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SAP Report No. 99-04C, September 16, 1999

REPORT:
FIFRA Scientific Advisory Panel Meeting, July 22, 1999, held at the Sheraton Crystal City Hotel, Arlington, Virginia

Session III -A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Higher Tier Ecological Risk Assessment for Chlorfenapyr

Mr. Larry Dorsey
Designated Federal Official
FIFRA/Scientific Advisory Panel
Date:_____

Mary Anna Thrall, DVM
Chair
FIFRA/Scientific Advisory Panel
Date:_____

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT
SCIENTIFIC ADVISORY PANEL MEETING
JULY 22, 1999

Session III - Higher Tier Ecological Risk Assessment for Chlorfenapyr

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PUBLIC COMMENTERS

Oral statements were received from the following individuals:
Joseph D. Wisk, Ph.D., American Cyanamid Company
Larry Brewer, Ecotoxicology and Biosystems Associates
Geoffrey Hill, Auburn University
Kelly Tucker, American Bird Conservancy
Mary Henry, Ph.D., US Fish and Wildlife Service
Damian Prezziosi, The Wineberg Group

Written statements were received from:
American Cyanamid Company
American Bird Conservancy

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency regarding Higher Tier Ecological Risk Assessment for Chlorfenapyr. Advance public notice of the meeting was published in the Federal Register on July 6, 1999. The review was conducted in an open Panel meeting held in Arlington, VA, on July 22 and July 23, 1999. The meeting was chaired by Mary Anna Thrall, DVM, Professor, Department of Pathology, College of Veterinary Medicine & Biomedical Sciences, Colorado State University, Fort Collins, Colorado. Mr. Larry Dorsey served as the Designated Federal Official.

In December, 1994, the Agency received a request for registration for the use of the pyrrole insecticide chlorfenapyr on cotton. The Agency sought SAP input regarding the use of available data to characterize the ecological risk of chlorfenapyr use in cotton agroenvironments. Specifically, the Agency sought guidance on the geographic scale of a probabilistic risk assessment and what data on chlorfenapyr fate, residues, effects and cotton agroenvironments would be necessary to accommodate extrapolations of risks to scales beyond the treated agroenvironment to much larger scales. Ms. Denise Keehner (Office of Pesticide Programs, EPA) opened the session discussing the goals and objectives of the Agency's presentations. Paul Mastradone, Ph.D. (Office of Pesticide Programs, EPA) summarized the chlorfenapyr risk assessment history. Edward Odenkirchen, Ph.D. (Office of Pesticide Programs, EPA) provided an overview of the chlorfenapyr risk assessment. This was followed by discussions on the environmental fate, aquatic risk, and avian risk by Mr. Alex Clem (Office of Pesticide Programs, EPA), Mr. William Evans (Office of Pesticide Programs, EPA), and Edward Odenkirchen, Ph.D. (Office of Pesticide Programs, EPA), respectively.

CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency background document entitled "Chlorfenapyr (PIRATE ™, ALERT ™, AC 303, 630), Insecticide--Miticide, Environmental Fate and Ecological Effects and Characterization for a Section 3 for Use on Cotton", dated July 1, 1999, and are presented below.

EFED's Risk Assessment

1. The following questions address EFED’s presentation of the environmental fate profile for chlorfenapyr:

A. Does this environmental fate profile raise any unique risk issues not adequately considered in EFED’s assessment?

B. Is the 28-day exposure model used for birds adequate?

C. Does the SAP have any suggestions to enhance EFED’s analysis of this type of data?

2. In 1996, the SAP provided several comments and recommendations for improvement of risk assessment methods and procedures that would help the Agency move beyond a screening level assessment. Among these was the recognized need for better characterization of risks and use of environmental fate data in assessment of terrestrial wildlife exposure. Has the progression of EFED chlorfenapyr risk assessments, culminating in the Agency's most recent 1998 assessment, demonstrated a consideration of environmental fate information in the assessment of wildlife exposures?

A. Specific to the 1998 assessment, has EFED made appropriate use of residue data in wildlife food items for a deterministic assessment?

B. Given the design of the insect residue study (executive summary Attachment 3), was EFED's selection of residues for risk assessment appropriate?

C. Is EFED's use of mean or composite residues from the weed seed study (executive summary Attachment 4) appropriate for risk assessment purposes?

D. Given the types of wild plant fruits that may be considered to be typically consumed by birds, are the fruit and vegetable types monitored for residue by the registrant appropriate surrogates for this route of exposure? If not, is it appropriate to use seed weed head chlorfenapyr residues as surrogates for wild fruit components of the avian diet?

3. Has EFED made appropriate use of allometric relationships and registrant-supplied information on dietary selections in establishing daily ingestion rates for food items?

4. EFED has attempted to incorporate registrant-supplied avian census information regarding avian use of cotton fields (executive summaries Attachment 6) into the risk assessment through modification of the proportion of diet originating from a treated field versus surrounding buffer areas. EFED assumed that 100% diet from a treated field was a reasonable worst case for short-term acute effects considerations. However, the risk characterization also evaluated avian risks for a 10% proportion of diet from treated fields, along with no chlorfenapyr residues in buffer zone dietary items, as a lower limit for exposure for longer-term effects.

A. Does the SAP find these assumptions to be reasonable?

B. Can the SAP make recommendations about how to better make assumptions for this type of data?

C. Since the avian census data were for the number of birds observed in cotton fields versus buffer areas, are the available data adequately representative of feeding behavior on cotton fields and buffer zones to allow for more in-depth evaluations?

5. EFED converted LC_{50} and reproduction NOEC endpoints from dietary concentrations to daily oral doses to facilitate more direct comparisons with dietary exposure and to account for ingestion rate differences between species as it affects actual ingested chlorfenapyr dose. EFED relied on observed body weights and the caged group feed consumption to make these conversions.

A. Is EFED's conversion approach for dietary concentration to oral dose reasonable?

B. Does the SAP have recommendations for additional methods to account for intra- and interspecies variability in sensitivity?

6. EFED recognizes the limited ability of 120-day avian reproduction effects protocol to elucidate reproduction and sublethal effects associated with shorter exposure periods. However, EFED's risk assessment suggests that dietary exposure levels of chlorfenapyr exceed the NOEC established for the existing reproduction study for multiple weeks. In addition, maternal effects (weight reductions) were observed following the first two weeks of exposure of test animals to chlorfenapyr in the reproduction study.

A. Does the SAP agree with EFED's conclusions with regard to reproduction effects in exposed individual birds?

B. Can the SAP provide guidance on potential ways for accounting for dose response characteristics for reproductive effects?

7. EFED has based the risk assessment on parent chlorfenapyr alone.

A. Do the toxicity data for birds, mammals and aquatic organisms suggest that degradates should also be considered in the assessment of risks to wildlife and aquatic organisms?

B. Are there sufficient data to allow for the consideration of degradates with the same level of confidence as the parent compound?

C. Can SAP suggest how these can be quantitatively incorporated into the assessment, using the existing residue and fate information?

8. Does the SAP have comments or concerns regarding the use of the MUSCRAT model for

evaluating aquatic exposures for pesticides used on crops within widely distributed cultivation?

9. Are the available toxicity data sufficient in scope to enable EFED to succinctly characterize the risk to untested terrestrial and aquatic phyla?

A. Does EFED need to incorporate interspecies extrapolation uncertainty in establishing toxicity thresholds? If so, can the SAP recommend appropriate methods for such extrapolation in avian, mammalian, amphibian, reptile, fish and aquatic invertebrate endpoints.

B. Are additional toxicity tests warranted in this case?

10. EFED is seeking guidance of the assessment of risks to sediment-dwelling organisms. The MUSCRAT model provided the Agency with dry-weight sediment concentrations, which were used to compare with the data from acute sediment toxicity tests.

A. Was this approach appropriate?

B. Does SAP have specific recommendations for improvement of the method?

Assisting EFED In Taking Steps Toward Probabilistic Risk Assessment With Chlorfenapyr

1. In progressing from deterministic to probabilistic risk assessment techniques for terrestrial organisms, EFED is concerned with accounting for intra- and inter-species variability in reproduction toxicity testing. Can the SAP recommend any approach for accounting for these areas of uncertainty in a probabilistic assessment?

2. Given the geographic, temporal, and measurement limitations of the available chlorfenapyr residue data in insects, does the SAP believe that a probabilistic risk assessment using these data should incorporate an expression of extrapolation uncertainty for the data's application to non-tested sites of potential chlorfenapyr use? If yes, can the SAP suggest appropriate methods for capturing this uncertainty in the probabilistic assessment?

3. Can the SAP provide guidance on capturing uncertainty in extrapolating from sampled fields to larger areas of chlorfenapyr treatment? Can the SAP recommend other data sets from the literature that would enhance a chemical-specific probabilistic risk assessment?

4. EFED is concerned with the uncertainty associated with using avian census data (number of observed birds in and out of fields) to predict dietary proportions obtained from treated and untreated areas.

A. Does the SAP have suggestions for ways to reduce such uncertainty?

B. Should EFED focus on mean values for censussed regions or consider the spectrum of species variability in observations in the data?

5. All previous deterministic approaches for avian risk assessments tend to focus on local effects (treated fields at the screening levels followed by assessment of treated fields and surrounding buffer areas at more data-intensive levels of assessment). Given the available data for chlorfenapyr, at what geographical scales should EFED concentrate a probabilistic assessment? How should population concerns over larger scales be addressed?

6. Probabilistic assessments for avian effects may involve assessing exposure and effects for generic birds (no species consideration), focal species levels, or for all species associated with the particular agro-environment treated with the pesticide. Can SAP provide guidance as to the level of avian species resolution that would be appropriate for assessing avian reproduction risks for chlorfenapyr use on cotton?

DETAILED RESPONSE TO THE CHARGE

EFED's Risk Assessment

1. The following questions address EFED's presentation of the environmental fate profile for chlorfenapyr.

A. Does this environmental fate profile raise any unique risk issues not adequately considered in EFED's assessment ?

The Agency has done a reasonably good job of summarizing the fate profile of chlorfenapyr as it relates to subsequent usage in the risk assessment. The Agency appears to have extended considerable thought and effort in attempting to include all relevant risks associated with chlorfenapyr in the immediate cotton agriculture ecosystem. As with any critical review, there are areas where improvements can be made in this data set and evaluation of these data.

The clarity of the assessment would benefit from an up front review of the basic environmental fate data. This could be facilitated by including a table of the physico-chemical and environmental fate parameters for chlorfenapyr. These data are contained in the text in various places and summarized to some extent on page 45 of the Agency's background document as input parameters to the MUSCRAT model. Some key properties were not included in the review such as the Henry's constant and octanol-water partition coefficient. A thorough treatment of physico-chemical and fate properties is the basis for subsequent exposure analysis. The current fate assessment is incomplete.

Many of the physical properties of chlorfenapyr are similar to chemicals that have been previously canceled in the U.S. PCBs, toxaphene, DDT, dieldrin, and chlordanes, for example, were banned by the USEPA due to their extreme persistence in the environment, their toxicity, and their tendency to bioaccumulate. Many organochlorine insecticides were initially used for insect control in southern states where they were volatilized and transported to colder regions of the U.S. Researchers have determined that the ultimate fate of organochlorine chemicals was large, cold water bodies such as the Great Lakes and Arctic regions where degradation rates are slow. Literally tons of organochlorine chemicals are present in the sediment, surface waters and animal tissues within these sensitive ecosystems.

The high degree of halogenation, low water solubility, and resistance to degradation found in chlorfenapyr are similar to these organochlorine chemicals that have persisted in the global environment for decades after the end of production. While chlorfenapyr is not highly volatile once associated with soil, losses during and just after application could release a significant pulse to the atmosphere. Since the targeted region for usage is the warm southern states, volatile losses could be larger than expected. Over time, small pulses in the atmosphere from millions of acres of cotton could transport significant quantities of this chemical to non-target areas. This type of impact on local and regional sensitive ecosystems should be considered in the registration of chlorfenapyr.

The registrant has conducted extensive toxicological testing of chlorfenapyr on avian and aquatic species. These tests have demonstrated significant toxic effects on many of the test species. These effects are disturbing in light of the long environmental persistence and possible buildup of this chemical in soil. As stated by the Agency, further testing of sediment toxicity is required for clarification as this compound will likely be associated with colloidal and carbonaceous sediment material in the water column and may impact sediment dwelling organisms.

Breakdown products and metabolites of chlorfenapyr, especially those with significant toxicity, should be included in the exposure assessment and in further testing. The structure of photoisomer 357806 should be noted in the record. This compound seems to be made in high yield in laboratory water and is equitoxic with the parent compound. The toxicity of the activated parent and activated 357806 are also equivalent. The degradation and toxicity of this isomer has not been evaluated, but these properties should be evaluated. No degradates were identified in the half life studies, but selected degradates should be evaluated given the toxicity of the dealkylated product 303256 and the photoisomer 357806. Combined risks are likely to be additive for chlorfenapyr degradates, having the same mode of action as chlorfenapyr.

The field dissipation data seem to indicate a high degree of uncertainty, but this does not adversely affect the outcome of the risk formulation since 1.3 year represents the 86th percentile of existing chlorfenapyr half life data. This is quite close to the estimated 90th percentile half life of 1.4 year.

The long-term persistence in soil causes concern about soil-living invertebrates (especially earthworms that may bioconcentrate chlorfenapyr or its degradation products). This may result in earthworm-eating birds that are particularly vulnerable, e.g., shorebirds, woodcock, etc. Experience with field studies indicates that sometimes only a few species are particularly vulnerable because of what they eat or what they do. No earthworm residue data were available (parent material or degradation products). According to the data reviewed, some earthworm evaluations may be underway, but we have not seen the information. This residue information could be very instructive. Another group of birds that may be particularly vulnerable would be the herbivores (plant-eaters like grouse). This residue information could be very instructive.

The registrant has conducted extensive toxicological testing of chlorfenapyr on avian and aquatic species. These tests have demonstrated significant toxic effects on many of the test species. These effects are disturbing in light of the long environmental persistence and possible buildup of this chemical in soil. As stated by the Agency, further testing of sediment toxicity is required for clarification as this compound will likely be associated with colloidal and carbonaceous sediment material in the water column and may impact sediment dwelling organisms.

B. Is the 28-day exposure model used for birds adequate?

The Panel recognizes that there is a limit to how many scenarios can be modeled and that these data for longer term residue values in food items are few or lacking altogether. We also recognize that, at the time of the Agency assessment, there was more latitude on the proposed label for application frequency and rate. In general terms, the 28 day exposure model is reasonable given: 1) acute and subacute toxicity tests have durations less than this period; and 2) even in the chronic test, effects were seen under 28 days.

However, given that, by the end of the 28 days, exposures remain high enough that Risk Quotients (RQs) for chlorfenapyr exposure are still exceeded for the avian reproduction NOEC, it would be useful to have the exposure model analysis extended for a longer period. Longer exposures would be important to evaluate additional effects (e.g., reductions in juvenile growth rates) that could occur beyond 28 days. As a general principle, it would be appropriate to extend scenarios for at least as long as RQs are exceeded in cases where species of concern are present in areas presenting exposure potential.

Concerning chlorfenapyr, we believe the case can be made that the avian reproduction study may also indicate chronic toxicity in non-reproductive individuals under energetic stress. This opinion is based on the types of effects seen in the reproduction study as well as on the mode of action of this chemical. Birds on migration or approaching migratory readiness could be considered to be at particular risk, and it is therefore critical, in the Panel's opinion, to examine the overlap between potential exposure and the migration period of birds. Accumulating appropriate energy reserves is critical to successful migration. From an exposure point of view, migrating individuals are most likely to be in a state of hyperphagia and have intake rates grossly

underestimated by the Nagy equations which are based on average field metabolic rate demands. This is extremely important given the overwintering of Canada Geese in cotton growing regions and the utilization of cotton fields during migration along the Central Flyway.

It would also be useful to extend each analysis for the case where subsequent product applications do not take place. For instance, how long are RQs exceeded if only one or two applications take place.

C. Does the SAP have any suggestions to enhance EFED's analysis of this type of data?

The Agency needs to address birds with particular traits that make them more vulnerable (range of species modeled should represent insectivores, fruit eaters, seed eaters and earthworm eaters that also probe and eat soil). The overall fate assessment lacks sufficient data. The process of collecting key field data on degradation, soil and tissue residues, and soil accumulation is the appropriate approach and is especially important for persistent chemicals that have with elevated risk quotients. The Agency's effort of this assessment to incorporate as much field data as possible is supported by the Panel. The most critical exposure data in the avian risk assessment are the estimates of dietary (seed, fruit, insects, etc.) chlorfenapyr residues and the extent to which the diet is obtained from treated areas. The current assessment is limited by a shortage of field data (different conditions, different sites) for incorporation into models used to calculate dietary exposure and subsequent risk quotients. One approach that has been used is to collect avian crop or stomach contents at study sites improve the understanding of the dietary composition, followed by in-depth analysis of those components (both residues and food type and caloric content). Residues define the relative amounts of chemical present, and caloric content provides an indication of the food resources necessary to survive. This is particularly important since birds with special food habits have been killed by registered products that were not screened thoroughly.

The assumption that 100% of the chlorfenapyr residues in the diet are bioavailable is biased on the conservative (e.g. protective) side. The physico-chemical properties (Koc) indicate that chlorfenapyr is highly sorptive and not likely to be completely bioavailable in the gut of birds. Appropriate data do not appear to be available to estimate the bioavailability, but considering its potential importance it should be obtained. Several techniques might be employed to assess bioavailability including feeding studies or acid extraction of dietary components (0-5 days after application). Also data from previous studies of halogenated compound adsorption following ingestion could be used to approximate bioavailability.

Earthworm-feeding birds should be modeled in the risk assessment. The long persistence of chlorfenapyr and metabolites in the soil column means that verminivores may experience prolonged exposures, event though the chlorfenapyr is present primarily in soil.

Another reason for extending scenarios is the possible synergism between chlorfenapyr and cytochrome-inducing chemicals. Although levels of chlorfenapyr are decreasing over time,

concerns over avian safety may not decline in a monotonic fashion following the use of the pesticide but may increase again following the use of another pesticide known to be a cytochrome inducer. An example of a class of inducers are triazole fungicides.

2. In 1996, the SAP provided several comments and recommendations for improvement of risk assessment methods and procedures that would help the Agency move beyond a screening level assessment. Among these was the recognized need for better characterization of risks and use of environmental fate data in assessment of terrestrial wildlife exposure. Has the progression of EFED chlorfenapyr risk assessments, culminating in the Agency's most recent 1998 assessment, demonstrated a consideration of environmental fate information in the assessment of wildlife exposures?

The Panel agreed that environmental data were considered and included in the assessment. The Panel commends the Agency for including those changes. Even so, there is likely to be insufficient data to proceed with probabilistic assessments. Also, transformation to potentially toxic degradates needs to be addressed. An exceedance analysis needs to be employed to evaluate the distribution of exposures versus effect.

A. Specific to the 1998 assessment, has EFED made appropriate use of residue data in wildlife food items for a deterministic assessment?

The general approach which the Agency used to incorporate field residue data has improved the 1998 chlorfenapyr risk assessment. A critical component of all risk assessments is the exposure characterization. Incorporation of site-specific (dietary) residues for avian risk assessment enhances the confidence in the risk estimates. Refining dietary composition and associated residues for the resident bird species is a critical next step in the avian risk assessment process. For example, ground nesting birds are not considered in the field evaluations. The Agency has made appropriate use of the available residue data for a deterministic assessment. It is pointed out that these data supplied by the manufacturer is limited and the potential exists that the variation encountered in the reported current residues may not be reflect the true distribution of values. For example, ground nesting birds are not considered in the field evaluations. This points to the fact that better characterization of exposure is desirable.

However, three Panel members disagreed. Use of maximum values in exposure assessment ignores much of the available information about the distribution. For example, using maxima provide exposure estimates that are arbitrary (because maxima will increase as sample size increases) and questionable (e.g., 4/5 maxima for chlorfenapyr residues in adult beet armyworms are higher in the 0.2 lb a.i./A application rate than their corresponding maxima in the higher application rate treatment; some maxima increase with time following application).

One member suggested that, when using the larval data to establish initial post-spray values, data for the 0.2 and the 0.35 lb applications at times 0.1 and 1 should be brought to a common application rate and collapsed so as to provide 20 replicates. Those 20 values are close

to being normally distributed which means that a set percentile of the distribution (e.g. 90% or 95%) could be used for a deterministic assessment or that the entire distribution could be entered in a probabilistic assessment.

However, the Agency may have accepted a few chlorfenapyr-specific residue values at the expense of a larger body of literature and scientific data. Although it is certainly appropriate to consider data generated specifically for the pesticide of concern, reliance on a few data points supplied by a manufacturer for a specific product obscures the variation encountered in climate, applicator, application equipment, etc.

B. Given the design of the insect residue study (executive summary Attachment 3), was EFED's selection of residues for risk assessment appropriate?

Failure to account for any surface residues in larvae collected more than 1 day after spraying (because in MRID 44464201, larvae collected after day 1 are only exposed to residues present in cotton leaves and have not received any spray) means that the larval residue concentrations measured after day 1 may underestimate residue loads. Given the lack of comparable data for time periods > 1 day, the Agency's use of maximal residues for time 0 is reasonable although a better approach is recommended above.

The registrant, in its ecological risk assessment (book 1, page 19) proposes that the "working level" concentration in dying insects be set at 5.7 ug/g of insect based on the oral LD50 to the tobacco budworm larva. However, this value ignores the fact that insect larvae will also carry surface residues. In the case of the tobacco budworm, the dermal LD50 is 450 ug/g. This indicates that the actual residue levels after spray will be substantially higher than the suggested 5.7 ppm. Also, the contribution of metabolized chlorfenapyr (especially the active CL 303268) to the total residue load is ignored, and represents a significant omission.

One recommendation for insect residues would be to model separately surface residues and ingested residues. The surface residues can be estimated from time 0 estimates plus a standard degradation curve such as the one measured for plant leaves. The concentration should be added the "working level" concentration of 5.7 ug/g for ingested residues (proposed by the manufacturer) given that the two are additive and should be added to the surface residue concentration. This may underestimate ingested residues in the case of insensitive invertebrates but would be an improvement over the current method. On the medium to long term, it would be expected that ingested residues would represent a proportionately higher proportion of total residues at increasing times after spray. A consideration of knock down time and chlorfenapyr's spectrum of activity against invertebrates could also be useful in assessing exposure.

Note that the Agency's choice of time 0 values is criticized by the registrant as being too high --- they point to the unpublished data by Fischer and colleagues who presented an industry average value of 5.7 ppm (adjusted for a 1 lb/a.i. application) for insects collected within 24 hours of a foliar spray. It is important to mention that the data summarized by Fischer and colleagues

are heavily biased by collection of live insects from pitfall traps, these data may underestimate time 0 residues. For example, without conducting an exhaustive search of the literature, a few published values (see following table) were located for residues in grasshoppers subjected to insecticide sprays. Incidentally, these values are quite relevant given the presentation to the SAP of Dr. Hill's research that showed that grasshoppers constituted the most important food item taken from and around cotton fields on his study site. Those values indicate an average time 0 concentration substantially higher than the average given by Fischer and colleagues even if one were to discount the two values obtained from a bird kill on the grounds that this may represent a biased sample. In light of these data, EFED's use of a 1lb/acre-adjusted RUD (Residue per Unit Dose) of 9.3 ppm to represent insect food contamination appears to be low and demonstrates the risk of relying on a single study in carrying out risk assessment. In this case, reliance on industry-wide data proposed by Fischer and colleagues would not seem to be advisable either.

One Panel member disagreed and believed the approach was appropriate and likely conservative. The selection of insect residues, 4.34 µg/g, represented the 96 centile (1/25) of chlorfenapyr parent found in the target species (larvae and adult) during the first day following application. This selection also represents very nearly the 99th centile (1/83) of all insect residues measured. Such an approach provides conservatism, but care must be taken since compounding conservatism may lead to unrealistically high risk predictions.

Table 1. RUD Residues per unit 1.0 lb a.i./acre application) from grasshopper data in the literature

Pesticide & application type	Nominal application rate (g a.i./ha)	Residues (ug/g)	RUD adjusted for 1 lb/acre application	Average weight of insects	Collection details	Ref.
Carbofuran aerial 1987	132	2.1	17.8 ppm	90 mg	With forceps from transect 3h post spray	Forsyth and Westcott 1994[1]
Carbofuran aerial 1988	132	3.9	33.1 ppm	220 mg	With forceps from transect 3h post spray	Forsyth and Westcott 1994
Carbofuran ground	140	2.5	20.0 ppm	370 mg	With forceps 2h post spray	Hawley and Somers 1988[2]
Carbofuran ground	140	0.9 0.5 2.0 5.7	7.2 ppm 4.0 ppm 16.0 ppm 45.6 ppm	370 mg	Retrieved from oesophagi of 4 gulls shot on treated site within 48 hours of spraying	Hawley and Somers 1988
Carbofuran ground	132	4.2 7.2	35.7 ppm 61.1 ppm	N/A	Min. and max levels retrieved from oesophagi of 5 poisoned gulls within 2h of spraying	Leighton and Wobeser 1987[3]
Acephate Aerial (low volume)	614	8.2	15.0 ppm	50 mg	Sweep nets 4h post spray	Stromborg et al. 1984[4]
Acephate Aerial (low volume)	614	9.4	17.2 ppm	50 mg	By hand 4h post spray (dead or moribund)	Stromborg et al. 1984

[1] Environm. Toxicol. Chemistry 13(2):299-306
[2] Alberta Environment Centre Report No. AECV88-R6
[3] Can. Vet. J. 28(3): 108-109
[4] Chemistry in Ecol. 2:39-45

C. Is EFED's use of mean or composite residues from the weed seed study (executive

summary Attachment 4) appropriate for risk assessment purposes?

Single composites of seed samples does not allow for any measure of variance which tends to limit the usefulness of the data. Therefore, weed seed residues utility are limited because it is based on treatments applied to one area with only single replicates taken for each treatment and time period. With four replicates, geometric means and measures of variance could be calculated for different time frames following applications. Regression models could be fit to this data to estimate residues vs time following each application. Geometric means (calculated or model estimates) or upper confidence limits are much more appropriate to use in exposure assessments than are maxima. The issue of whether these data can be extrapolated to other fields remains, and can likely only be resolved by additional field studies.

Use of composite samples may not be appropriate across weed species given the high interspecies variability shown in Table 2 of the Agency's background document. Composite samples may be acceptable within a weed species provided individual seeds do not indicate doses approaching an effects dose for the wildlife species of interest (i.e., seeds are not large). In the "small seeds" scenario, wildlife individuals will likely feed on many weed seeds and thus their exposure is effectively averaged over time, which is equivalent to using composite samples.

Birds have preferences for certain seed types in line with optimal foraging requirements. Also, proximal mechanisms for the formation of search images are such that individuals are likely to concentrate on a single weed species while foraging. Whether the assessment is deterministic or probabilistic, scenarios should allow species to have favored food items.

It is of concern that the measured seed head residues were no higher than concentrations found in extracted seeds. This is surprising in light of the protective cover that the seed head should be affording to the various seed types. This fact raised the issue with one panel member of how representative the registrant's values really are and whether calculated residue values on their own represent a substantial improvement over generic nomogram values. Also, the registrant's residue data measured in the weed seed heads are suspect because these data appear to not be "well behaved". When brought to a common application rate (e.g. 1.0 lb/acre), they do not show the characteristic variation about a central value but, rather, appear to show a strong relationship to application rate (Table 2).

Given that the discharge rate per acre is the same for all application rates, the most likely hypothesis for the bias is that there are bound and unextractable residues bound to the collection bags -- that amounts to an increasing proportion of the total residue load with decreasing application rate. A field spiking component would have resolved this. Field spiking would have resolved other issues of storage stability that arise due to numerous high temperature excursions spikes during sample storage; at least one member believes it should be standard procedure. The problem of unextractable residues appears to be specific to this study -- it is not seen in cotton leaf or insect larvae residues reported in MRID 44464201. Finally, the percent recovery for avian food items in MRID 44452605 averaged 83% only. Such a high level of analytical loss may

influence the results of a risk assessment.

On the other hand, the registrant may have omitted a factor, which is the fact that small granivores are likely to husk their seeds before ingestion thus reducing the likely residue loading of each seed. One would have to look at the seed types present in the vicinity of cotton fields across the cotton belt to determine whether this is likely to be an issue. The proportion by which seed-borne residues can be reduced by husking will be seed-specific.

Table 2. RUD (Residues per unit 1.0 lb/acre application) calculated from MRID 44452608

Item	Actual application rate (lb/acre)			
	0.35	0.18	0.0355	0.01
seed heads	78 ppm	63 ppm	49 ppm	38 ppm
seeds	71 ppm	48 ppm	40 ppm	38 ppm

Table 3. RUD (Residues per unit 1.0 lb/acre application) calculated from MRID 44464201

Item	Actual application rate (lb/acre)	
	0.35	0.20
cotton leaves	173 ppm	229 ppm
larvae (plant)	7.1 ppm	6.4 ppm
moths	10.5 ppm	21.2 ppm

D. Given the types of wild plant fruits that may be considered to be typically consumed by birds, are the fruit and vegetable types monitored for residue by the registrant appropriate surrogates for this route of exposure? If not, is it appropriate to use seed weed head chlorfenapyr residues as surrogates for wild fruit components of the avian diet?

This answer is tempered by a lack of consideration of the size and structure of the seed heads (e.g. the volume-area relationship again). It is of concern that the measured seed head residues were no higher than concentrations found in extracted seeds. This is surprising in light of the protective cover that the seed head should be affording to the various seed types.

The Panel agreed with the Agency that large fruits are not useful surrogates. This assertion is substantiated by the amount of variability in seed concentrations between weed groups, which suggests that extrapolation to other food sources such as fruits would be fraught with uncertainty. Moreover, residues of nonsystemic compounds will be a function of volume to surface ratio of the fruit. Wildlife species at risk will be consuming small fruit and berries.

Residues in grapes, for which the registrant has registration abroad, could serve as a reasonable surrogate, although for passerine consumption, they would be rather large as well.

In general, the monitored food items are reasonable with the caveat that a few values for any given food item may not be reflective of the broad range of residues possible. The Panel finds however, that the assessment is weakened by not including a foliage-eating bird. Quail species, whether Northern Bobwhite quail, California quail, Gambel's quail or Scaled quail may consume appreciable quantities of foliage along with seeds and fruits (e.g. Campbell-Kissock et al. 1985, Southwestern Naturalist 30(4):543-553). Of course, foliage represents the highest exposure risk as a dietary item and is responsible for a number of bird kills in the incident record, even from pesticides that are considered to be less acutely toxic and less persistent than chlorfenapyr.

In the specific case of chlorfenapyr, the Panel suspects a quail scenario was not developed because of the relatively high LD50 reported for the Bobwhite quail. Also, because acute RQs are exceeded without foliage consumption and without the benefit of a safety or extrapolation factor for inter-species variation, the introduction of a scenario for a generic foliage-eating quail may have seemed like overkill. However, the fact that because the Bobwhite quail is not particularly sensitive to chlorfenapyr does not necessarily mean that another quail species or a grouse will likewise have a low sensitivity. It has been difficult to explain pesticide sensitivity on the basis of familial relationships. It would therefore be quite appropriate, scientifically, to model a foliage eater (perhaps not a true herbivore but a species that does have a moderate foliage intake such as a Scaled quail) at the HD5 of possible species' sensitivity.

3. Has EFED made appropriate use of allometric relationships and registrant-supplied information on dietary selections in establishing daily ingestion rates for food items?

Allometric relationships were used in adjusting food intake rates, and this is perfectly reasonable because it reflects real differences in wildlife species' metabolic rates and relative food consumption. The Agency should be commended for this and other improvements they have made to the risk assessment.

A further extension of allometric relationships is that a scenario could easily be developed for altricial chicks in the nest being fed contaminated food items by their parents. Food intake proportionate to body mass is at its highest in nestling birds, in part because of small body size but also because food conversion efficiency is lower. In the absence of toxicity benchmark values specific to chicks, it would be appropriate to take adult values. It is expected that chicks will be at least as sensitive as adults to the toxicant and possibly more sensitive This is expected to be an important part of the risk where there is overlap between pesticide use and the breeding season. It is unclear whether the equations used by the Agency also reflect increases in free-living metabolism encountered by a bird raising broods, although this may be partially covered because the Nagy equations were developed in part with data from breeding birds. Clearly not covered are increases in food consumption that are part of the normal life cycle of birds -- see earlier comment about hyperphagia and migratory readiness. Also, didn't ECOFRAM recommended

consideration of gorging should be considered in any avian risk assessment?

The assessment does not implicitly recognize the fact that allometry also seems to influence susceptibility to acute intoxication (Mineau et al. 1996, Reg. Toxicol. Pharmacol. 24:24-29). However, by basing the scenario on the red-winged blackbird, there is partial factoring in because this is a relatively small species. Three species are too few to get a good handle on how scaling contributes to species sensitivity for chlorfenapyr. However, the slope of 0.4 (Log weight versus Log LD50 in mg/kg) through these three points suggests that chlorfenapyr, like for the majority of pesticides tested, chlorfenapyr appears to be more toxic to small species.

One Panel member expressed concern that the measured seed head residues were no higher than concentrations found in extracted seeds. This is surprising in light of the protective cover that the seed head should be affording to the various seed types. Thus, the Panel member questioned whether calculated residue values on their own represent a substantial improvement over generic nomogram values. The Panel member also commented that it appeared the registrant's residue determination studies did not include the use of field spiked samples.

4. EFED has attempted to incorporate registrant-supplied avian census information regarding avian use of cotton fields (executive summaries Attachment 6) into the risk assessment through modification of the proportion of diet originating from a treated field versus surrounding buffer areas. EFED assumed that 100% diet from a treated field was a reasonable worst case for short-term acute effects considerations. However, the risk characterization also evaluated avian risks for a 10% proportion of diet from treated fields, along with no chlorfenapyr residues in buffer zone dietary items, as a lower limit for exposure for longer-term effects.

A. Does the SAP find these assumptions to be reasonable?

The assumption that individual birds could obtain 100% of their diet from treated fields is reasonable for short-term effects considerations in a screening level assessment. For longer exposures, the assumption is not reasonable for the average bird given that more food is likely to be available in the buffers and surrounding habitat. For chronic exposures, the census data collected by the registrant are inadequate to determine a reasonable assumption regarding proportion of the diet from treated fields. The census data indicate the proportion of time birds spent perched in or flying over fields. This does not necessarily equate to proportion of the diet from treated fields. The study by Geoffrey Hill, however, provides information that can be used to estimate proportion of time spent foraging in treated fields and in field edges. However, even percent time foraging in a certain habitat does not necessarily equate with the proportion of food taken from that habitat. Indeed, if foraging is particularly successful, a bird may spend less time in a foraging area and more time in other parts of its territory and on other activities. Also, this study is, however, limited to only one area in Louisiana. Are there other studies in the literature that have examined this issue or for other areas?

The Panel does not believe that census data should be used to estimate the proportion of total food intake originating from treated areas (or nearby areas likely to receive pesticide spray). Although not a true representation of a percentage of the diet consumed in a field, a more appropriate source of information than census data would be a radio-telemetry study such as MRID 44452616. Unfortunately, it only has adequate data for a single species, the Northern cardinal. Nevertheless, the proportion of time birds spend in the fields or in the immediate vicinity of the fields is closer to 50% of the time. This argues for a value intermediate to the 100% and 10% used by the Agency. The best way to accurately address this question is by coupling radio-telemetry to assess bird location during periods of activity and evaluation of food brought to nestlings following an activity period.

One Panel member took a somewhat more conservative position, that 100% foraging is possible for some ground nesting species with small foraging ranges and that 100% foraging should be incorporated. However, another Panel member disagreed. The 100% foraging is a worst case and the 10% value probably does not represent a lower limit of foraging success. It is more likely a reasonable median, given the foraging data presented by Dr. Hill for studies in Mississippi. Finally, one Panel member believes that the assumption that the Agency used (10% of diet obtained in treated area) is acceptable as first alternative assessment to an assumption of 100%, although it is probably a little on the low side.

Another source of information is the type of observational data on foraging time presented by Dr. Hill. This is better than census data where the methodology employed can radically alter one's knowledge of "typical" behavior and which only samples a single point in time. However, even percent time foraging in a certain habitat does not necessarily equate with the proportion of food taken from that habitat. Indeed, if foraging is particularly successful, a bird may spend less time in a foraging area and more time in other parts of its territory and on other activities.

Potentially more important to the overall assessment than the proportion of food items obtained from the field is where, in the buffer zone, the birds will be foraging and what the level of contamination will be in the buffer zone. The Agency assumes no off-field contamination which is unrealistic and underestimates risk. Intake of chlorfenapyr from edge habitats contaminated by spray drift needs to be considered (particularly for aerial applications). The models being presented to the SAP regarding development of spray drift versus distance relationships could be used to estimate residues at different distances from field edges.
Surveys of birds carried out in non-outbreak conditions when insect infestation is low may also be seriously misleading. The two unsolicited bird kills reported in cotton occurred during an insect outbreak and consisted of flocking birds probably obtaining 100% of their food in the field proper. All of these problems in assessing realistic exposure levels could be solved in large measure through the development and use of a suitable bio-marker or through more use of residues in birds or their stomach contents.

It could be argued that the scenarios have missed an important source of exposure in not considering spray solution and dew gleaned from the fields. Irrigated areas are very attractive to

wildlife in arid areas and spray droplets can offer a much needed source of water. Spray solution has been responsible for bird mortality in orchards (Chilean Dept. of Agriculture, pers. comm.) as well as in cole crops (work by the German BBA) where it can accumulate in leaf whorls. Weeds and non-target plants should be examined for their potential to physically accumulate spray solution and dew. Dermal exposure may be important. While birds exposed to 4 times the label rate survived exposure, the more important question is not whether dermal exposure is sufficient to kill birds but whether it contributes to total exposure and by how much. As reported to the SAP following questioning, the registrant has collected data on residues measured in birds that were exposed through the dermal and other routes; but, for some reason, these data have not been considered. Also, the Agency should examine the mammalian data on applicator exposure. Given that dermal absorption is usually related to K_{ow}, chlorfenapyr should be relatively well absorbed through the dermal route.

One Panel member took a somewhat more conservative position, that 100% foraging is possible for some ground nesting species with small foraging ranges, and that 100% foraging should be incorporated.

However, another Panel member disagreed. The 100% foraging is a worst case and the 10% value probably does not represent a lower limit of foraging success. It is more likely a reasonable median, given the foraging data presented by Dr. Hill for studies in Mississippi.

B. Can the SAP make recommendations about how to better make assumptions for this type of data?

Data from censussing appeared to omit birds in the middle of the cotton fields. Therefore, the usefulness of the census data is limited for this purpose. The bird use of cotton fields with irrigation may be quite different from that in fields without irrigation. Field situations seem to be variable with no single general assessment. The presence of birds at a location does not necessarily mean that the birds are eating there in proportion to their abundance at the location. Some places may be feeding sites and other sites may be used for some other purposes. There is a need for more detailed observations about what the birds are doing (foraging or not foraging). Foraging also may relate to previous sprays in the area which would influence the insect availability. If there is an insect outbreak, the use of the area may totally change as more birds could perhaps move into the fields. Therefore, field studies without insect outbreaks may yield totally different bird use patterns from field studies at the same site with an insect outbreak.

Two additional factors are critical to this analysis. First, determining the amount of diet (dose) obtained in the treated area and second, the amount of diet (dose) obtained in adjacent buffer areas. It is difficult to make these assumptions a priori. Actual site-specific field data, i.e., crop/stomach content and time spent feeding in a given area, are needed. The assumption that the Agency used (10% of diet obtained in treated area) is acceptable as a first alternative assessment to an assumption of 100%, although it is probably a little on the low side. Sensitivity analysis does provide a means to determining the need for actually obtaining site specific data. Depending

upon the chemical of interest, sensitivity analyses using assumptions of 10, 25 and 50% of the diet obtained from treated fields may be appropriate and could be used to justify requiring or not requiring additional site specific data. Additionally, the Agency could make use of registrant off-site contamination data or information generated by the Spray Drift Task Force to generate possible dietary residue scenarios for adjacent buffer zones. This is important since a major portion of the diet is obtained in the adjacent buffer zones. As part of the Agency's review it is important to remember that the label for use on cotton requires a no spray zone along the edges of the cotton fields.

C. Since the avian census data were for the number of birds observed in cotton fields versus buffer areas, are the available data adequately representative of feeding behavior on cotton fields and buffer zones to allow for more in-depth evaluations?

This issue was discussed in 4A. above. In addition, it has been found by researchers that individual birds vary enormously in the extent to which they use specific fields (e.g. research Hart and colleagues in the U.K.). The extent that individuals will forage in specific fields cannot be taken to be the same as the differential bird count in and off field. For acute exposures, values ranging from the very low to 100% are all defensible. However, the problem is for chronic exposure. Given the breadth of species potentially exposed and those known to have been killed by other cotton insecticides (see below), the Agency is essentially correct in concluding that the data submitted do not provide sufficient information on the proportion of avian diets that originate in cotton fields or nearby field edges.

5. EFED converted LC50 and reproduction NOEC endpoints from dietary concentrations to daily oral doses to facilitate more direct comparisons with dietary exposure and to account for ingestion rate differences between species as it affects actual ingested chlorfenapyr dose. EFED relied on observed body weights and the caged group feed consumption to make these conversions.

A. Is EFED's conversion approach for dietary concentration to oral dose reasonable?

The Panel agreed that oral dosages should be used. Despite the possible error in estimating food consumption, it is essential to perform this calculation and not to directly compare residue levels in wild foods with those in the lab diet as proposed by the registrant. There are however a few cautions. As birds grow they eat less per unit body mass. The sensitivity to this weight change over time is more important in a 28 day feeding trial than in a 5 day feeding trial, but the approach seems reasonable. The laboratory diet in some tests is likely much more nutritious than wild foods thus having the effect of reducing ingestion rate.

However, the Agency and the registrant should not rely on LC50s, LD50s and NOECs, or LOECs to estimate acute and chronic risks, respectively. Using LC50s or LD50s in the denominator of the acute risk quotients means that even with quotients less than one, severe risks could be occurring. Clearly, dose-response modeling should be conducted to estimate a lower

toxic effect (e.g., LD10) that could more reasonably be used as the quotient denominator. The EFED approach of using lower quotient cutoffs (e.g., 0.5) for determining whether potential for risks exists when comparing exposure to an LD50 ignores the possibility that the slope of the dose-response relationship may not be steep. A quick look at the toxicity studies provided by the registrant indicated that most studies had 6-7 treatments and that relationships were monotonic and readily apparent. Such data are amenable to regression analyses. The regression approach should also be used where possible to estimate effects doses for chronic studies as well. Suter, Chapman and many others have all clearly showed that NOECs are an inappropriate measure of toxicity because they cannot be statistically defined and LOECs are typically $\geq$20% effective.

However, other Panel members disagreed. For the reasons stated in EFED's assessment, it is more appropriate to use doses rather than dietary concentrations to estimate exposure. However, estimating doses from toxicity feeding studies can be difficult because food ingestion rate in the laboratory is variable between treatments and over time and is somewhat uncertain because of spillage and other issues (particularly for mallards). Concentration based data also facilitate direct comparison with measured residues in avian diet in the field. Admittedly, this approach does not account for body weight/size differences. Several panel members supported the concept of using dose instead of concentration, but it is not clear that it is more precise for the present risk assessment.

Another strategy would be to apply factors that account for differential consumption between the laboratory species and the modeled field species as well as a factor that corrects for the differential caloric content of the laboratory vs. wild foods. This would avoid having to deal with the estimation error in the specific studies in question.

B. Does the SAP have recommendations for additional methods to account for intra- and interspecies variability in sensitivity?

The Agency's assessment did not have an explicit problem formulation and thus ended up attempting to estimate risks for all birds species that could come in contact with treated fields. Inter-species differences in sensitivity are an issue because the Agency is trying to estimate risks to many bird species. An explicit problem formulation would narrow down the species for which toxicity data are required. This step involves consideration of pesticide properties, uses, fate and concentrations in the environment to determine which exposure routes will be the most important and of bird species geographic distributions, diets and life histories to determine which species and life stages are likely to be maximally exposed. Toxicity studies could then be targeted at these or appropriate surrogate species, selection of which may be partially size and family related. Those bird species that are sensitive and/or at highest risk of exposure become the focal points for estimating risk.

Currently, the Agency does not apply a safety factor to account for either inter- or intraspecific variation. An LOC of 0.5 is intended to provide a margin of safety and to prevent serious harm to the environment in case the risk calculation is in error. On the other hand, inter-

and intraspecific species variability are empirical facts. There are adequate data on both to allow their consideration in either deterministic or probabilistic risk assessments.

Interspecific variability

It is not reasonable to assume that, from three species tested, the most sensitive species has been found. For a deterministic assessment, it is reasonable to use benchmarks that will be protective of most species. The 95% proportion has been used by several researchers. The use of empirically determined extrapolation factors has been accepted by the ECOFRAM committee even if there are still some discussions about the best approach. The following table shows the two currently considered approaches which estimate the upper 95 proportion of toxicity by applying an empirically derived uncertainty factor to the mean LD50 for two or three of the commonly tested avian species.

Table 4. Determination of the HD_5 (LD_{50} calculated to be at the 5% tail of the distribution for birds) based on different approaches.

Species	Measured LD50 or geometric mean of several measured LD50s (mg/kg)	Estimated HD5 calculated with 50% confidence based on species-specific extrapolation factors and product-specific scaling relationship[a].	Estimated HD5 calculated with 50% confidence but based on a 'species-independant' extrapolation factor and ignoring any scaling relationship[b]	Estimated HD5 calculated with 95% confidence but based on a 'species-independant' extrapolation factor and ignoring any scaling relationship[b]
Bobwhite	34	3.9	6.0	1.0
Mallard	10	1.0	1.7	0.30
RW Blackbird	2.2	0.56	0.39	0.07
Bobwhite & Mallard	21	2.2	3.7	1.1
All three species	9.1	No factor calculated	1.6	0.58

[a] Based on the work of Baril et al. 1994 (CWS tech. report 216), Baril and Mineau 1996 (unpublished SETAC poster), Mineau et al. 1996 (Regulatory Toxicol & Pharmacol. 24:24-29), Mineau et al. In prep.

[b] Based on the work of Luttik and Aldenberg 1997 (Environm. Toxicol. And Chem. 16(9):1785-1788).

Based on the work of Baril, Mineau and others, the best estimation of the HD5 would be the value of 0.56 extrapolated from the Red-winged blackbird. This is because this species has the extrapolation factor with the smallest measurement error -- the species is the most consistent relative to computed HD5 values. Based on Luttik and Aldenberg, the HD5 would lie between 0.58 and 1.6 depending on the degree of tolerated error B the median estimate versus a 95% confidence level. These values make the most use of available data. A benchmark acute toxicity value in that range is appropriate and scientifically defensible. The use of the lowest of three species tested is not.

Intra-specific variation

All acute benchmarks are based on 50% of the test population being killed. This is seldom an acceptable kill level. It is recommended that the probit relationship of the acute studies be used to specify an acceptable level of kill for the deterministic approach. For a probabilistic approach, the entire relationship can be used so that a probability of kill can be computed from any exposure. This procedure was accepted by ECOFRAM and demonstrated in one of their case studies.

Yet another factor not taken into account is the difference in the toxicity of the technical product from that of the formulation. Liquid formulations as a rule tend to have higher toxicity than the technical active ingredient. This is known in the case of chlorfenapyr. At the meeting, the registrant provided formulation data for the Bobwhite although it should be ascertained whether these data were expressed as mg a.i. or of formulation. In the absence of formulation toxicity data in birds, the toxicity differential in the rat could be used to correct the avian acute toxicity values used as benchmark.

6. EFED recognizes the limited ability of 120-day avian reproduction effects protocol to elucidate reproduction and sublethal effects associated with shorter exposure periods. However, EFED's risk assessment suggests that dietary exposure levels of chlorfenapyr exceed the NOEC established for the existing reproduction study for multiple weeks. In addition, maternal effects (weight reductions) were observed following the first two weeks of exposure of test animals to chlorfenapyr in the reproduction study.

A. Does the SAP agree with EFED's conclusions with regard to reproduction effects in exposed individual birds?

Effects will be seen in reproduction. It is meaningful that maternal effects were seen at two weeks of exposure. If one considers the time course of decreased egg production, one can see that there is also a suggestion it is operating as soon as laying has stabilized. A simple plot of egg production in the mallard, although not very rigorous statistically, does provide an indication of an early effect on laying (Figure 1). Because the current avian reproduction study suffers from low statistical power, egg production in the 1.5 ppm group is not significantly different from control. Figure 1 suggests that there may indeed be lowered egg production at that level of dose. It has been argued that effects on egg production are largely a reflection of maternal toxicity and

this may indeed be the case here given effects seen on adult body weight and food consumption at 1.5 mg/kg.

Of possibly greater interest is the equivalent Bobwhite study listed as supplemental by the Agency. There should be a closer examination of that study. Although no effects were seen on either adult condition, food consumption, or egg production, there were clear effects on the proportion of viable and 17 day embryos/set, hatchlings/set and survivors/hatched. From a purely reproductive point of view, this is a more serious finding because it suggests that a sufficient amount of chlorfenapyr is being passed into the egg to affect the development and eventual survival of the developing embryo. Figure 2 plots the percentage of 14 day survivors over the total number of eggs set as the overall integrated measure of embryonic fate. Again, this is not a statistically rigorous analysis as much as a useful visualization tool. Again, the effect appears to begin very early in the breeding period, as soon as the number of eggs set is high enough to provide a reliable estimate of chick survival (the first few points are based on very small samples of eggs). An early effect in the study would not be surprising if indeed the problem is caused by chlorfenapyr transfer into the egg. After many weeks on treated feed, the parents have come to equilibrium with the toxicant concentration in their feed. As far as extrapolating these results to wild birds, the relevant question is whether female birds are being exposed to chlorfenapyr residues during egg maturation and yolk deposition (assuming such a relatively lipophilic compound is deposited in the yolk). A chicken metabolism study may help to interpret these findings.

B. Can the SAP provide guidance on potential ways for accounting for dose response characteristics for reproductive effects?

The study as currently designed makes dose-response extrapolations nearly impossible. First, there are too few dose levels. Also, because of the relatively low power of the existing test, there is the very real problem of choosing whether to include in the dose-response, an apparent decline in reproductive output in the absence of statistical confidence. Egg production in the mallard (Figure 1) is a case in point. Even if it were possible to estimate an effect magnitude based on a crude dose-response extrapolation, the risk assessment would not be that much improved. This is because the questions of species differences and species sensitivity represent a far greater source of uncertainty. The two species tested showed a difference, not only in their NOEC but also in the type of effect that was first seen. Based on a large review of such avian reproduction studies, it has been concluded (Mineau et al. 1994, Ecotox. and Environ. Safety 29:304-329) that such inter-species differences are the norm.

In formulating a higher tier assessment, EFED should ask whether the lowest chronic NOEL of those established for two species will be a benchmark sufficiently protective of all wild bird species likely to be exposed to chlorfenapyr. There is no reason, in the absence of better information, that inter-species extrapolation factors calculated from acute toxicity data should not also be applied to chronic toxicity endpoints. The range of sensitivities to chronic toxicity should be at least as great as the range in acute responses. This is more scientifically credible than to

suggest that the mallard is (by chance) the most reproductively sensitive bird species to chlorfenapyr. The registrant could counter that the current avian reproduction tests are worst case situations because of the prolonged exposure period. However, as discussed earlier, the long exposure period may not be required to produce the effects that were seen if the birds quickly come to equilibrium with ingested residues. Also, the current reproduction test, by removing most of the parental involvement in breeding (except for copulation and laying) is a very truncated and unsatisfactory depiction of the environment. The only scientifically credible way of reducing uncertainty is to carry out extensive studies of reproduction in the wild.

If a sufficient number of treatments are available, regression analyses with a log-log model and underlying Poisson error distribution (for number of young) or a normal distribution (for biomass or growth rate) can be conducted. If possible, the endpoint used in the modeling should account for reductions in reproduction due to reduced mating success, numbers of embryos, embryo mortality, juvenile mortality, and juvenile weight. Biomass of young produced per mated female could account for all of these toxic effects. The reproduction studies provided by American Cyanamid would need four or more treatment levels to support dose-response modeling.

7. EFED has based the risk assessment on parent chlorfenapyr alone.

A. Do the toxicity data for birds, mammals and aquatic organisms suggest that degradates should also be considered in the assessment of risks to wildlife and aquatic organisms?

The data in the Agency's assessment document suggest that at least three metabolites should be considered/investigated, AC 303268 (proposed toxic transformation product) and AC 312094 (field metabolite identified as >10%). Evaluation of AC 303268 for birds, fish and mammals and AC 312094 for birds may be appropriate. Additionally, further evaluation of AC 357806 for aquatic organisms should be considered further considering that it is an aquatic photolytic degradate that appears to be highly toxic to aquatic species. Acute screening level studies would be sufficient for a further screening assessment. Since it is recognized that chlorfenapyr functions as a direct result of being transformed to a metabolite (AC 303268), this transformation process and stability of the metabolite in the environment and in organisms needs further assessment. The Panel also commented that data were presented at the meeting that indicated that the metabolite AC 312094 may be relatively non-toxic. These data need to be reviewed and may be sufficient to negate the need for further testing with this metabolite.

It also would be appropriate to consider whether accumulation of some of the metabolites could result in tainting of wild food items. One may be concerned about scenarios of fish-eating birds ingesting high residue levels from prey but the issue is also relevant from a human exposure point of view.

One panel member disagreed and stated that the metabolites were sufficiently understood for registration decisions to be based only on the parent compound.

B. Are there sufficient data to allow for the consideration of degradates with the same level of confidence as the parent compound?

Based on the Panel responses to question 7A and question 7C, several Panel members concluded that these data are not sufficient to allow for the consideration of degradates with the same level of confidence as the parent compound. At present the potential for synergistic, antagonistic, or additive effects from the parent and/or any of the metabolites is unknown.

C. Can the SAP suggest how these can be quantitatively incorporated into the assessment, using the existing residue and fate information?

There are fewer or no toxicity and residues data for the degradates than exists for the parent compound. Without toxicity data there is no way to realistically incorporate these data into a risk assessment. If the toxic degradate is truly minor in its occurrence, modeling the degradates would have limited value. The data needed that can be used to incorporate degradates into the risk assessment should be generated if the toxicities and occurrence of these degradates are sufficient to warrant concern. This additional information may be justified for 303268, 312094, and the photolytic metabolite 357806. Modeling will be inaccurate unless more is known about the toxicity of the breakdown products--especially the toxic forms. If it is a concern because of changes over time, particularly in soil, some mixed tests (parent material and degradate) could be conducted, but the problem now is that we do not know how these components interact together. Is there additivity, synergism, or additivity, etc.? More data are needed to address this issue.

8. Does the SAP have comments or concerns regarding the use of the MUSCRAT model for evaluating aquatic exposures for pesticides used on crops within widely distributed cultivation?

MUSCRAT is a model that incorporates PRISM and EXAMS. It is not a probabilistic model, because it incorporates point values and can be effectively used to allocate resources to geographic areas expected to be a problem. On the other hand, it also can be used to describe areas which may be expected to not be or lead to problems. However, it does not describe a cumulative frequency of potential exposures, toxicity of species, or--more critically-- the joint distributions. The Panel strongly recommends that MUSCRAT be used to identify areas of problems (i.e. problem formulation) and then used to incorporate species response distributions, overlain by species use curves (as Dr. Hill noted). Then we can arrive at an estimate of which species would be expected to be at risk a given proportion of the time for a given area. Much better planning would occur and it would better give limits of use, label rates, and expected problems. Unfortunately, no field validation data sets were provided for the MUSCRAT model. Therefore, in addition to uncertainties about the inputs, the Panel is also uncertain about model structure. In the end, lack of validation reduces the confidence in exposure estimates produced by the MUSCRAT model.

9. Are the available toxicity data sufficient in scope to enable EFED to succinctly

characterize the risk to untested terrestrial and aquatic phyla?

This answer assumes that the question relates to the parent compound. Relative to terrestrial phyla, few organisms have been evaluated: two species of mammals, rats and mice; three species of birds (red winged blackbirds, mallard duck, and Bobwhite quail); one species of earthworm; and one species of honey bee. These data are minimal within any single phyla, but the use of seven species across these phyla begins to build a minimal data set for a broader terrestrial risk assessment. Because the birds appear to be the most sensitive group of terrestrial organisms, this raises questions as to whether or not species sensitivity is adequately characterized. It is recommended that additional acute toxicity studies be performed with species known to inhabit cotton fields.

Relative to aquatic phyla, species sensitivity of freshwater organisms is reasonably well evaluated and these data are consistent, i.e., daphnids are highly sensitive and fish are less sensitive and the acute to chronic ratios (ACRs) are consistent from species to species (ACR values are generally less than 2; indicating less of a concern for long term chronic toxicity as compared to acute toxicity). However, it is pointed out that the LOEC to LC50 values are so similar that some investigation may be warranted. Is this due to the binding of chlorfenapyr to food in the chronic studies or does the lack of difference between acute and chronic studies simply indicate that chronic effects are primarily the result of longer term exposure resulting in greater survival effects? A simple acute test with daphnids conducted with and without food would assist in answering this question. If chronic toxicity is reduced due to binding to solids, this has implications for interpretation of chronic data under field conditions. This would suggest that laboratory studies would tend to overestimate the potential for chronic toxicity in all but the cleanest surface waters (i.e., low suspended solids and low dissolved organic carbon).

Marine phyla are insufficiently characterized. The Agency has indicated that acceptable data consist of mysid shrimp and sheepshead minnow acute tests and a mysid shrimp chronic toxicity study. These data are too limited for several reasons. Principally, the marine test results indicate that marine species appear to be more sensitive than freshwater organisms, at least for the mysid shrimp and the marine amphipod. It is somewhat unusual for marine organisms to be consistently more sensitive than freshwater organisms. A basic understanding of why this is occurring was not discussed. Secondly, the acute to chronic ratio for the mysid shrimp was approximately 10 as compared to <2 for the freshwater species. In terms of the risk assessment, it is the marine toxicity data that result in hazard quotients that exceed 1.0. It is therefore important to understand why these differences exist (freshwater/saltwater chemistry differences). Additionally, it was pointed out at the review that the estimates of surface water concentrations for chlorfenapyr are most likely overestimated by the use of the MUSCRAT model to estimate water concentrations in a marine environment.

Residue data for sediments and tissues from benthic organisms are needed to assess the potential for trophic transfer. These type of data are also needed for soil dwelling invertebrates. Chlorfenapyr exposure and potential accumulation in these organisms is poorly defined. Since

birds are sensitive to chlorfenapyr, and since several species of birds are insectivores (aquatic or terrestrial), it is important to assess the potential for trophic transfer to birds by terrestrial and freshwater invertebrates.

A. Does EFED need to incorporate interspecies extrapolation uncertainty in establishing toxicity thresholds? If so, can the SAP recommend appropriate methods for such extrapolation in avian, mammalian, amphibian, reptile, fish and aquatic invertebrate endpoints.

Terrestrial: More LD50 data will help, although an extremely low value exists for red-winged blackbirds which is a very sensitive species, there may undoubtedly be several species that are even more sensitive. Moreover, to conduct probabilistic risk assessments, better estimates of toxicological response distributions are needed. Extrapolation factors have been developed to estimate response distributions for birds (see studies by Mineau and co-workers for example). Such factors or distributions could be applied to the existing data to account for risks to untested biota. This approach is most robust for cholinergic compounds and more confidence is obtained with acute data from at least four avian species.

Evaluation of risks to non-avian species is best designed following a refined and explicit problem formulation. Once the species at highest risk of exposure have been identified (based on geographic distributions relative to treated cotton fields, feeding strategies, life-history characteristics, etc), there should be a limited number of species that require detailed risk characterization. Toxicity studies could then be targeted at these species or closely related surrogates. Existing data are unlikely to provide meaningful estimates of toxicity thresholds for amphibians and reptiles that account for interspecies differences in sensitivity.

Aquatic: Much more data are needed on the role of sediment-dwelling organisms. If the answer to the geographic distribution of sites with potential to move into water is modeled (estimated), a region of potential difficulties can be estimated. Overlain on this could be a distribution of terrestrial or aquatic species presence (ideally with a distribution of laboratory-generated sensitivities to the compound). Finally, given the persistence of the compound, it is critical to see how much chlorfenapyr moves from the sediments into organisms that consume soil or sediments. Also, for planktonic organisms, it may be critical in waterbodies that have high loadings of suspended sediments, as they may be ingested by other organisms. Some factor of lipid content in biota would also be recommended in any extrapolation of chlorfenapyr accumulation.

However, as discussed in question 5B, inter- and intraspecific extrapolation factors are warranted and scientifically defensible. Extrapolation between large phyla (e.g. bird or fish to amphibian) are much more fraught with error. Nevertheless, it has been proposed that early life stage data for fish could be used to model amphibians. The number and types of species for which extrapolation is needed may be limited by modeling the geographic distribution of sites with characteristics that will allow chlorfenapyr to move into water. Overlain on this could be a

distribution of terrestrial or aquatic species presence (ideally with a distribution of laboratory-generated sensitivities to the compound). This will identify regions/habitats of concern and extrapolations can be confined to species inhabiting these areas.

B. Are additional toxicity tests warranted in this case?

Additional tests appear to be warranted as described in answer to question 9A. Amphibians are an obvious concern, given their world wide decline. Given that chlorfenapyr is the first of a new class of insecticides, a limited amount of data on selected phyla such as amphibians and possibly reptiles also should be mandatory. Recognition of the pesticide's mode of action may help in selecting species B it would be advisable for instance to consider species that have a high energetic demand in one part or another of their life cycle.

However, before testing, potential exposure and toxicity risks for amphibian and reptiles should be addressed with an explicit problem formulation that will identify which if any genera are at high risk of exposure. Species that are at risk, that have not been tested (and for which tests on close surrogates are not available) may then require additional toxicity tests to reduce uncertainties.

10. EFED is seeking guidance of the assessment of risks to sediment-dwelling organisms. The MUSCRAT model provided the Agency with dry-weight sediment concentrations, which were used to compare with the data from acute sediment toxicity tests.

A. Was this approach appropriate?

Estimation of sediment dry weight concentrations is the appropriate place to begin the exposure assessment; however this does not provide an adequate basis for a thorough or screening level sediment risk assessment. Unfortunately, sediment toxicity data submitted by the registrant did not report organic and moisture content of the test sediments. Without this information, it is difficult to determine whether the bioavailabilities of chlorfenapyr in field and test sediments were comparable.

Additional details and recommendations are provided in response to question 10B below. Also, see response to question 8 above regarding the limitations of MUSCRAT input parameters.

B. Does SAP have specific recommendations for improvement of the method?

The following recommendations are provided to the Agency for conducting sediment assessments of non-ionic organic compounds.

1. There is a need to adequately characterize the sensitivity of freshwater and marine benthic organisms. This can be done by performing a series of acute toxicity studies with benthic organisms. Standard methodologies exist for several freshwater and marine acute tests. This

need arises from the fact that chlorfenapyr has a fairly large sediment partition coefficient and will rapidly partition to sediments from water.

2. Relative to chlorfenapyr, there is an approximate factor of 100 difference between the marine and freshwater amphipod data. This is even larger than the difference observed for water column organisms. Part of this variability could come from the fact that a low organic carbon (OC) sediment may have been used in the test (personal communication with registrant) Assuming that the marine and freshwater studies used 0.6 and 6% OC sediments, this would account for a factor of ten difference between the freshwater and marine amphipod test results. The uncertainty in the sensitivity of the marine organisms must be verified through testing with additional species, if less uncertainty in the risk assessment is desired.

3. The results of both acute and chronic testing need to be reported as mg/Kg OC, i.e., the data need to be normalized to organic carbon content. This allows for extrapolation to sediments with different OC content than those used in the toxicity study.

4. Interstitial water concentrations should be calculated and measured in all of the sediment bioassays. This allows for an assessment of the partitioning of chlorfenapyr to sediments/water and facilitates the interpretation of the data and extrapolation of the data to untested sediments.

In addition, the Agency should incorporate probabilistic techniques to describe situations for individual plots within watersheds. The present approach to delimit watersheds is going on in other Program Offices of the EPA. The use of a watershed, the distribution of bird species using a watershed (seasonally), overlapped by distributions of compound application, and given a series of species sensitivities, should be used to estimate the percentile distribution of species potentially affected by application of this material. Evaluation of these distributions will require validation studies for MUSCRAT or evaluation of modeling studies in the literature reviewed.

Assisting EFED In Taking Steps Toward Probabilistic Risk Assessment With Chlorfenapyr

1. In progressing from deterministic to probabilistic risk assessment techniques for terrestrial organisms, EFED is concerned with accounting for intra- and inter-species variability in reproduction toxicity testing. Can the SAP recommend any approach for accounting for these areas of uncertainty in a probabilistic assessment?

This question is partially answered in response to question 9, above. Intra-species variability could be partially accounted for by using concentration- or dose-response models. If multiple test results are available for the same species, then meta analysis could be used to combine data and include additional sources of uncertainty in the concentrations-response relationship (e.g., contributions to toxicity test variability arising from different laboratories). Using this approach, an entire species distribution can be entered with a product-specific mean and a standard deviation calculated from a historical database of pesticides. The probit slope, when available, can also be used to convert values from a probability of RQ exceedance to a

probability of impact.

The approach currently used for the analysis of reproductive toxicity data are not really a deterministic analysis; statistical methods are used in the evaluation of the data. The decisions derived from these data are categorized into yes/no answers through the use of NOEC's as the basis for inference. This alone can contribute greatly to the inter-species variation in response; different studies may have different exposures and, since the NOEC must be at an experimental exposure, the design can actually contribute to the uncertainty. A better approach would be the use of a regression method utilizing all of the experimental groups and estimating a probability of response. Assuming this regression method is used, uncertainty in the estimates could be addressed through either parametric or nonparametric resampling methods. For toxicity endpoints, it is generally preferred to use a nonparametric resampling scheme (bootstrapping) by resampling with replacement from the original data basically replicating the experiment numerous times to assess variation. Uncertainty in the choice of the biological model is difficult to assess without testing multiple species; given data from multiple species, one could either use a mixing technique or simply examine the various responses for differences. Evaluating uncertainty in the choice of the model for analysis can be done through a sensitivity analysis of multiple mathematical constructs. Of course, mechanistic understanding and mechanistic studies could be used to derive biologically-based mathematical models which would allow a careful comparison across species.

2. Given the geographic, temporal, and measurement limitations of the available chlorfenapyr residue data in insects, does the SAP believe that a probabilistic risk assessment using these data should incorporate an expression of extrapolation uncertainty for the data's application to non-tested sites of potential chlorfenapyr use? If yes, can the SAP suggest appropriate methods for capturing this uncertainty in the probabilistic assessment?

As discussed above, an explicit and refined problem formulation may limit the necessity of having to extrapolate insect residues data to untested fields. If models are available to estimate insect residues in pesticide-treated fields (preferably ones that account for degradation, transport, site and climatic conditions, etc.), then such models could be calibrated to the existing data and subsequently applied to non-tested fields. Such models should treat major input variables as distributions. In the absence of a modeling approach, monitoring studies should be carried out in other fields with widely different geological, biological, site and climatic conditions. The results from these studies should at least allow us to bound estimates of chlorfenapyr residue levels in insects in treated fields.

However, one Panel member stated that it is highly unlikely that further refinement of the risk analysis including a move to a (credible) probabilistic assessment will change substantially the current assessment. This is because the Agency, in it's refinement of the risk assessment, has already moved beyond a worst case to what is arguably an 'average' solution. Given the substantial exceedance of RQs under this average scenario, a probabilistic assessment is likely to

return a similar answer, albeit with a distribution attached. In the opinion of this Panel member, to move the risk assessment further, in my opinion, will require data as intensive as the type of data generated in the course of a full blown field study. This will entail looking at a large number of birds and species including breeding individuals. The approach used in MRID 44452616 (the radio-telemetry study) is undoubtedly a good start. It will need to be combined with food habits data, better residue information, or the use of a biomarker to measure exposure etc.

3. Can the SAP provide guidance on capturing uncertainty in extrapolating from sampled fields to larger areas of chlorfenapyr treatment? Can the SAP recommend other data sets from the literature that would enhance a chemical-specific probabilistic risk assessment?

It is not clear that a full probabilistic assessment is warranted from these data. Given the concerns expressed under question 2B, it is not clear these data are of sufficient scientific quality to support a more detailed analysis. If, however, it is determined that these data are sufficient for screening, the paucity of these data will make it very difficult to evaluate whether the variability associated with a full probabalistic use of these data is truly justified by the data or due solely to assumptions chosen in the modeling. One initial assessment would be to focus on enumeration of the variability by choosing all possible combinations of these data rather than a Monte Carlo analysis. Eventually, projection to other sites will require a model relating exposure in the field to insect residue levels. These models also may not be well-supported by these data. Care should be used in evaluating the quality of the estimates of variation resulting from any models fit to these data; does the variability differ dramatically given the choice of the model? Given a model form, resampling of the data or simple Monte Carlo analysis at predicted points could be done using standard methods.

Two basic approaches could be considered to enable extrapolation to non-sampled fields. A systematic sampling program that covers a variety of cotton-growing regions could be conducted. If the sampling program is set up to be representative of the range of application practices, site conditions, climatic conditions, etc,, then distributions for diet, residue levels in soil, and prey items, etc. could be developed. Such a sampling program should consider edge habitat within the spray drift zone. This type of sampling program would be quite costly. If costs are prohibitive, then EPA should prepare an explicit problem formulation that identifies the application practices and site conditions that create the highest risks of exposure and focus the probabilistic risk assessment on only these areas. The sampling program could then be targeted to the high exposure areas of concern. The second approach is to develop or use a model that accounts for application practices and site conditions to estimate prey and soil residue levels (both in the field and in the edge habitat). The model could be calibrated to existing data and then run for other areas of interest. Major inputs to the model should be treated as distributions. There are many useful databases available on the internet to gather information on regional climatic variables, geography, geology, soil types, flow rates for streams, and other variables that would be needed for a probabilistic MUSCRAT and terrestrial exposure models. These databases often have long records and can be used to develop distributions that take account of temporal variability. Combining stations can be done to consider spatial variability. The Wildlife Exposure

Factors Handbook useful information that can be used to develop distributions for dietary composition, ingestion rates, gross energies of prey items, assimilation efficiencies, etc.

4. EFED is concerned with the uncertainty associated with using avian census data (number of observed birds in and out of fields) to predict dietary proportions obtained from treated and untreated areas.

A. Does the SAP have suggestions for ways to reduce such uncertainty?

As discussed in detail earlier, the Panel agrees that avian census data are not very useful for determining bird foraging patterns. The detailed observational data collected by Geoffrey Hill and co-workers is much preferred. Perhaps similar sorts of studies could be conducted for areas identified to be at high risk of exposure during problem formulation. Even then, the study may not be useful unless carried out during a pest outbreak situation. (This may be the pest being controlled or another invertebrate species.) The study will offer data that are applicable to the specific species, site, and year of the study. In order to provide a probabilistic assessment with a distribution of probable values, there will be a need to generate such data sets under different time, climatic, and geographical conditions. If further field data are not available or are not gathered, the literature may contain detailed observational studies for crops in the cotton belt area.

B. Should EFED focus on mean values for censussed regions or consider the spectrum of species variability in observations in the data?

The spectrum (or some representative portion) of birds that forage in cotton fields (or fields in which chlorfenapyr registration is sought) needs to be considered if there is a hope of performing a meaningful probabalistic risk assessment.

The following table offers a short summary of kills due to monocrotophos and other insecticides in cotton. This should enhance the survey data and help zero in on relevant species and guilds that should be covered in any insecticide risk assessment in cotton. If nothing else, it reinforces the fact that a large number of species are exposed to cotton insecticides in the course of insecticide treatments. Therefore, the risk assessment must consider species variability and species poorly captured by a field study. An example is flocking birds whose presence on treated fields is highly stochastic. Yet, if chlorfenapyr does impact migrating birds as feared, this may be quite relevant to the risk case.

Table 5 . Kills of birds associated with insecticide use in cotton. X indicates that the species was found dead or moribund. There is no attempt at quantification.

Species affected	California Jul.-Sept. 1965-1968 Azodrin	Arizona Sept.1967 Azodrin	Alabama 1970 Azodrin	Texas June 1978 parathion incident	Texas June 1993 disulfoton incident
California/Gambel's quail	X				
Red-winged blackbird	X		X		
Scrub jay	X				
Goldfinch (sp?)	X				
Sparrow (sp.?)	X	X			
Eurasian sparrow	X				
Ring-necked pheasant	X				
doves (sp.?)	X				
Mourning dove	X	X			
Ground dove	X	X			
Horned lark	X				
Meadowlark	X				
Kildeer	X				
Northern mockingbird	X		X		
Virginia rail	X				
Red-tailed hawk	X				
Burrowing owl	X				
Northern pipit	X				
Vesper sparrow		X			
Chipping sparrow		X			
Orange-crowned warbler		X			
Western tanager		X			
Spotted sandpiper		X			
Northern harrier		X			
Northern Bobwhite			X		
Northern cardinal			X		
Brown trasher			X		
Rufous-sided towhee			X		
Laughing gull				X	
Swainson's hawks					X

Sources: Bischoff 1965 (Unpublished Report M-81-67), California Dept. of Fish and Game 1967 (Unpublished Report M-14-68), 1968, Henderson and Hillen 1967 (Unpublished report, Fishery and Wildlife Services), Mineau et al. 1999 (J. Rapt. Res. 33(1):1-37), EPA pers. comm.

5. All previous deterministic approaches for avian risk assessments tend to focus on local effects (treated fields at the screening levels followed by assessment of treated fields and surrounding buffer areas at more data-intensive levels of assessment). Given the available data for chlorfenapyr, at what geographical scales should EFED concentrate a probabilistic assessment? How should population concerns over larger scales be addressed?

The Panel's agreed that initial assessments should begin in worst-case single fields and move to larger areas if risks in single fields are significant. The best approach for the initial probabilistic assessment is at the scale where the field data have been collected. This ensures that the best available site-specific data possible are being utilized. Given the avian data available, a probabilistic assessment would need to focus first at the local scale and at the species level of organization. The reason for this is that the data collected to date for exposure (avian dietary residue data/field dissipation data) and bird usage have been collected at the local geographical scale.

Several approaches could be used to address the issue of how population concerns over larger scales should be performed. One approach would be to collect appropriate avian exposure data at the scale of interest, i.e., watershed scale or scale occupied by bird population(s) of interest (i.e., let the bird population dictate the scale). This approach is data intensive and costly. Alternatively, existing local scale exposure data can be used in fate models (like MUSCRAT) to generate exposure data across a broader scale of interest (assumes some site-specific data on soil type, rate of application, number of applications, etc., is known). In conjunction with the expanded scale, exposure data assumptions have to be made about bird usage (percentage of diet) of treated and buffer areas, and changes in dietary composition across the expanded scale. Meta population models that explicitly account for species demographics and movements of individuals between spatially distinct sub-populations could be used to estimate risks to populations at say the regional scale. Applied Biomathematics and others have developed software for meta populations that treat inputs as distributions (e.g., RAMAS metapop). Developing distributions for demographic variables, however, is not easy and typically available information is limited. The probabilistic assessment could evaluate many of the input parameters to the assessment model to determine the sensitivity of each of these parameters. It is likely that better tissue residue levels could provide better assessments of chronic or acute toxicity. Regional monitoring of tissue residues in birds following chlorfenapyr spraying could be carried out to determine the proportions of birds that could experience adverse effects.

In summary, the exposure assessment at scales larger than the local scale must account for differences in residue concentrations and exposure due to site-specific differences and differences in bird usage and bird (feeding) behavior.

Although not the focus of this meeting, it is worth noting that American Cyanamid's conclusion that risks to bird reproduction are minimal is not justified because of serious flaws in their probabilistic assessment. The largest flaw was their use of a distribution in the exposure equation to estimate the probability that a field will be treated in a given year. Because only a

small proportion of cotton fields are sprayed in any given year, this has the effect of reducing the exposure estimates by an order of magnitude or more. This would be the correct approach if we wanted to estimate risks to bird individuals near all cotton fields. However, what we really are trying to do is estimate risks to birds near fields treated with chlorfenapyr. Assessing effects at the population level for larger geographic scales requires the use of appropriate population models.

6. Probabilistic assessments for avian effects may involve assessing exposure and effects for generic birds (no species consideration), focal species levels, or for all species associated with the particular agro-environment treated with the pesticide. Can SAP provide guidance as to the level of avian species resolution that would be appropriate for assessing avian reproduction risks for chlorfenapyr use on cotton?

The focus of the assessment, deterministic or probabilistic, should be on bird species that frequently forage in or around cotton fields, particularly those occurring in areas where chlorfenapyr levels are likely to be highest. A well thought out problem formulation exercise is essential. Also the Agency should adopt more generic models representative of guilds -- e.g. small insectivores -- and then see through sensitivity analysis whether specific conditions (types of food resources, etc.) are likely to change an assessment. This is different from the approach adopted by both the Agency and the registrant which assumes bird feeding habits are static in time and place.

General Comments

Following is a compilation of general comments provided by the panel members. These additional comments address the general subject of the risk assessment or address specific points that were not raised in the questions presented to the Scientific Advisory Panel.

The history of using insecticides which are toxic, persistent, and have the potential to bioaccumulate indicates that chemicals with these properties have the highest potential to cause ecological effects. Chlorfenapyr is toxic to several species (birds and aquatic organisms), it appears to be persistent, and its bioaccumulation potential has not been completely characterized. The potential for this chemical to be transported by atmospheric means has not been ruled out. Additionally, the toxicity and bioaccumulation potential of the metabolites of chlorfenapyr are not well characterized. The physico-chemical and fate properties of chlorfenapyr, as they are known to date, indicate that questions persist regarding the environmental safety use of this insecticide. To date, little or no data are available to assess residues in aquatic systems and therefore it is difficult to assess potential for trophic transfer. Additionally, data are lacking on residues in birds and bird eggs. It is recommended that before registration, the above larger-scale issues as well as specific questions dealing with potential risk to birds following application to cotton fields need to be answered.

There is a need for a biomarker and/or more residue data with birds and their eggs, especially for comparing laboratory studies with field situations. Cytochrome-c-oxidase in heart, brain, spinal chord, kidney or liver may be suitable. Also, little or no information on reptiles and amphibians is available for the southern US. Birds exposed to chlorfenapyr may not die immediately (it will take several days), and a bird that is sick always tries to find a place to hide which will make it next to impossible to find in the field situation. Using marked individuals (the Georgia study) may provide a means of recognizing missing individuals, but the species chosen in Georgia were not species that spend the most time in the cotton fields according to the information provided.

Two totally different conclusions have been reached by the two parties and a limited field study is needed that picks the proper species or group of species in the proper field situations. However, some bird residues and egg residues are needed from the laboratory studies to compare with the field findings. EPA and American Cyanamid need to go back to the field to more thoroughly evaluate this new chemical and to obtain some missing data to aid in interpreting the available data. This approach will require a thorough problem formulation step. Types of studies that may be warranted following such a formulation are 1) nest box studies to evaluate hatchability, egg residues, bird residues, and survival and/or 2) evaluating birds in natural nests to more thoroughly evaluate potentially higher dermal doses.

One panel member has had the opportunity to review a large number of risk assessments carried out by the Agency over the years. The assessment for chlorfenapyr stands out among all others in terms of its attempt to be as balanced and as scientifically defensible as possible. This is

still a deterministic assessment and included are suggestions on how it could be improved, but it should be noted at the outset that the Agency is on the right track and should be commended for it.

The Agency should place more emphasis on a review of the radio-tagging field study (MRID 44452616). The registrant places a lot of weight on this study in arguing that its 'weight of evidence' case demonstrates the Agency's RQ approach is in error. The Agency must consider the study in its assessment even if it the study is not compelling enough to dispel the presumption of high risk. The fact is that the study is a step in the right direction. By necessity, the Panel members' review of this study was far from thorough. One panel member would like to offer the following observations:

1. Only one species (the Northern Cardinal) was covered with sufficient intensity in the study. In light of Dr. Hill's evidence presented to the SAP, this choice is perhaps unfortunate because this species appears to spend less time foraging in cotton fields than others.

2. Mortality detected in control fields is very difficult to interpret in light of the other pesticide treatments being carried out.

3. Dr. Hill's assignment of birds to various 'outcomes' needs to be reviewed carefully: For example, one bird (freq. 150.008) on a treatment field remained 'stationary' for a period of 10 days beginning on treatment day and then 'disappeared' (possibly scavenged), but this was not counted as a mortality but rather as an unknown. Unfortunately, only a single day of activity, pre-spray, is shown which makes it difficult to ascertain whether birds present, pre-spray, had established a consistent pattern of field use.

A discussion on the value of Section 18 field monitoring exercises is also warranted because, once again, the registrant places much weight on these 'data'. These data for one such program were submitted to the SAP for review. The monitoring program in Mississippi claims that about 70 acres of edge around 33 treated fields were surveyed. Not a single bird carcass was found -- which by itself is surprising given that researchers occasionally find carcasses in control fields -- and that several fields were being treated with organophosphorus insecticides as well. First of all, the search intensity in all of the fields was very low. This level of searching intensity seldom results in many carcasses being found. One notable exception that comes to mind is the organophosphorus insecticide monocrotophos (as shown in the table of kills presented later in the document). There is an important difference between chlorfenapyr and other highly toxic insecticides: speed of kill and a high probability of delayed effects (whether reproductive or long-term survival) with chlorfenapyr. In the Mississippi exercise, most fields were searched on the day after spraying. It should be noted that in MRID 44452613, the median time to death for Red-winged blackbirds exposed to 10 ppm in feed (the dose level closest to the LC50 of 11.3 ppm) was approximately 80 hours. The first mortality (one of 10 birds) occurred 54 hours after the introduction of the treated diet. Even at the highest dose level (19.5 ppm), the first mortality did not take place until approximately 30 hours and the median time to death was over 50 hours.

This invalidates the bulk of the surveys carried out in Mississippi and makes it very unlikely that any avian mortalities following chlorfenapyr will actually be located on the treated cotton field.

One panel member believes it important to consider what other chemicals are currently used to control pests targeted by chlorfenapyr and what are the relative risks to birds from these chemicals? This question frames the environmental context of the ongoing risk assessment.