 fold differences in sensitivity among species? Pending the results of sensitivity analysis, there may be a need for additional species to be tested (single oral dose study) at Level 1.

Also, the Terrestrial Workgroup suggestion to eliminate the dietary test at initial level assessments needs further evaluation. In general, species are more sensitive to acute oral exposure than dietary exposure. If the summation of daily doses over duration of exposure is compared to the results of an LD_{50} test, the estimate of risk should be relatively conservative and would meet the objective of the initial screening level of assessment. However, this could lead to identifying chemicals for further assessment which could be screened out with the addition of dietary toxicity data. This could contribute to increased iterations of the review cycle, requiring the additional data, lengthening the time and resources needed to complete the assessment. Further evaluation of the consequences of this proposal is planned, but EFED's initial position is to continue

requiring the two dietary tests with the appropriate modifications, as recommended by the Workgroup, to make them more applicable to probabilistic assessments.

However, EFED believes that, for chemicals with limited toxicity to non-target species (i.e., limit studies that demonstrate very low sensitivity), a single acute oral toxicity study may provide adequate information to identify a chemical as relatively safe from a lethal effects perspective. As the models become better defined, experience is gained with the new process and models, and databases are enhanced for new classes of pesticides, some exposure toxicity ratio should be able to be established to limit the lethal effects testing to a single study. EFED plans to explore this option further as the implementation plan progresses.

b. Level 2: A Limited Probabilistic Risk Assessment (Lethal Effects)

Level 2 is designed to be protective, and to begin to quantify the magnitude of the risk and associated uncertainty which will allow the Agency to focus resources on the pesticides potentially posing the greatest risk. Some pesticides will exit level two and be identified for minimal risk mitigation measures which will reduce exposure. For these chemicals further refinements would not be necessary. Other pesticides may not need to proceed to the next level because the refined assessment at Level 2 has indicated little concern. However, for the remaining cases, further refinement (Level 3) would be the outcome of Level 2 assessments.

i Level 2 Exposure Assessment

At Level 2, generic species with the same range of body weights and feeding strategies, as in Level 1, are being considered. However, for several of the major variables, distributions are replacing the conservative point estimates used in Level 1 (Table 3). For each route of exposure, oral, dermal and inhalation, distributions would be used to generate a distribution of total dose correcting for difference in sensitivity using TEF's (see Implementation Issues Section).

ii Level 2 Effects Assessment

At Level 2, no additional data for lethal effects would be required. Toxicity estimates would be based on the same standard laboratory toxicity used in Level 1. The sensitivity of the generic species being considered would be estimated using the extrapolation methods in Level 1, but instead of the lower 95 % C.L of the 5th percentile species being used, the dose-response curve for the 5^{th} percentile species would be considered. Table 3 presents the major variables of the model and outlines the proposed method to estimate value of the variables or identifies the proposed default value as well as the minimum data that is proposed to support this level of assessment. In cases where additional developmental work is needed, this is identified.

iii Level 2 Data Requirements

To conduct a Level 2 acute risk assessment, there are no additional data requirements beyond those identified in Level 1.

c. Level 3: A Refined Probabilistic Risk Assessment (Lethal Effects)

Level 3 is designed to move away from conservative assumptions, comprising appreciably more data and further use of probabilistic tools. Level 3 is envisioned to be a hierarchical Monte Carlo simulation (or other potentially appropriate methods) to account for uncertainty (absence of knowledge) and stochastic variability (natural variation) separately.

i Level 3 Exposure Assessment

Focal species will be identified and specific natural history information from available literature will be used to estimate habitat use patterns in and around representative application areas. Both temporal and spacial components will be considered on the local and where appropriate and feasible, regional levels. Spray drift onto adjacent habitat and

water sources will be considered through the application of models developed by the Spray Drift Task Force. Table 4 presents options for refining the exposure assessment.

In order to make the exposure assessment more reflective of the interactions of focal species with use site habitats, EFED proposes the delineation of various standard agro-ecological scenarios for the major crops by region. This will entail defining ranges of characteristics of the agro-ecological landscape by region, defining cropping practices, habitat types and their quantity and spacial occurrence, vegetative types, wildlife species, meteorological conditions, and soils.

Once specific focal bird species are identified, literature searches and possibly ethological field study data would be required to generate distributions for many of the exposure model parameters identified for the models previously discussed. Among the parameters in the models applicable to this focal species refinement are (but not limited to): bodyweight, food intake rate, proportion of dietary mass attributable to food type, incidental soil ingestion rate, drinking water intake rate, dermal surface area, and percent of diet from treated and buffer areas.

Other data that would be applicable to a Level 3 assessment would include measured residue data for avian food items, drinking water sources, air, and soil residues under the range of field conditions appropriate to the chemical/use combination and the regionally-specific areas of use that coincide with the occurrence of the selected focal species. The Agency currently does not have specific avian exposure field residue protocols, but is anticipating working closely with HED to modify human health-based residue studies and field dissipation studies to facilitate collection of these data.

ii Level 3 Effects Assessment

EFED proposes that additional laboratory toxicity studies (a minimum of four species) will be required to better define the species toxicity distribution. At present, EFED has not

ascertained which species should be added for expansion of the acute toxicity data set. Avian inhalation and dermal toxicity studies will be considered for those chemicals for which these routes of exposure appear to significantly influence the distribution of risk. At Level 3 Extrapolation Factors are not applied. The sensitivity of the focal species is based on the 5th percentile of the species toxicity distribution, if the focal species has not been tested. In cases where the focal species has been tested, the focal species dose-response curve is used directly, considering the uncertainties with the lethal estimates and the slope of the dose response curve. Table 4 presents the major variables for the Level 3 model and outlines the proposed method to estimate their values or identifies the proposed default value as well as the minimum data that is proposed to support this level of assessment. In cases where additional developmental work is needed, this is identified.

iii Level 3 Data Requirements

Level 3 will require an expanded data set of species-specific exposure. The basic approach will be to review available literature on species occurrence in the agro-ecosystem identifying the species that appear to be at the highest risk from pesticide use and, for these species, compiling the needed natural history information. EFED anticipates that, for many species, available information will be scant and initial models will have to rely on a great deal of assumptions based on expert opinion.

Additional data regarding ecological, physical, and chemical aspects of proposed use sites will be required under Level 3. We envision delineating various standard agro-ecological scenarios for the major crops by region. This will entail defining ranges of characteristics of the agro-ecological landscape by region, defining cropping practices, habitat types and their quantity and spacial occurrence, vegetative types, wildlife species, meteorological conditions, and soils. In it's initial application, this information will be obtained from literature review, agricultural statistics and Geographical Informational Systems(GIS).

As discussed in the effects assessment section above, EFED proposes a requirement for

additional lethal effects testing. Additional testing will result in a total of four single oral dose and four dietary tests involving four species. EFED also proposes consideration of additional acute effects testing specific to routes of exposure other than oral (e.g., dermal and inhalation toxicity).

d. Level 4: The Most Refined Risk Assessment (Lethal Effects)

Level 4 is the highest level of refinement and is envisioned to be driven by sensitivity analysis of Level 3 assessments on a case by case basis (chemical and use-site specific). Refinements will achieved by improving estimates of distributions for exposure and/or effects. Options for improving these estimates of exposure and effects may include (1) additional toxicity studies with species of high concern, (2) varying exposure durations,(3) varying routes of exposure, and (4) focused field studies that address specific question raised in the Level 3 assessment. These later studies could range from addressing specific natural history questions for species identified at high risk to addressing specific environmental fate parameters under field conditions for the chemical being reviewed. For chemicals where avoidance has been identified as a potential mitigating factors, further laboratory studies or field studies could be employed to better quantify the significance of this behavior.

2. Levels of Refinement for Chronic Avian Risk Assessment (Reproduction Effects)

This section of the document outlines an approach, similar to the level of refinement approach listed for lethal effects, for iterative refinement of chronic exposure/reproduction effects risk assessment. As the case for lethal effects, development of a new risk assessment process for reproduction effects, with any significant degree of improvement, will require additional research.

a. Level 1: A Refined Deterministic Risk Quotient Screening Approach (Avian Reproduction)

The Level 1 risk assessment approach follows, in general, the approach currently employed by the

Agency to assess the risk for reproduction effects. This approach involves the generation of a risk quotient (RQ) that is in the form of a ratio of dose level to observed effect level NOEL. This RQ is then compared to Agency established levels of concern. Risk quotients exceeding some threshold presumed to be indicative of adverse reproduction effects in the field. The goal of the Level 1 approach is to provide a quick, low resource requirement, screening to differentiate between those chemical/use combinations that are clearly not a concern and the potentially problematic chemical/use combinations. As such, the selection of parameters for dose estimation and effects should be conservatively biased so as to limit the possibility of fallacious predictions of "no risk".

i Level 1: Exposure Assessment

Exposure calculations for Level 1 reproduction risk estimation would basically follow those calculations made for Level 1 acute lethal effects. Essentially, daily oral dose would be based upon a single daily dose. This dose would include the contributions to total bodily dose from consumption of food and drinking water, incidental soil ingestion, dermal exposure, and inhalation. The methods that are currently available for calculating such exposures have already been outlined in earlier sections. As for the short-term effects assessments, reproductive assessments would be conducted on a generic set of bird size categories as well as for herbivorous, insectivorous, and grainivorous feeding preferences.

EFED recognizes that basing the exposure portion of the RQ on a peak daily dose is conservative, given the possibility that more prolonged (though largely un-quantified at present) dosing may be necessary for reproduction effects to occur. However, because the goal of the screening process is to identify those chemicals that are clearly not a concern, reliance on the peak daily dose will likely limit the possibility for false negative findings.

Unlike the exposure modeling conducted for lethal effects, there will be no adjustment of dose contribution from the different routes by application of toxicity equivalency factors.

EFED considered using the TEF approach discussed for acute lethal effects from different routes of exposure. However, there are no multiple exposure route reproduction effects data consistently available for bird or mammal test systems that would allow for establishment of such TEFs for reproduction effects. EFED believes that the combined uncertainties of extrapolating across taxonomic groups and extrapolating from acute to reproduction effects is too great to use the acute toxicity TEFs to relate multiple exposure routes in birds for reproduction effects. Therefore, in the absence of data to the contrary, the contribution of toxicant dose is assumed to be equipotent for all routes of exposure with respect to reproduction effects.

ii Level 1: Effects Assessment

The primary input to the effects assessment under the refined Level 1 assessment are the dietary reproduction tests conducted with northern bobwhite quail and mallard ducks. The current avian reproduction tests with these two species have several limitations. One of these limitations is the potential for inaccuracy in calculating daily intake of food and therefore dosage of toxicant. Investigation into potential modifications to the existing testing protocol for reproduction effects to allow for better determination of individual food intake are warranted. For the moment, the Level 1 screening assessment will be based on conversion of dietary exposure to oral dose using the available intake data supplied in the reproduction study results. For the moment, the Level 1 screening assessment will be based on conversion of dietary exposure to oral dose using the available intake data supplied in the reproduction study results.

Another limitation that must be considered in the Level 1 screening process is the potential for interspecies differences in sensitivity to the toxicant. As discussed in the general effects model, EFED proposes a factor of at least 10 be applied for interspecies uncertainty.

iii Level 1 Data Requirements

Exposure assessment data requirements for a Level 1 reproduction risk assessment are the same as those discussed earlier for the Level 1 acute effects assessment.

The effects data requirements at level one are limited to standard reproduction effects testing in two bird species. As new OECD protocols are developed for shorter term exposure, EFED will evaluate their suitability for this assessment processs.

b. Level 2: A Limited Probabilistic Risk Assessment (Avian Reproduction)

Level 2 assessment of avian reproduction risks is performed in situations where the Level 1 assessment indicates a presumption of risk for reproduction endpoints. The focus of the Level 2 assessment is to provide, in generic terms, information on the probability and (if data allow) the magnitude of reproduction effects. Two options exist for presenting this analysis. The first option (Option A) consists of a probability of exceedence relationship established through the comparison of a distribution of possible bird doses with a point estimate of the threshold of effects (NOAEC). This option would not provide information on the magnitude of effects, but would not require additional effects testing. The second option (Option B) is a joint probability assessment encompassing a distribution of potential doses and data regarding a dose-response relationship for the most sensitive reproduction endpoint identified in the standard avian reproduction studies. This second option would provide risk managers with information on the probability and magnitude of reproduction impairment and would require an additional avian reproduction test using a method providing a dose response result.

i Level 2 Exposure Assessment

Perhaps one of the most difficult issues to address in refining the assessment of reproduction risks is the question of relating the duration and pattern of exposure utilized

in the existing reproduction testing protocol to the patterns and duration of exposure exhibited in the field. The current avian reproduction test involves up to 120 days of exposure to the toxicant. It has frequently been argued that comparing test results from such a long-term exposure to the frequently observed declining exposure trends (e.g., dissipating residues on wildlife food items) in the field is overly conservative. EFED agrees that the duration of exposure can play a critical role in eliciting reproduction effects and, for most chemicals, residues do not remain constant over prolonged periods. However, little information in generally available to focus exposure modeling on chemical-specific critical exposure durations. There are a few studies (Bennett and Bennett 1990, Bennett et al. 1990 Bennett and Ganio 1991,, Bennett et al. 1991) that suggest that exposures of as little as one week can elicit reproduction effects at toxicant dosages comparable to those observed to cause adverse effects in the standard long-term reproduction tests. Furthermore, avian reproduction physiology has numerous biochemical targets that may require only short periods of disruption to result in important reproduction impairment, especially in determinant egg-laying species.

The Level 2 exposure assessment will focus on a daily dose averageing time of 7 days. This is consistent with the limited data available on minimal exposure time observed to cause reproduction effects (Bennett and Bennett 1990).

As in Level 1, all routes of exposure outlined in the short-term avian exposure assessments for lethal effects assessment will be considered in Level 2 assessments of reproduction effects. Also consistent with the Level 1 reproduction assessment, all routes of exposure will be considered to be of equal potency.

ii Level 2 Effects Assessment

As in Level 1, an uncertainty factor for interspecies variability would be applied to the available effects data. This factor would be unmodified from the Level 1 factor.

The need for additional effects data is dependant upon the type of Level 2 assessment output desired. The Option A assessment at Level 2 utilizes the most sensitive NOAEC from the available standard avian reproduction tests, which is modified for daily dose. No additional effects data are required for Option A. However, Option B relies on a dose response relationship to facilitate the prediction of the magnitude of effects. Option B therefore requires at least an additional reproduction test that focuses on the most sensitive species heretofore tested, with a testing protocol designed to provide dose-response data for the most sensitive reproduction parameter identified. The development of this dose-response protocol remains to be a critical step in the advancement of risk assessment techniques for avian reproduction effects.

c. Level 3: A Refined Probabilistic Risk Assessment (Avian Reproduction)

The Level 3 avian reproduction risk assessment method improvements over Level 2 include replacement of the large interspecies sensitivity uncertainty factor with a distribution of species sensitivity based in additional reproduction effects testing for and expanded set of bird species. In addition, biologically-based exposure model variables will incorporate distributions based on available data for focal bird species, not the generic bird classifications of the Levels 1 and 2 assessments. The output of the assessment is the same as Level 2 with an Option A probability of exceedance of a NOAEL toxicity benchmark dose and an Option B joint probability using a dose distribution specific to the focal species and a dose response relationship based on enhanced reproduction testing.

i Level 3 Exposure Assessment

The Level 3 reproduction risk exposure assessment is primarily focused on enhanced realism in modeling of exposure. Problem formulation for this level of assessment involves the selection of focal species and regionally specific use patterns to focus on areas of greatest concern for reproduction effects. Data requirements to enable such a problem

formulation include literature and field studies of the species of birds utilizing the environments in and around proposed use sites. These data needs, for many of the major agricultural applications could be fulfilled by groups of registrants and natural resource trustees in order to reduce the overall cost to individual registrants and to avoid development of costly redundant data sets.

Once specific focal bird species are identified, literature searches and possibly ethological field study data would be required to generate distributions for many of the exposure model parameters identified for the models previously discussed. Among the parameters in the models applicable to this focal species refinement are (but not limited to): bodyweight, food intake rate, proportion of dietary mass attributable to food type, incidental soil ingestion rate, drinking water intake rate, dermal surface area, and percent of diet from treated and buffer areas.

Other data that would be applicable to a Level 3 assessment would include measured residue data for avian food items, drinking water sources, air, and soil residues under the range of field conditions appropriate to the chemical/use combination and the regionally-specific areas of use that coincide with the occurrence of the selected focal species. The Agency currently does not have specific avian exposure field residue protocols, but is anticipating working closely with HED to modify human health-based residue studies and field dissipation studies to facilitate collection of these data.

In the absence of chemical-specific avian reproduction data targeted to identify exposure duration requirements for reproduction effects, EFED proposes the retention of the 7-day averaging time incorporated in the Level 2 assessment.

ii Level 3 Effects Assessment

The core of refinement in the effects assessment of Level 3 lies with generation of data to eliminate the reliance upon a set uncertainty factor to account for interspecies variability in

sensitivity to the toxicant. EFED envisions expansion of the extant reproduction effects testing data set to include additional species. This expanded data set will allow for establishment of a distribution of potential toxicity. A selection of some lower percentile on this distribution will serve as the assumed sensitivity of the focal bird species. At the present time EFED has not ascertained the minimum number of species that should be tested. However, it is recognized that the species number should at least be expanded to be representative of one or more passerines and be representative of reproductive strategies that are consistent with the focal avian species considered in the risk assessment. The type of testing must also be considered. EFED anticipates working with the Office of Research and Development to identify appropriate candidate species for testing as well as investigate a testing protocol that will allow for generation of dose-response relationships for multiple species.

d. Level 4: The Most Refined Risk Assessment (Reproduction Risks)

As in Level 3, the goals of the Level 4 risk assessment is to reduce the uncertainty of extrapolation from the generic to specific chemical/use combinations and sites of use. The focus of the Level 4 assessment is to reach the most practicable representation of actual field conditions. At this level of refinement the primary assessment option is the joint probability assessment using the probability distribution of dosages and dose-response information.

ii Level 4 Exposure Assessment

Level 4 exposure assessments may rely on the use of geospatial data analysis to determine specific use-site characteristics that would have the highest potential for risks. Data requirements for Level 4 exposure assessments may include GIS data on the proximity of specific chemical use sites to other habitats and to determine the relative quality of these habitats with respect to focal species of concern for the assessment. It is expected that, where sensitivity analysis suggests valuable contribution to elimination of uncertainty, that field studies of actual in-field exposure potential could be considered as a basis to

supplement exposure modeling.

Other potential areas to explore at Level 4 might include actual pharmacological investigations to determine the degree to which absorption of toxicant from various environmental media encountered in the field may differ from absorption of the same toxicant from diet in laboratory-based reproduction studies. These data could be used to modify assumptions of freely absorbed toxicant.

An important aspect of Level 4 exposure assessments is the elimination of assumed short averaging times for exposures. This is accomplished through consideration of specific reproduction studies incorporating information of the timing of pesticide application as well as the pattern of residue dissipation in environmental compartments. By considering such data, exposure assessment averaging times can be set for durations applicable to minimum exposure period requirements to elicit adverse effects on reproduction.

ii Level 4 Effects Assessment

The Level 4 effects assessment focuses on elimination of interspecies extrapolation altogether. This would be accomplished through the generation of laboratory and/or field assessments of reproduction effects using the actual focal species.

In addition, exposure regimes for reproduction testing can be modified to coincide with expected seasonal pesticide application periods at the use site (i.e., setting the exposure period in the laboratory to occur during specific stages in the reproduction cycle to coincide with actual application periods in the field). In addition, reproduction tests could also incorporate exposure patterns that follow the patterns of decline of residues in avian food items, drinking water, air, and soil.

E. Implementation Issues

In developing the basic terrestrial model and defining the process which it will be used, EFED has identified several issues that need attention to move forward to implementing probabilistic assessments. The following sections briefly outline a number of these issues and EFED's initial ideas to resolve them.

1. Avoidance

EFED has not included a pesticide avoidance variable in the initial exposure models and has deferred it until the final level of assessment. Basically, this is what is recommended by the ECOFRAM Workgroup. However, the Workgroup carried the parameter forward at each level assuming no avoidance occurs. The principle difficulty in assessing the effect of avoidance is that the avoidance response is highly variable, and is influenced by many factors and quantifying this variation is even a more difficult task then most, if not all, the other variables that need attention in the model. It seems, as suggested by the Workgroup, quantifying this variable should be deferred until the later stages of the assessment. The Workgroup provides an excellent over view on determining whether avoidance is a factor that is worth detailed investigation at the higher levels of refinement. However, a detailed assessment of avoidance requires nonstandard data and only a few chemicals and species have been evaluated. Therefore, given the state of understanding of this behavior and its high variability between species and between chemicals EFED believes that it's most appropriated to defer its evaluation to the most refined assessments, and then address it on a case by case basis.

2. Associating Toxic Effects with Multiple Exposure Route Modeling

Currently, the effects testing battery available to the Agency for avian effects is limited to studies involving oral dose exposure. However, total exposures are from a number of routes, believed to be significant, that are in addition to the oral route (e.g., dermal and inhalation). EFED believes

that, even at the initial levels of the refinement process, exposure from all appropriate routes should be quantitatively considered.

The ECOFRAM Workgroup indicated that inhalation and dermal doses cannot generally be combined with ingestion doses to give a total dose. The primary reason is that the fraction of the external dose that actually becomes available at a site or sites of toxic action within the organisms differs between ingestion, inhalation and dermal exposure pathways giving different dose-response curves for each pathway. Additional developmental work and research are needed.

In the interim, EFED is exploring a few methods that may provide rough estimates for screening and initial probabilistic level assessments to account for the different pathways of exposure. In the absence of any inhalation or dermal toxicity information, the assumption could be made that the various routes of exposure are additive and toxicity is equivalent to oral estimates. However, EFED believes that, in general, the pathways are not equivalent. An alternative would be to develop default toxicity equivalence factor distributions for each pathway relative to oral exposure, based on extensive laboratory toxicity data develop for mammalian species for the different pathways. Theses equivalency factor distributions could be segregated by chemical class, given sufficient toxicity data.

Another alternative, for most chemicals, chemical specific oral, dermal, and inhalation mammalian toxicity tests are available from the human toxicity data requirements. Therefore, if it is assumed that the differential sensitivity or tolerance to the different routes of exposure is similar in mammals and birds, toxicity equivalence factors could be applied to dose estimates for each route of exposure to account for the difference in sensitivity to the different exposure pathways. The model then would be:

$$D_{totaldose} = D_{oral} + D_{dermal}/TEF_{dermal} + D_{inhal}/TEF_{inhal} \quad (12)$$

where:

TEF = Toxicity Equivalence Factor

$$TEF_{dermal} = \frac{LD50_{dermal}}{LD50_{oral}}$$

$$TEF_{inhal} = \frac{LD50_{inhal}}{LD50_{oral}}$$

Further evaluation of this approach is needed to determine a method to account for its uncertainty, especially the uncertainty surrounding the assumption of potency relationships being conserved across major taxonomic groups. However, it appears this method shows promise for accounting for the difference in sensitivity between pathways in initial assessments. At higher levels of refinement, if sensitivity analysis indicates these factors are significant, avian tests on dermal and inhalation toxicity could be developed.

Research should be initiated to better define the uncertainties associated with estimating the contribution of the non-oral routes to total dose. Methods should also be developed to better characterize the potential effects from multi-exposure pathways.

3. Granular Exposure Model Evaluation

EFED believes that additional research is needed on more species and in additional regions to better define the distribution of input variables for the GEM model.

The Terrestrial Workgroup indicated this new tool for characterizing pesticide exposure from granules (GEM) should be considered a prototype or “beta model” subject to validation and further refinement. They also indicated that, this model is specific to direct ingestion of granules and does not account for exposure via ingestion of residues transported from intact granules or dissolved in food, water or soil, ingestion of residues on feathers or pelage during preening/grooming activity, dermal contact with residues in/on soil, vegetation, water and the granules themselves and inhalation of volatilized molecules. The model assumes these routes of exposure are minimal and direct ingestion of granules is considered the primary route of exposure.

EFED believes that, while inhalation and direct dermal exposure from granules may be minimal,

oral ingestion of pesticide from intact granules impinged on food sources, incidentally ingested from granule release to surrounding soil, or released from granules to subsequently contaminated food and water sources need further evaluation. As acknowledged by the ECOFRAM Workgroup, the data used to support the model are not extremely robust, limited by species and locations evaluated. Further research is needed to better define the major variables in estimating the risk to non-target organisms from granular products

4. Assigning Values to Dermal Exposure Model

A number of the parameters needed for the dermal exposure model using Fick's law of diffusion are not currently available from the suite of required wildlife tests, these include the diffusion coefficient and blood concentrations. However, given the indication that this route of exposure can be significant, overall exposure modeling must account for this route. This is a major area that needs further development. Initial plans are to review current methods and tests used to support the methods used to estimate human dermal exposure to determine their applicability to wildlife. Other methods that could be used will be explored as well. In initial assessments this route of exposure could be accounted for by assuming some bounding estimates for overall transdermal absorption and apply this to an assumed total mass of pesticide in contaminated media in contacted with the integument. If found to be a significant uncertainty in the estimate of risk, additional data would be developed to address the appropriate parameters to better define this route of exposure.

EFED believes that the application of the TEF approach may, in part obviate the need to model exposure from pesticide absorption across the skin. TEFs are not based on absorbed dose, but on extrapolations from data regarding the topically applied dose. Of course, there is considerable uncertainty in assuming that applied dose in mammals (the basis for the TEFs) is the same as would be encountered for birds. The challenge for the future will be to better account for this uncertainty and to develop a way to directly estimate absorbed doses from both direct impingement of applied material and from pesticide contacting the skin from other media.

5. Establishing the Minimum Number of Experimental S pecies for Acute Toxicity Testing

While EFED plans to move forward with the distribution-based toxicity extrapolation factors, it is believed that further work is necessary to evaluate the minimum number of species required to define the species distribution adequately. This position is supported by the Terrestrial Workgroup. A sample of four seems relatively small. Also, the bias from the use of LD_{50} values determined with the Approximate Lethal dose method needs to be examined. This method, which provides an approximate estimate of the median lethal dose, lacks precision and any confidence bounds. A large part of the data that were used to develop the EF consisted of determination made with the Approximate Lethal dose methods. Further work should be carried out to determine the influence of these data on the distribution-based extrapolation factor method.

6. Interspecies Extrapolation factor for reproduction Effects

EFED has, in the absence of current data for multiple species, proposed an uncertainty factor of at least 10 to be applied to the most sensitive reproduction endpoint. Over the next few months EFED will conduct a search of all available literature for pesticidal and non-pesticidal toxicant avian lethality and reproduction data. The focus of this search will be to identify data on bird species not presently addressed by the Agency's pesticide data requirements. These data, if available, would be used to refine the currently proposed uncertainty factor.

7. Estimating Intraspecies Uncertainty Factor Distributions

EFED believes that further review of techniques for establishing uncertainty factors for describing within species variation in sensitivity to a toxicant. EFED proposes this review incorporate the techniques as suggested at the Peer Input Workshop to develop default values and additional research to better define these factors.

There is considerable challenge to estimating the distributions for the intraspecies uncertainty factor in the face of currently limited data. The Terrestrial Workgroup concluded that for most of the factors influencing the laboratory to field extrapolations, data were insufficient to allow incorporation into probabilistic assessments. However, the Peer Input Workshop discussion suggested that the absence of adequate data should not be ignored but accounted for in probabilistic assessments. For several of the factors that influence laboratory to field extrapolation some data are available and much of these data were cited by the Workgroup. These data warrant closer scrutiny.

8. Duration of Exposure

Duration of exposure presents some issues which need to be addressed to implement the new process. There is potentially significant uncertainty arising from matching dosing regimes from current studies to the expected exposure predictions. Estimations of dose in the exposure model are calculated on the basis of mass of chemical per unit body mass per day and the cumulative dose is the sum of daily doses for the duration of the exposure period based on dissipation rates in the environment. Depending on the half-life estimate of the compound, the duration of exposure could range from a few hours to several weeks. However, current acute and dietary toxicity tests are of fixed duration up to five days. For chemicals which the exposure periods are less than five days, direct comparisons of exposure and toxicity appear appropriate, accounting for inter-species variability. The LD_{50} study results, a single "bolus" exposure, relevant to short exposure up to a day, and the dietary LC_{50} study, for exposures up to five days. However, for chemicals with greater environmental stability, and hence longer exposure periods, difficulties arise when trying to match a dosing regime from the current studies to the exposure period since toxicity is a function of both duration and intensity.

The ECOFRAM Terrestrial Workgroup suggested modification of the current dietary test as one possible solution to this issue. Also, the modifications suggested address another difficulty with the current test of estimating dose ingested over time. In the current test, exposure is through food and the amount of residues consumed by test individuals is not reliably estimated. Currently,

results are reported as the concentration mixed with food that produces a response, rather than the dose ingested (mg/kg-bw/time). Although food consumption is measured, calculation of the mg/kg-bw/time is confounded by undocumented spillage of feed. Also, the group housing of birds only allows for a measure of the average consumption per time for a group and is further confounded if animals die within the experimental groups. The interpretation of this test is also confounded because the response of the test individuals is not only a function of the intrinsic toxicity of the pesticide, but also the willingness of the birds to consume treated food.

In the short-term, EFED recommends the use of the the current avian dietary test to provide an estimate of the dose-response relationship during a five-day exposure period. This will require an estimate of dose in mg/kg-bw/day from estimates of food consumption. However, the Workgroup did not address, for the short term, ways to account for longer exposure periods. Regression analysis of the mortality patterns over the initial test period may provide a way to estimate mortality for longer exposure durations. Depending on the mortality pattern and the duration of the exposure period, nonlinear regression techniques may be the most appropriate. The utility of this approach will be evaluated and is briefly outlined below.

For the future the test must be redesigned. EFED plans, as recommended by the Workgroup, to use the proposed guideline for a dietary toxicity test being developed by OECD as a base for redesigning the current test. The OECD test addresses many of these issues and is more suited for probabilistic risk assessment.

In the interim as discussed above, exposure duration is a factor that must be accounted for in acute effects risk assessments and a method is needed for establishing exposure duration windows, over which daily doses may be accumulated for the purposes of assessing lethal risks.

Initial efforts at defining an appropriate exposure duration under the assessment process can proceed along two lines. The first is establishing an exposure duration that is consistent with the existing exposure duration of the acute dietary study. This approach would set the exposure duration at five days. Exposure over the course of the five days could be calculated as either

cumulative (the sum of five days of exposure) or average (the average of five days of exposure). One concern for this method is that potentially lethal contributions of pesticide residues for chemicals with moderate to long environmental persistence could extend beyond the first five days of application, resulting in under prediction of the true frequency of lethal effects.

In order to better account for the potential of residues beyond five days contributing to the overall lethal risk, a second possible approach to setting exposure duration could be used. This approach first uses existing acute single oral toxicity study dose-response data to set a minimal single daily dose, below which EFED has little concern for direct mortality (possibly the LD_5). This endpoint would be converted to a dietary concentration equivalent. The duration of the exposure window would be calculated by solving the first-order decay equation as follows:

$$T = \frac{\ln(\text{Initial residue}/LD_5 \text{ based target residue})}{K} \quad (13)$$

where: T is the exposure duration in days

K is the dissipation rate constant for the most persistent environmental compartment contribution to overall exposure.

Exposures would then be calculated as either the cumulative or daily average over this duration. This dose calculation could not be directly compared to the dose response data from the 5-day dietary study. Instead, partial mortality data from these studies could be regressed over time to extrapolate an LC_{50} (and subsequent dose response relationship) for exposures consistent with the calculated exposure window. A rapid check of the resulting extrapolated LC_{50} would be to compare this endpoint to the doses used in the avian reproduction studies. The extrapolated LC_{50} should not be equal to or lower than those doses shown not to cause lethality in the avian reproduction study.

For subsequent levels of risk assessment refinement, the patterns of residue dissipation can be factored directly into dietary toxicity studies to reduce the uncertainty involved in extrapolating

short-term effects data to longer term exposures. Durations of expanded toxicity testing can be made to coincide with the dissipation patterns.

At present, EFED has not established a preference for either of the above approaches. The Team believes that additional investigation, through the inclusion of case studies, is warranted to determine the feasibility of either approach in practice and is open to alternative approaches the SAP may propose at this time.

9. Slope Estimate

The slope of the dose response curve is thought to differ among species due to the difference in morphological, biochemical, and physiological processes which interact with inherent pharmacokinetic characteristics of the compound. The methods suggested by the Terrestrial Workgroup for extrapolation factors to account for inter-species variability in sensitivity do not account for inter-species variability of slopes. However to define the dose-response curve for the generic species, the cumulative distribution (CDF) of the effects, a slope estimate is required. The Terrestrial Workgroup briefly examined this issue and concluded that predictions about the slope based on taxonomic relationships is not possible because of data limitations.

However, the Terrestrial Workgroup questioned if predictions about the slope cannot be made based on taxonomic relationships, is the variability introduced by species differences any greater than the existing variability from other sources? To address this issue they evaluated four sources of variability, within-test, within laboratories, between tests and among species. Their brief analysis showed that variance, as determined by the standard error of the estimate or the standard deviation of the mean of the replicates, originating from within-test and from replicate test variability rarely exceeded 30%. Conducting tests in different laboratories did not result in variability (S.D./mean) exceeding 50%. When test results, including different species, were added to the analysis, the variability ranged between 26 and 122% with a median of 53%. The Terrestrial Workgroup concluded that the levels of variability tend to suggest that inter-species differences do not contribute much more than what is already present. They acknowledged their

evaluation was not a formal statistical approach and the question merits greater attention. The Terrestrial Workgroup suggested that additional analysis of the application of variance component models may be appropriate. However, they suggest that data may be a limiting factor, and additional research is needed to define this question.

In the interim the Workgroup provided the following options for considered for use when extrapolating from test species data to the focal species in a probabilistic assessment
:

1. When only one dose-response is available:
    a. Use the slope as the mean of a distribution of slopes and a coefficient of variation of 53%
    b. Use as in A to determine the 5th percentile of this distribution to set a lower "conservative" bound (a small slope value is considered conservative since it predicts mortality at lower doses than a higher value for the slope.)
    c. Do the same as in A or B, but using the standard error of the estimate from the study itself, as a measure of the variance.
2. When more than one dose-response is available:
    a. Do as in A or B above, but substitute the mean of n slopes for the mean of the distribution.
    b. Use a uniform distribution with the minimum and maximum values defining the range.

A determination of which of these options is the most appropriate is not readily apparent and will require further evaluation. EFED believes that once the model code is developed, an initial sensitivity analysis should be performed to determine of the impact that slope variability may have on the output of the model. Depending on the results of this sensitivity analysis, recommendations for appropriate implementation options can be made or, if warranted, additional research efforts can be initiated to further define the issue.

10. Site Specific Data Needs

There are a number of site-specific data needs at higher levels of risk assessment refinement. These include identifying the focal species that are to be addressed for the specific crops and regions being considered, habitat use parameters for each focal species for the specific crop, i.e. the distributions for proportion food obtained from contaminated area, proportion of time in a contaminated area, dietary diversity, soil ingestion rate, grit use, and water resource used need to be defined. The distributions of treated to non treated areas as well as the spacial arrangement of habitats (crops, edge and non-crop areas) as well as the type of non-crop areas being included need to be defined. Also, the distribution and availability of water sources need to be specified. Further, spray drift and meteorological events need to be factored into the models that are to be developed.

EFED envisions delineating various standard agro-ecological scenarios for the major crops by region. This will entail defining ranges of characteristics of the agro-ecological landscape by region, defining cropping practices, habitat types and their quantity and spacial occurrence, vegetative types, wildlife species, meteorological conditions, and soils. In it's initial application, this information will be obtained from literature review, agricultural statistics and Geographical Informational Systems(GIS). However, EFED believes that such sources of these data will be severely limited and recommends that efforts be devoted to development of protocols and workgroups of stakeholders to facilitate data collection in these areas.

For the majority of the species specific factors, the basic approach will be to review available literature on species occurrence in the agro-ecosystem identifying the species that appear to be at the highest risk from pesticide use and, for these species, compiling the needed natural history information. EFED anticipates that, for many species, available information will be scant and initial models will have to rely on a great deal of assumptions based on expert opinion. Again EFED recommends that efforts be devoted to development of protocols and workgroups of stakeholders to facilitate data collection in these areas.

11. Reproduction Testing Limitations and Developmental Challenges

As the ECOFRAM Terrestrial Workgroup noted, there are a number of significant technical challenges to developing a refined approach for assessing the risks of avian reproduction impairment following exposure to pesticides. Among these are the following:

1. Focus of existing reproduction testing protocols on generation of thresholds of effects (LOAEC and NOAEC) not dose response relationships.
2. A current testing protocol requiring prolonged exposures, without the ability to identify lower limits of effective exposure duration.
3. The current reproduction testing protocol does not allow for reliable determination of dietary intake of individual birds and therefore reliable calculation of daily dosages of toxicant
4. Lack of data to quantify interspecies differences in reproduction effects sensitivity, with a limited suite of species for effects testing that focuses on indeterminant egg-layers
5. Focus of reproduction testing protocols on gross measurements of offspring production, with only limited study (14-day survival) of offspring fitness (e.g. lack of second generation fecundity and no histopathological data on offspring).
6. Lack of data enabling establishment of relationships between laboratory effects observations and in-field manifestation of effects.

At the present time EFED has not ascertained the minimum number of species that should be tested. However, it is recognized that the species number should at least be expanded to be representative of one or more passerines and be representative of reproductive strategies that are consistent with the focal avian species considered in the risk assessment. The type of testing must also be considered. EFED anticipates working with the Office of Research and Development to identify appropriate candidate species for testing as well as investigate a testing protocol that will allow for generation of dose-response relationships for multiple species

12. Minimum Number of Reproduction Test Species for Refined Assessments

At the present time EFED has not ascertained the minimum number of species that should be tested. However, it is recognized that the species number should at least be expanded to be representative of one or more passerines and be representative of reproductive strategies that are consistent with the focal avian species considered in the risk assessment. The type of testing must also be considered. EFED anticipates working with the Office of Research and Development to identify appropriate candidate species for testing as well as investigate a testing protocol that will allow for generation of dose-response relationships for multiple species.

F. Next Steps

Over the course of developing this conceptual approach document, EFED has identified a number of data needs and requirements for modifications to existing and creation of new test protocols for obtaining information critical to conducting credible probabilistic risk assessments. The summary that follows defines the initial (first pass) scope of these additional data and protocols. It is anticipated that, as probabilistic risk assessments are performed, sensitivity analyses and refined problem formulation steps will identify additional and frequently encountered needs for other types of data and study protocols.

Exposure Assessment Needs (not in order of importance)

1. Development of a screening method to calculate air concentrations for bare ground and vegetation canopy application scenarios. This model should rely on existing physical/chemical and fate property data.

2. Development of a screening method to estimate pesticide concentrations in drinking water sources including puddles and water on plant surfaces. This model should rely on existing physical/chemical and fate property data.

3. Development of a screening-level dermal exposure model that accounts for both direct impingement of applied pesticide at time of application as well as dislodgement of residues from environmental media. This model should rely on existing physical/chemical and fate property data. If additional data requirements are necessary to implement such a model, these need to be proposed.

4. Investigate the proposed Toxicity Equivalency Factor method for converting exposures from different routes into oral dose terms. Examine the available HED toxicity data to determine overall approach feasibility.

5. Investigate the ECOFRAM-proposed granular exposure model. Determine the extent of species forming the basis of the model. Ascertain the portability of the model to other avian species including a consideration of various feeding strategies. Determine the feasibility of accounting for granular exposure not included in the grit selection model, e.g., consumption of granules incidentally entrained on wildlife food items.

6. Develop a screening method to model the disintegration of granular formulations and release of pesticide to surrounding media.

7. Develop protocols for measuring initial pesticide residues and decline of residues with time in wildlife food items, air, soil, and drinking water. Investigate the feasibility of incorporating these measurements into existing terrestrial field dissipation or HED crop residue studies.

8. Investigate the inclusion of avoidance factors into exposure models. Are existing dietary studies reliable for screening for avoidance? What is the portability of avoidance factors established in one species to untested species. Do different feeding strategies present extrapolation problems for applying avoidance factors? Are avoidance factors established in adults or juveniles suitable for other life stages (e.g., nestlings). Are their situations where intoxication of avian food items attractive to birds?

9. Literature and bench investigation into exposure duration. How should duration be accounted for in acute and chronic risk assessments. Can simple models be developed in the absence of pharmacokinetic information on uptake, clearance and tissue partitioning?

10. Literature investigation to determine distributions for inhalation rates, drinking water ingestion rates, surface area proportions for use in dermal contact modeling.

11. Development of experimental protocols to establish data sets for distributions of proportional treated field use by birds.

Effects Assessment Needs (not in order of importance)

1. Protocol modifications of the acute single oral dose, dietary toxicity, and reproduction studies to enable expanded species testing. Species expansion for reproduction protocol should consider determinant egg-laying reproduction strategy.

2. Protocol modifications to acute single oral dose and dietary toxicity studies to allow for reporting important sublethal effects.

3. Protocol modifications of dietary toxicity study to allow for more accurate dietary ingestion rate information for individual test animals. These data would allow for more certain conversions of dietary concentration exposures to oral dose.

4. Protocol modification or redesign of reproduction study to allow for determination of dose-response relationships for sensitive endpoints. This new protocol should also allow for more accurate determination of individual dietary ingestion for test organisms for extrapolation to a dose estimate. Protocol design should also consider the possibility of incorporating tests for modified behavior as it relates to parental care of offspring.

5. Literature and database investigation of interspecies extrapolation factors for reproduction effects endpoints.

6. Literature and data base investigation of interspecies variability to estimate the minimum number of toxicity studies required to adequately define the distribution of effects for both lethal and reproductive parameters at each level of refinement.

Figure 1. Example of the methods to predict the 5th percentile of the distribution of species sensitivities.

Examples of pre-determined extrapolation factors and the associated standard deviations:

Species	n	EF	Log EF	stdev EF
Bob	1	4.5	0.65	0.51
Bob, Mall	2	4.9	0.69	0.36
Bob, Mall, Hsp	3	4.0	0.60	0.30

1. LD_{50} for one to three (n) species

2. Log transform LD_{50} values such that $X = \log LD_{50}$

3. Calculate the mean of the transformed LD_{50}'s:

$$\overline{X} = \frac{\sum \log LD_{50}}{n}$$

4a. Predict the 5th percentile as a single fixed value.
Median estimate:

$$5^{th}\ percentile = 10^{\left(\overline{X} - EF\right)}$$

One sided 95% left confidence limit:

$$5^{th}\ percentile = 10^{\left(\overline{X} - [EF + 1.64 \times S_{EF}]\right)}$$

4b. Predict the 5th percentile as a distribution of values.
Normal distribution of extrapolation factors with mean =EF and standard deviation = S_{EF}

Sample distribution

Calculate 5th percentile:

$$Log\left(5^{th}\ percentile\right) = \overline{X} - EF$$

Run Monte Carlo simulation m times and generate distribution of m estimates of the 5th percentile
Output: Normal distribution of m estimates of log 5th percentile.

Figure 1. Cont.

LD_{50}'s for four or more(n) species

Pre- determined extrapolation constants $K_n(50\%)$ and $K_n(95\%)$ to compensate for small sample size n.

n	$K_n(50\%)$	$K_n(95\%)$
4	1.92	5.49
5	1.85	4.47
6	1.81	3.93

1. Log transform LD_{50} values such that :

$$X = \log LD_{50}$$

2.Calculate the mean of the transformed LD_{50}'s:

$$\overline{X_n} = \frac{\sum \log LD_{50}}{n}$$

and the standard deviation

$$S_n = \sqrt{\frac{\sum X^2 - \frac{\left(\sum X\right)^2}{n}}{n}}$$

3. Calculate the predicted 5th percentile:

$$5^{th}\ percentile = 10^{\left(\overline{X_n} - K_n \times S_n\right)}$$

$K_n50\%$ = median estimate of the 5th percentile

$K_n95\%$ = one sided 95% left confidence limit of the estimate of the 5th percentile.

Table 1. Overview of Levels of Refinement

Level 1: A Refined Deterministic Screen	
Exposure	Exposure based on calculated total dose for oral, dermal, and inhalation exposures. All parameters are set to fixed values that represent conservative bounds to distributions. Residues: Conservative point estimates from literature or media-specific models Biological: Conservative point estimates (e.g., fixed body weights, 100% diet Parameters attributed to each food item, 100% diet from treated field)
Effects	Acute Effects: Standard number of single oral and dietary tests (possibly one additional single oral study) Dietary studies modified to allow for dose calculation (use LC_{50} converted to dose) Toxicity thresholds based on LD_{50} or LC_{50} Application of Inter-species uncertainty factor to approximate 5th percentile species sensitivity Application of intra-species uncertainty factor to account for variable sensitivity within focal species Chronic Effects: Two standard reproduction tests with conversion to approximate dose Application of inter-species uncertainty factor to approximate 5th percentile species sensitivity
Analysis/ Presentation	Risk Quotients: Estimated Exposure / Toxicity Threshold (LD50 or NOEAL)
Level 2: A Limited Probabilistic Risk Assessment	
Exposure	Exposure based on calculated total dose for oral, dermal, and inhalation exposures. Exposure is expressed as a PDF. Residues: Distributions from literature or media-specific models with distributions for input parameters Biological: Retention of some conservative point estimates (e.g., 100% diet from treated field) Use of distributions for some factors (e.g., body weights, food ingestion rate)
Effects	Acute Effects: Number of studies as in Level 1 Dietary studies modified to allow for dose calculation Dose-response relationships for the basis for effects Application of Inter-species uncertainty factor to approximate 5th percentile species sensitivity Application of intra-species uncertainty factor to account for variable sensitivity within focal species Chronic Effects: Two standard reproduction tests with conversion to approximate dose or Additional reproduction testing to derive a dose-response relationship for sensitive endpoints observed in standard reproduction testing Application of inter-species uncertainty factor to approximate 5th percentile species sensitivity

Analysis/ Presentation	Acute Risks: Probability and magnitude of effects (PDF for exposure and CDF for effects from dose/response) Chronic Risks: Probability of exceeding threshold (PDF for exposure and fixed effects endpoint, NOAEL) or Probability and magnitude of effects (PDF for exposure and CDF for effects from dose/response)
Level 3: A Refined Probabilistic Risk Assessment	
Exposure	Exposure based on calculated total dose for oral, dermal, and inhalation exposures. Exposure is expressed as a PDF. Focus of refinements are for actual use site conditions and for focal species associated with those use sites. Consideration of the ecological and physical setting of the treated site. Residues: Distributions from literature or media-specific models with distributions for input parameters. Potential for supplementation of residues with monitoring data Consider the effects of off-site spray drift on residues outside treated area Biological: Use of distributions for biological and behavioral factors (e.g., body weights, ingestion rates, dietary matrices,) Focus on literature data for focal species as source for input parameters Consider habitat relationships as they affect exposures to on-field and off-field residues
Effects	Acute Effects: Additional single oral dose and dietary studies to better define the species sensitivity distribution (minimum number to be determined) Potential for testing focal species Potential for testing effects from dermal and inhalation exposures Dose-response relationships for the basis for effects Application of Inter-species uncertainty factor to approximate 5th percentile species sensitivity, when focal species not tested Application of intra-species uncertainty factor to account for variable sensitivity within focal species Chronic Effects: Expanded number of species tested for reproduction effects. Emphasis to be places on including determinant egg layers (minimum number and species to be determined) Application of inter-species uncertainty factor to approximate 5th percentile species sensitivity
Analysis/ Presentation	Acute Risks: Probability and magnitude of effects (PDF for exposure and CDF for effects from dose/response) Chronic Risks: Probability of exceeding threshold (PDF for exposure and fixed effects endpoint, NOAEL) or Probability and magnitude of effects (PDF for exposure and CDF for effects from dose/response)

Level 4: The Most Refined Probabilistic Risk Assessment	
Exposure	Exposure based on calculated total dose for oral, dermal, and inhalation exposures. Exposure is expressed as a PDF. Focus of refinements are for actual use site conditions and for focal species associated with those use sites. Consideration of the ecological and physical setting of the treated site. Residues: Distributions from literature or media-specific models with distributions for input parameters. Potential for supplementation of residues with monitoring data Consider the effects of off-site spray drift on residues outside treated area Biological: Use of distributions for biological and behavioral factors (e.g., body weights, ingestion rates, dietary matrices,) Focus on literature data for focal species as source for input parameters Consider habitat relationships as they affect exposures to on-field and off-field residues
Effects	Focus on the generation of effects data that either parallels field conditions in the laboratory or is generated under actual field conditions. Consideration of the impacts of effects on individuals to populations at varying geographical scales. Acute Effects: Potential for testing focal species Potential for effects testing from multiple exposure routes Incorporation of exposure regimes that parallel residue decline patterns in the field Potential for in-field acute effects testing under representative field conditions Dose-response relationships for the basis for effects Chronic Effects: Expanded number of species tested for reproduction effects. Emphasis to be places on including determinant egg layers (minimum number and species to be determined) Potential to conduct reproduction effects testing on focal species Reproduction studies designed to consider pesticide application timing (visa vis the reproduction cycle) as well as residue decline patterns and duration of exposure Potential for reproduction field effects/population studies
Analysis/ Presentation	Acute Risks: Probability and magnitude of effects (PDF for exposure and CDF for effects from dose/response) Chronic Risks: Probability of exceeding threshold (PDF for exposure and fixed effects endpoint, NOAEL) or Probability and magnitude of effects (PDF for exposure and CDF for effects from dose/response)

Table 2. Input Parameter Options for the Level 1 Refined Deterministic Risk Quotient Screening Approach

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
EXPOSURE $D_{total} = D_{oral} + D_{dermal} + D_{inhalation}$ $D_{oral} = D_{food} + D_{water} + D_{soil} + D_{granular} + D_{preening}$				
D_{food}		Total dietary dose	calculated	point estimate
	N_i	Exposure duration	Based on pesticide dissipation rate	Point estimate
	N_k	Number food types	one for three dietary strategies	
	N_J	Number feeding areas	one	
	pf_{ij}	% food from area j, day i	100% upper bound	Point estimate
	pd_{ijk}	% food type k from area j, dayi	100% upper bound	Point estimate
	$TFIR_i$	Total food ingestion rate day i	$TFIR = 0.398W^{0.85} \times 3(g)\, passerines$ $TFIR = 0.648W^{.0648} \times 3(g) allbirds$ or other appropriate allometric equations	Point estimate
	C_{ijk}	Food residue on food type k, area j day i	Upper 95% C.L. for food type from Fletcher (1994)	Point estimate
	W	Body weight	Generic species (15, 35, 1000g)	Point estimate
D_{water}		Total oral dose from water ingestion	Calculated	Point estimate
	N_i	Exposure duration	Based on pesticide dissipation rate	

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
	N_k	Number water sources	one, water source with highest average residues over duration of exposure	
	N_J	Number of areas water obtained	one	
	ptw_{ijk}	% water from area j, day i	100% upper bound	Point estimate
	pw_{ij}	% water from area j, day i, source k	100% upper bound	Point estimate
	$TWIR_i$	Total water ingestion rate day i	$TWIR = 0.059W^{0.67} \times (C)allbirds$ C = factor to estimate upper bond (to be determined)	Point estimate
	C_{ijk}	water residue area j, day i, source k	upper bound of average water residues for duration of exposure. Puddle concentrations calculated from direct application to assumed puddle of standardized dimensions. Water concentrations on for dew on vegetation from simple partitioning with vegetation residues	Point estimate
	W	Body weight	Generic species (15, 35, 1000g)	Point estimate
D_{soil}		Total dose from soil ingestion	calculate	Point estimate
	N_i	Exposure duration	Based on pesticide dissipation rate	
	N_J	Number areas soil ingested	one	
	ps_{ij}	% soil from area j, day i	100% upper bound	Point estimate
	$TSIR_i$	Total soil ingestion rate day i	$TSIR = X\%(TFIR)$ *X = 95% CL for % soil in diet* (to be estimated using Beyer et al.1994 and other literature sources)	Point estimate

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
	C_{ij}	Soil residues area j, day i	Calculated on a mass per unit area/depth for initial concentration, p-chem properties applied for dissipation half-life for long term residual	
	W	Body weight	Generic species (15, 35, 1000g)	
$D_{granular}$		Total dose from granular ingestion	caculated	Point estimate
	N_i	Exposure duration	Based on pesticide dissipation rate	
	N_J	Number areas granules ingested	one	
	pg_{ij}	% granules from area j, day i	100% upper bound	Point estimate
	$TGIR_i$	Total granule ingestion rate	GEM model presented in ECOFRAM Report Appendix C3 (to be evaluate) Upper 95% C.L. of granule ingestion rate	Point estimate
	GnlWt	Granule weight	upper 95% C.L. from wt. distribution of granular Will be required for all granular formulations	Point estimate
	C_{ij}	Granule residue area j, day i		
	W	Body weight	Generic species (15, 35, 1000g)	Point estimate
$D_{inhalation}$		total inhalation dose	calculated	Point estimate
	N_i	Exposure duration	Based on pesticide dissipation rate	
	N_J	Number areas	one	
	pt_{ij}	% time area j, day i	100% upper bound	Point estimate

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
	AIR	inhalation rate	$AIR(ml/\min) = 284W^{0.77} \times 3(kg), or$ upper bond $AIR(m^3/day) = 0.4089W^{0.77} \times 3(kg)$	Point estimate
	C_{ij}	air residue area j, day i	Applications to bare ground assume concentration is zero. Application to vegetation canopy may rely on PRZM sub-routine predictions.	
	W	Body wight	Generic species (15, 35, 1000g)	
$D_{preening}$	Needs to be developed			
D_{dermal}	Needs to be developed			
ACUTE EFFECTS	$DRR_j = DRR_{tested} \times Intra_F \times InterF_j \times SubIF$			
DDR_j		Dose-response species j	calculated 5th percentile of species distribution	Point estimate
	DRR_{tested}	Dose-response tested species	Minimum test required to be determined	
	$Intra_F$	Intra-species variability factor	Dose-response curve for 5th percentile species	Point estimate
	$InterF_j$	Inter-species variability factor	See figure one	
	UF	Lab to field uncertainty factor	to be developed	
	SublF	Sub-lethal factor	to be developed	
REPRODUCTION EFFECTS	$NOAEL = NOAEL_{tested}/10$			
$NOAEL_{tested}$	most sensitive species no observed adverse effect concentration (converted to oral dose level with study data on ingestion rate and bodyweight)			Point estimate
10	minimum interspecies extrapolation factor			Point estimate

Table 3. Input Parameter Options for the Level 2 Limited Probabilistic Risk Assessment

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
EXPOSURE	$D_{total} = D_{oral} + D_{dermal} + D_{inhalation}$ $D_{oral} = D_{food} + D_{water} + D_{soil} + D_{granular} + D_{preening}$			
D_{food}		Total dietary dose	distribution calculated	Calculated
	N_i	Exposure duration	Based on pesticide dissipation rate	Point estimate
	N_k	Number food types	one for three dietary strategies	
	N_J	Number feeding areas	one	
	pf_{ij}	% food from area j, day i	100% upper bound	Point estimate
	pd_{ijk}	% food type k from area j, dayi	100% upper bound	Point estimate
	$TFIR_i$	Total food ingestion rate day i	$TFIR = 0.398W^{0.85} \times 3(g)\, passerines$ $TFIR = 0.648W^{.0648} \times 3(g)\, allbirds$ or other appropriate allometric equations $95\%\, CL_{\log FIRj} = \log FIR_j \pm c\left[d + e\left(\log wt_j - \log Wt\right)^2\right]^{0.5}$ U.S. EPA 1993 from Nagy 1987	Normal
	C_{ijk}	Food residue on food type k, area j day i	Distribution estimated from Fletcher(1994) and the Uptake Accumulation Transpiration and Biotransformation database for each food type based on mean and S.D. reported	log normal
	W	Body weight	Generic species (15, 35, 1000g) S.D. to be estimated based literature reported mean S.D. for avian species	normal
D_{water}		Total oral dose from water ingestion	distribution calculated	calculated

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
	N_i	Exposure duration	Based on pesticide dissipation rate	
	N_k	Number water sources	To be determined	
	N_J	Number of areas water obtained	one	
	ptw_{ijk}	% water from area j, day i	100% upper bound	Point estimate
	pw_{ij}	% water from area j, day i, source k	100% upper bound	Point estimate
	$TWIR_i$	Total water ingestion rate day i	$TWIR = 0.059W^{0.67} allbirds$ need to identify method to estimate distribution statistical parameters	normal ?
	C_{ijk}	water residue area j, day i, source k	As presented in Level 1, but includes distribution of partitioning data and information of application uniformity across fields	lognormal ?
	W	Body weight	Generic species (15, 35, 1000g)S.D. to be estimated based literature reported mean S.D. for avian species	normal
D_{soil}		Total dose from soil ingestion	calculated distribution	calculated
	N_i	Exposure duration	Based on pesticide dissipation rate	
	N_J	Number areas soil ingested	one	
	ps_{ij}	% soil from area j, day i	100% upper bound	Point estimate
	$TSIR_i$	Total soil ingestion rate day i	$TSIR = X\%(TFIR)$ *distribution* to be estimated using Beyer et al.1994 and other literature sources)	To Be Determined (TBD)
	C_{ij}	Soil residues area j, day i	As in Level 1	
	W	Body weight	Generic species (15, 35, 1000g)S.D. to be estimated based literature reported mean S.D. for avian species	normal

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
$D_{granular}$		Total dose from granular ingestion	calculated distribution	calculated
	N_i	Exposure duration	Based on pesticide dissipation rate	
	N_J	Number areas granules ingested	one	
	pg_{ij}	% granules from area j, day i	100% upper bound	Point estimate
	$TGIR_i$	Total granule ingestion rate	GEM model presented in ECOFRAM Report Appendix C3 (to be evaluate) calculated distribution	calculated
	GnlWt	Granule weight	Distribution of granular weight will be required for all granular formulations	Point estimate
	C_{ij}	Granule residue area j, day i	GEM model presented in ECOFRAM Report (to be evaluated)	
	W	Body weight	Generic species (15, 35, 1000g)S.D. to be estimated based literature reported mean and S.D. for avian species	normal
$D_{inhalation}$		total inhalation dose	calculated distribution	calculated
	N_i	Exposure duration	Based on pesticide dissipation rate	
	N_J	Number areas	one	
	pt_{ij}	% time area j, day i	100% upper bound	Point estimate
	AIR	inhalation rate	$AIR(ml/\min) = 284W^{0.77}(kg), or$ $AIR(m^3/day) = 0.4089W^{0.77}(kg)$ Distribution to be based on literature review	TBD
	C_{ij}	air residue area j, day i	As per Level 1, but distributional data for PRZM subroutine inputs considered	
	W	Body wight	Generic species (15, 35, 1000g)S.D. to be estimated based literature reported mean S.D. for avian species	normal

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
$D_{preening}$	Needs to be developed			
D_{dermal}	Needs to be developed			
EFFECTS	$DRR_j = DRR_{tested} \times Intra_F \times InterF_j \times SubIF$			
	PDF of DRR_j = $RT = LD_{50}' 10^{(z/S_j)}$			
DDR_j		Dose-response species j	estimated distribution for 5th percentile of species distribution using method out line in figure 1	lognormal
	S_j	Slope of dose-response curve for species j	Estimated from test species. Method TBD	normal
	z	random value from standard normal distribution	$Y = \frac{N_i}{s\sqrt{2p}} e \frac{-(X-m)^2}{2s^2}$ $m = 0, s = 1$	normal
	DRR_{tested}	Dose-response tested species	Minimum test required to be determined	
	$Intra_F$	Intra-species variability factor	dose-response curve for the 5th percentile species	log normal
	UF	Lab to field uncertainty factor	to be developed	
	$InterF_j$	Inter-species variability factor	See figure one	
	SublF	Sub-lethal factor	to be developed	
REPRODUCTION EFFECTS	*$NOAEL = (NOAEL_{tested}/10)$* or *dose-response curve for most sensitive endpoint identified, shifted for interspecies factor*			
$NOAEL_{tested}$	most sensitive species no observed adverse effect concentration (converted to oral dose level with study data on ingestion rate and bodyweight)			Point estimate
10	minimum interspecies extrapolation factor			Point estimate
dose-reponse	dose response curve established from modified reproduction test for most sensitive endpoint identified in regular reproduction test (data requirement to be determined)			log normal

Table 4. Input Parameter Options for the Level 3 Refined Probabilistic Risk Assessment

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
EXPOSURE	$D_{total} = D_{oral} + D_{dermal} + D_{inhalation}$ $D_{oral} = D_{food} + D_{water} + D_{soil} + D_{granular} + D_{preening}$			
D_{food}		Total dietary dose	distribution calculated	Calculated
	N_i	Exposure duration	Based on pesticide dissipation rate	To Be Determined (TBD)
	N_k	Number food types	based on literature on focal species	
	N_J	Number feeding areas	based on focal species	
	pf_{ij}	% food from area j, day i	distribution to be develop from literature review on focal species	TBD
	pd_{ijk}	% food type k from area j, dayi	distribution to be developed from literature review on focal species	TBD
	$TFIR_i$	Total food ingestion rate day i	$TFIR = 0.398W^{0.85}(g)\ passerines$ $TFIR = 0.648W^{.0648}(g)\ allbirds$ or other appropriate allometric equations $95\%CL_{\log FIRj} = \log FIR_j \pm c\left[d + e\left(\log wt_j - \log Wt\right)^2\right]^{0.5}$ U.S. EPA 1993 from Nagy 1987	Normal
	C_{ijk}	Food residue on food type k, area j day i	Distribution estimated from Fletcher(1994) for each food type based on mean and S.D. reported. Potential for inclusion of actual field dissipation data under conditions commensurate with proposed use sites.	log normal
	W	Body weight	Distribution for focal species estimated from literature review	normal
D_{water}		Total oral dose from water ingestion	Calculated	calculated

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
	N_i	Exposure duration	Based on pesticide dissipation rate	TBD
	N_k	Number water sources	based on focal species natural history	
	N_J	Number of areas water obtained	Based on focal species	
	ptw_{ijk}	% water from area j, day i	distribution to be determined based on focal species and scenario that is develop	TBD
	pw_{ij}	% water from area j, day i, source k	distribution to be determined based on focal species and scenario that is develop	TBD
	$TWIR_i$	Total water ingestion rate day i	$TWIR = 0.059W^{0.67} allbirds$ need to identify method to estimate distribution statistical parameters	normal ?
	C_{ijk}	water residue area j, day i, source k	As in level 2 plus potential for inclusion of actual field dissipation data under conditions commensurate with proposed use sites.	lognormal ?
	W	Body weight	Focal species based on literature review	normal
D_{soil}		Total dose from soil ingestion	calculated distribution	calculated
	N_i	Exposure duration	Based on pesticide dissipation rate	TBD
	N_J	Number areas soil ingested	distribution to be determined based on focal species and scenario that is develop	TBD
	ps_{ij}	% soil from area j, day i	distribution to be determined based on focal species and scenario that is develop	TBD
	$TSIR_i$	Total soil ingestion rate day i	$TSIR = X\%(TFIR)$ *distribution* to be estimated using Beyer et al.1994 and other literature sources	TBD
	C_{ij}	Soil residues area j, day i	Potential for inclusion of actual field dissipation data under conditions commensurate with proposed use sites.	

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
	W	Body weight	distribution to be determined based on literature review on focal species	normal
$D_{granular}$		Total dose from granular ingestion	calculated distribution	calculated
	N_i	Exposure duration	Based on pesticide dissipation rate	TBD
	N_J	Number areas granules ingested	To be based on the scenario that is developed and focal species selected	
	pg_{ij}	% granules from area j, day i	To be based on the scenario that is developed and focal species selected	TBD
	$TGIR_i$	Total granule ingestion rate	GEM model presented in ECOFRAM Report Appendix C3 (to be evaluate) calculated distribution	calculated
	GnlWt	Granule weight	Distribution of granular weight Will be required for all granular formulations	normal
	C_{ij}	Granule residue area j, day i	Potential for inclusion of actual field dissipation data under conditions commensurate with proposed use sites.	
	W	Body weight	distribution to be determined based on literature review on focal species	normal
$D_{inhalation}$		total inhalation dose	calculated distribution	calculated
	N_i	Exposure duration	Based on pesticide dissipation rate	TBD
	N_J	Number areas	To be based on the scenario that is developed and focal species selected	
	pt_{ij}	% time area j, day i	To be based on the scenario that is developed and focal species selected	TBD
	AIR	inhalation rate	$AIR(ml/\min) = 284W^{0.77}(kg), or$ $AIR(m^3/day) = 0.4089W^{0.77}(kg)$ Distribution to be based on literature review	TBD

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
	C_{ij}	air residue area j, day i		
	W	Body wight	distribution to be determined based on literature review on focal species	normal
$D_{preening}$	Needs to be developed			
D_{dermal}	Needs to be developed			
EFFECTS	$DRR_j = DRR_{tested} \times Intra_F \times InterF_j \times SubIF$ PDF of DRR_j = $RT = LD50 \times 10^{(z/S_j)}$			
DDR_j		Dose-response species j	estimated distribution for 5th percentile of species distribution using method out line in figure 1 or dose-response for focal species if available	lognormal
	S_j	Slope of dose-response curve for species j	Estimated from test species. Method TBD	normal
	z	random value from standard normal distribution	$Y = \frac{N_i}{s\sqrt{2p}} e \frac{-(X-m)^2}{2s^2}$ $m = 0, s = 1$	normal
	DRR_{tested}	Dose-response tested species	Minimum four species	
	$Intra_F$	Intra-species variability factor	dose-response curve for 5th percentile species or focal species	log normal
	UF	Lab to field uncertainty factor	to be developed	
	$InterF_j$	Inter-species variability factor	See figure one	
	SublF	Sub-lethal factor	to be developed	
REPRODUCTION EFFECTS	*NOAEL= ($NOAEL_{tested}$/10)* or *dose-response curve for most sensitive endpoint identified, shifted for interspecies factor*			

Out put variable	Input Variable	Description of Variable	Value of Variable	Distribution Shape
$NOAEL_{tested}$	most sensitive species no observed adverse effect concentration (converted to oral dose level with study data on ingestion rate and bodyweight) (number and type of expanded species testing to be determined)			Point estimate
10	minimum interspecies extrapolation factor (may be dropped if expanded species testing indicates modified uncertainty factor)			Point estimate
dose-reponse	dose response curve established from modified reproduction test for most sensitive endpoint identified in regular reproduction test (data requirement to be determined)			log normal

Literature Cited

Baril, A. and P. Mineau. 1996. A distribution-based approach to improving avian risk assessment. Presented at the 17th Annual Meeting of the Organization for Economic Cooperation and Development. Washington D.C.

Bennett, J. K. and R. S. Bennett. 1990. Effects of Dietary Chemical L on Northern Bobwhite Egg Production and Eggshell Quality. Environ. Toxicol. Chem. 19: 907-912.

Bennett, R. S. and L. M. Ganio. 1991. Overview of Methods for Evaluating Effects of Pesticides on Reproduction in Birds. U. S. EPA. Environmental Research Laboratory, Corvallis, OR. EPA 600/3-91/048.

Bennett, R.S., R. Bently, T. Shirotama, and J. Bennett. 1990. Effects of the duration and timing of dietary methyl parathion exposure on bobwhite reproduction. Environ. Toxicol. Chem. 9: 1473-1480.

Bennett, R.S., B.A. Williams, D.W. Schmedding, and J. Bennett. 1991. Effects of dietary exposure to methyl parathion on egg-laying and incubation in mallards. Environ. Toxicol. Chem. 10: 501-507.

Driver, C.J., M.W. Ligotke, P.Van Voris, B.D. McVeety, B.J. Greenspan, and D.B. Drown. 1991. Routes of uptake and their relative contribution to the toxicologic response of northern bobwhite (*Colinus virginianus*) to an organophosphate pesticide. Environ. Toxicol. Chem. 10:21-33.

Ecological Committee on FIFRA Risk Assessment Methods (ECOFRAM) Terrestrial Draft Report 1999. http://www.epa.gov/oppefed1/ecorisk/aquareport.pdf

ECOFRAM Peer Input Workshop Comments. 1999. Various authors. http://www.epa.gov/oppefed1/ecorisk/index.htm

Lasiewski, R.C., and W.A. Calder. 1971. A preliminary allometric analysis of respiratory variables in resting birds. Resp. Phys. 11:152-166.

Luttik, R and T. Aldenburg. 1995. Extrapolation factors to be used in case of small samples of toxicity data (with a special focus on LD_{50} values for birds and mammals). Repot No. 679102029. National Institute of Public Health and Environment Protection, Bilthoven, The Netherlands.

Mayer, F. L., Jr. and M.R. Ellersieck. 1986. Manual of acute toxicity: interpretation and data base for 410 chemicals and 66 species of freshwater animals. U.S. Department of the Interior, Fish and Wildlife Service. Resource Publication 160, Washington D.C.

Mineau, P., B.T. Collins, and A. Baril. 1996. On the use of scaling factors to improve interspecies extrapolation of acute toxicity in birds> Regulatory Toxicology and Pharmacology 24:24-29.

U.S. Environmental Protection Agency.1993. Wildlife Exposure Factors Handbook. Volume 1. EPA/600/r-93/187a. Office of Research and Development, Washington D.C.

Appendix 1:
Summary of the Terrestrial ECOFRAM Draft Report

The ECOFRAM Terrestrial draft report presents a probabilistic approach to ecological risk assessment that proceeds through multiple levels of analysis, from single deterministic quotients through probabilistic methods conducted on generic data, to issue-specific probabilistic assessment at the highest levels. The concept of levels of assessment, as presented in the draft document, is not intended to be a fixed series of tiers of assessment. Instead, the approach is intended to be flexible in the selection and implementation of levels of refinement as specific instances require. A consequence of the flexible approach advocated by the authors of the draft Terrestrial report, is that most completed assessments would include elements at more than one Level of Refinement. For the overall assessment, the Level of Refinement refers to the extent that "biological realism", risk and uncertainty are incorporated in the risk characterization. In general the draft Terrestrial report bases the progression of assessment through levels of refinement on:

- Point estimates for parameters in the exposure assessment replaced with distributions
- Additional parameters in the exposure model are considered
- Improved estimate of unit dose over time for toxicological test organisms
- Increased number of species tested for effects
- Refinements in exposure patterns for toxicity testing
- Increased realism in the risk assessment
- Increased explicit consideration of assessment uncertainty
- Decreased uncertainty in the risk estimate
- Increased understanding of risk, and increased credibility of the assessment

The focus of the draft Terrestrial report is on the prediction of probability and magnitude of direct lethal effects of pesticide exposure via the dietary exposure route (or granular ingestion route) in birds. The report recognizes the need to expand the assessment methods to include (1) other taxonomic groups in addition to birds, (2) other effects such a direct impacts on reproduction and indirect effects, (3) additional routes of exposure, including dermal, drinking water, and inhalation. To this end, the report makes some recommendations to modification/additional testing for reproduction effects testing, and proposes a number of modeling approaches for additional routes of exposure.

Level 1

Description

Level 1 uses simple, relatively conservative assumptions that, together, are used to calculate deterministic risk quotients. The quotients are then compared to established criteria termed levels of concern. The Level 1 assessment method is intended to be protective but not predictive in terms of the probability and magnitude of effects.

Objectives

The objectives of the Level 1 assessment are to:

- Identify pesticide/use combinations that have minimal ecological concern, even under a conservative exposure and effects scenario
- Identify sensitive taxa (birds, mammals, other terrestrial organisms) for further risk assessment refinements
- Determine whether acute and/or chronic effects are of concern
- Identify patterns of use, crops, or formulations of pesticide that are of potential environmental significance and require further risk assessment refinements.

Although the objective of ECOFRAM was to move away from deterministic risk quotients, they have been retained in the Level 1 assessment in order to :

- Serve as an interim bridge for risk assessors and managers between current and new probabilistic methods
- Be consistent with ECOFRAM Aquatic methods
- Provide a benchmark against which new probabilistic assessments can be compared
- Provide possible risk issue scoping.

Exposure Characterization

Because Level 1 is intended as a simple screening tool, the inputs for exposure parameters would be point estimates. Some of these input values will represent conservative assumptions rather than average or typical estimates. The output at Level 1 comprise point estimates of dose fro a variety of time scales (short, medium, and long). The Terrestrial report presents a generalized exposure model for the dietary route (recognizing that similar exposure models will need development for drinking water, dermal, and inhalation routes). This model follows the general Pastorok equations as follows:

$$\text{one day dose}_{\text{dietary (day i)}} = \sum(PT_i)(TFIR_i)(PD_{ik})(FDR_{ik})[1-(AV_i)]C_{ik}/W$$

The parameter definitions for the above exposure model are defined below along with Level 1 suggested approaches for establishing values for them:

Avoidance factor (AV): Conservative assumption that the animal does not avoid food contaminated with pesticide

Residues in food (C): Estimate residues from application rates using the Fletcher et al. (1994) empirical relationship. Dissipation of residues

	estimated from Willis and McDowell study or soil degradation half-lives. Intake and depuration modeling would be used to predict vertebrate prey residues.
Body weight (W):	Use average estimates for relevant species from the literature
Proportion of food from treated area (PT):	Conservative assumption that 100% of diet is from treated area
Total food intake (TFIR):	Use existing allometric relationships. Adjust for gorging behavior using a factor of 3 x. Assume feeding rate is constant over time.
Proportion of diet from each food type (PD):	Conservative assumption that diet is 100% of each food type
Dry to fresh weight adjustment (FDR):	Use average estimates for relevant food types from the literature

The output of the exposure estimate would be conservatively high. The output for short-term exposure would be a single point estimate. Medium and long-term exposures would be presented as a time series of point estimates.

Effects Characterization

The approach for effects characterization is divided into considerations for short- medium- and long-term periods of exposure**.**

For effects associated with short-term exposures**,** a single dose-response test that quantifies mortality is required. A regression analysis is performed on this data set and a slope and LD_{50} are estimated. Interspecific variability with respect to toxic sensitivity is factored into the characterization through the use of extrapolation factors based on historical data. The toxicity endpoint is extrapolated to a fixed LD_{50} for a sensitive (i.e. 5^{th} percentile). Level 1 does not account for (1) variability in sensitivity as a result of age differences, (2) variability in the slope of the dose response relationship among species, (3) environmental condition effects on sensitivity, and (4) sublethal endpoints.

For medium-term exposures under Level 1, effects testing requirements are essential the same as short-term exposures. The same approaches are used for dose response

relationships and interspecies extrapolations are used. The same uncertainties are not addressed as for short-term effects.

Level 1 long-term exposure effects testing included reproduction toxicity testing in two bird species. The lowest no observed effects level (NOEL) from these two studies forms the basis for effects characterization contribution to the Level 1 risk assessment. Short of extrapolation factors for interspecies sensitivity uncertainty, the Level 1 assessment relies on the most sensitive species tested as representation of a focal species. No intraspecific variability is considered. The magnitude of effects is not considered because of test protocol limitations.

Level 2

Description

In the broadest of terms, a Level 2 assessment involves at least one input and the output in the form of probability distributions. However, the inputs are usually generic or hypothetical, and may be based on relatively incomplete information concerning the nature of input distributions (e.g., means and standard deviations of parameters as reported in available literature).

Objective

Level 2 is intended to be protective but also introduces greater realism into the assessment by substituting some of the conservative point estimates from level 1 with more realistic values, and deterministic values with distributions. The Level 2 assessment may e based on generic species or be focused on specific organisms associated with the target use of the pesticide. The uncertainty in the effects assessment is decreased by additional toxicity data and more accurate estimates of dose.

Exposure Characterization

Level 2 suggested approaches for establishing values for he basic exposure model described in Level 1 include:

Avoidance factor (AV):	Estimate avoidance from food consumption in dietary toxicity tests
Residues in food (C):	Use hypothetical distributions for initial residues and dissipation based in means and confidence limits from literature. Where data are unavailable, use models (under development)
Body weight (W):	Use confidence limits for available literature data to define

	hypothetical distributions
Proportion of food from treated Proportion of area (PT):	Account for the proportion of diet from untreated areas. Use existing information and expert judgement to estimate the distribution of the diet originating from treated area.
Total food intake (TFIR):	Estimate distributions based on confidence intervals for existing allometric relationships. Allow for food intake to vary over time.
Proportion of diet from each food type (PD):	Establish hypothetical distributions based on published data. Consider seasonal variation in dietary proportions
Dry to fresh weight adjustment (FDR):	Use confidence limits for relevant food types from literature to define hypothetical distributions

The output of the exposure estimate would be more realistic than Level 1 because exposure estimates are based on approximate distributions for some exposure parameters. The output would be a distribution of doses for short-term exposures and a distribution of exposures for each time point in medium and long-term exposures.

Effects Characterization

Under Level 2, the draft Terrestrial report refines the short-term extrapolated mortality estimate with the conduct of a toxicity test on the focal species for the risk assessment or, if this is not possible, testing of another acceptable species. An ALD (up-down) tests for one or two additional species may be adequate for estimation of the LD50 and slope of the dose-response. At Level 2 an interspecific variability extrapolation factor is applied to the geometric mean value of the LD_{50}s for each test species to extrapolate to an estimated LD_{50} for the focal species that is based on the 5^{th} percentile of the distribution of LD_{50} values. In cases where the chemical of concern is formulated as a granule, a separate acute oral dose-response test would be conducted with the granular formulation. As in Level 1 this approach does not account for variable age-specific response, dose-response slope variability among species, the effects of environmental conditions of sensitivity, and sublethal effects.

There are specific criteria for advancing a medium-term effects characterization to Level 2. These include:

1. The test chemical is from a relatively unknown or new chemistry

2. The mechanism of toxicity suggests that a medium-term effect could occur (e.g., delayed action)
3. There is a potential for bioaccumulation of the test chemical
4. The test chemical is likely to be persistent in wildlife food items

At Level 2, a full concentration-response dietary study for 1 test species is required. The protocol for this study would be new and would require monitoring of sublethal effects, individual test organism caging and monitoring of food intake for individual daily dose calculation, and assessment of avoidance. There would also be the provision for a dynamic exposure regime that could be aligned with dissipation curves from residue analysis and model predictions. The preferred method for analysis of effects from medium-term exposure would be to use interspecific extrapolation factors derived from historical data from dietary toxicity studies. Sources of variability unaccounted for at Level 2 are similar to those described for the short-term effects characterization.

In order to estimate the magnitude of reproductive effects (long-term exposures) modified reproduction testing would be required that would allow for the establishment of a dose-response relationship. In addition, the exposure regime of such a study could be made to be compatible with the dissipation patterns of residues in wildlife food items. Research into the development of such a modified study would also address methods to assess effects on parental care and criteria for necessitating measurements for sublethal effects.

Level 3

Description

As for Level 2, at least one input and the output in Level 3 are in the form of distributions. Input distributions are generally not specific to the pesticide and use scenario, but are likely to include statistically-fitted distributions and/or empirical distributions. Level 3 assessments are likely to include probability distributions for a greater number of parameters than Level 2 assessments.

Objective

Level 3 is similar to Level 2 in the overall objective to better approach realism in the risk assessment. The objective of Level 3 is to provide improved distributions for various exposure and effects parameters and will consider additional parameters in the exposure assessment.

Exposure Characterization

The Level 3 options for addressing valuation of parameters defined for the exposure model include:

Avoidance factor (AV):	Estimate avoidance from food consumption in dietary toxicity tests
Residues in food (C):	Use raw data from published studies to estimate distributions. Where data are unavailable, use models (under development)
Body weight (W):	Consider the effects of age and sex differences in body weight. Obtain raw data from published studies to estimate distributions of body weight.
Proportion of food from treated area (PT):	Account for the proportion of diet from untreated areas. Use existing information and expert judgement to estimate the distribution of the diet originating from treated area. Take into account, under appropriate scenarios, drift zone residues and the proportion of diet obtained from drift zones.
Total food intake (TFIR):	Estimate distributions from original data on input parameters for TFIR, including field metabolic rate, gross energy in food, and energy assimilation efficiency. Account for mixed diets and assess the frequency of short-term gorging scenarios
Proportion of diet from each food type (PD):	Use raw data from published studies to estimate distributions.
Dry to fresh weight adjustment (FDR):	Use raw for published studies to estimate distributions.

The output of the exposure estimate would be more realistic than Level 2 because exposure estimates are based on approximate distributions for more exposure parameters. The output would be a distribution of doses for short-term exposures and a distribution of exposures for each time point in medium and long-term exposures.

Effects Characterization

The draft Terrestrial report further refines the short-term extrapolated mortality estimate with the conduct of additional toxicity tests so that at least four LD_{50} values are available. ALD (up-down) testing for three species beyond the single species tested in a full dose-

response study may be adequate for estimation of the LD50 and slope of the dose-response. Level 3 effects characterization for short-term effects includes defining the parameters of the estimated dose-response distribution for the focal species. The uncertainty in the slope and LD_{50} parameter values is represented by the standard error of the mean of the tested LD_{50} values As in Levels 1 and 2 this approach does not account for variable age-specific response, dose-response slope variability among species, the effects of environmental conditions of sensitivity, and sublethal effects.

At Level 3, a full concentration-response dietary study for more than one test species is required. The preferred method for analysis of effects from medium-term exposure would be to use interspecific extrapolation factors derived from historical data from dietary toxicity studies. And apply them to the geometric mean of the multiple full concentration-response dietary study results. Sources of variability unaccounted for at Level 3 are similar to those described for the short-term effects characterization.

In order to estimate the magnitude of reproductive effects (long-term exposures) modified reproduction testing would be required that would allow for the establishment of a dose-response relationship. In addition, the exposure regime of such a study could be made to be compatible with the dissipation patterns of residues in wildlife food items. Research into the development of such a modified study would also address methods to assess effects on parental care and criteria for necessitating measurements for sublethal effects.

Long-term exposure effects characterization at Level 3 is the same as defined for Levels 2.

Level 4

Description

Level 4 is similar to Level 3 in the inclusion of frequency distribution data for a variety of input parameters. However, level 4 is designed to be more representative of specific pesticide/use scenarios. This level may also employ spatially-explicit models.

Objective

Level 4 is the highest level of assessment refinement. The approach considers landscape factors in spatially explicit exposure models and so may be crop and regionally specific. Improvements to distributions for exposure and effects could include focused field studies that provide more accurate measurements of exposure and effects parameters.

Exposure Characterization

The level 4 approaches for valuation of parameters included in the basic exposure model are described below:

Avoidance factor (AV):	Conduct special studies with captive animals to quantify the distribution. A range of environmental/biological conditions would be addressed
Residues in food (C):	Field studies to validate/calibrate models, or measure distributions on residues under relevant field conditions
Body weight (W):	Collect data on body weights of subject species under actual field conditions associated with pesticide use.
Proportion of food from treated area (PT):	Collect data on the contribution of treated areas to the diet of subject species under actual pesticide use conditions. Incorporate landscape models using geographical information systems (GIS), to consider species movement impacts on residue distributions.
Total food intake (TFIR):	Collect data on total food intake by subject species under actual pesticide use conditions.
Proportion of diet from each food type (PD):	Collect data on he dietary matrix of subject species under actual pesticide use conditions.
Dry to fresh weight adjustment (FDR):	Field measurement of water content of food items under pesticide use conditions. Consider the impact of dessication of moribund invertebrate prey items as a result of intoxication with the pesticide.

The likely output of the level 4 exposure assessment is a distribution of doses over time based on field data for specific use scenarios and for specific organisms. If landscape models are incorporated in the Level 4 assessment, the exposure assessment output could include spatial distribution maps of potential exposure at different points in time.

Effects Characterization

Effects characterizations for short-, medium-, and long-term exposures at Level 4 involve focused studies under captive pen or field conditions. These studies would be highly case specific in design and would be conducted to further assess key parameters identified in sensitivity analyses. Most of these studies would focus on refining the assessment of exposure rather than effects, or on reducing uncertainty associated with the parameters of food intake rate and avoidance. The study of effects in the field may also provide estimates of mortality based on more realistic exposure regimes than are possible with simple models. In addition, the field studies would also provide input values for modeling

longer-term effects regarding population dynamics. It is important to note that Level 4 studies should be site and scenario specific and therefore would not account for uncertainty associated with regional, crop, and focal species differences that depart from those accounted for in the study scenario.

Appendix 2:
DRAFT Summary of ECOFRAM Peer Review Workshop Comments on Terrestrial Document

The Peer Review Workshop, convened in 1999 to discuss the Draft ECOFRAM Terrestrial Report, produced over 150 pages of written comments. Many of these comments focused on highly specific aspects of the effects and exposure characterization sections of the ECOFRAM Report. However, there were a number of general areas upon which a majority of peer reviewers provided opinion. These included the following:

- The Peer Workshop members were generally in favor of a level of refinement approach for conducting terrestrial risk assessments. This approach was believed to allow the focus of data generation and complex analysis on those variables shown by uncertainty analysis to be most important to the overall risk predictions. However, a number of comments expressed concern that the level of refinement approach should be modified to identify data requirements at each level and that the focus of research and an analysis be standardized in some manner to facilitate consistency within pesticide program decision-making.

- Many comments included concerns over the large amount of new data that would be required at levels of refinement beyond the screening assessment and initial probabilistic assessment levels. The need for better collaboration between regulators and the regulated community to address data-gaps at higher level of refinement was identified. The Peer Workshop members suggested that data gaps could be addressed through the use of professional judgement, with the goal of approximating the level of uncertainty associated with resulting parameter and assessment predictions.

- The need to identify the "level of acceptability" for the risk assessment output at each level of refinement was discussed by the Peer Workshop members. A number of the comments fexpressed that this was a critical aspect to the level of refinement approach.

- The Peer Workshop members identified the need to harmonize the probabilistic risk assessment approaches described in the Draft ECOFRAM Terrestrial and Aquatic Reports.

- A number of commenters suggested that the Draft ECOFRAM Terrestrial Report be modified to explore other methods for propagating uncertainty in risk assessments in addition to Monte Carlo.

- The Report focused on the assessment of pesticide risks to birds and did not present approaches for assessing the risks of pesticides to other terrestrial organisms. The commenters expressed the need for the development of similar assessment approaches for mammals, reptiles, amphibians, terrestrial invertebrates, and plants.

- The Report did not provide sufficient guidance on the assessment of reproduction risks and did not adequately include the acute dietary toxicity testing data. Commenters stated that, although the existing reproduction study did not provide adequate information for dose-

response and there is uncertainty in extrapolating from laboratory studies to field effects, (a) the study design could be modified to provide dose-response information and (b) uncertainty in extrapolations from laboratory to field should not preclude consideration of reproduction endpoints using probabilistic tools.

- The methods presented in the report focused mainly on field scale mortality probability. There was need for improved guidance on population effect analysis. Developing methods for population effects analysis would need to involve initial identification of what information was needed for such modeling and establishing a process for conducting and analyzing these data.

- The Draft ECOFRAM Report lack of a discussion of methods for assessing indirect effects was cited as a limitation of the proposed risk assessment approach.

- There were concerns over the protracted time requirement to develop suitable integrated exposure models. Consideration should be given to interim modeling approaches for short-term application after successful validation against real data. Alternatively, regression-based models using existing data could be employed. However, some commenters expressed the need to initially collect data to determine the predictive ability of existing models and not wait till very high levels of refinement to collect data against which model outputs would be be compared. The concern was that models would not get an unbiased evaluation if only the worst cases proceeded to actual field data generation.

- All Peer Workshop members expressed the need for case studies. These case studies would provide insight as to the applicability of the proposed approaches given the amount and quality of existing data sets.