Summary of Chlorfenapyr Risk Benefit Assessment

Introduction. The purpose of human health and ecological risk assessments and the assessment of the benefits of pesticide use is to enable EPA risk managers to make informed regulatory decisions regarding registration of pesticides. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Sec. 3.C.(5) provides that "the Administrator shall register a pesticide if the administrator determines that, [among other things]... it will perform its intended function without unreasonable adverse effects on the environment...". Unreasonable adverse effects are defined as "(1) any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide." The Administrator may also conditionally register a pesticide under certain circumstances. Consult FIFRA for additional information about conditional registration.

The purpose of this document is to summarize and make available for public comment EPA's ecological risk and benefit assessment of American Cyanamid's application for registration of the pesticide chlorfenapyr (Pirate®[*], Alert®) on cotton. Four documents summarizing the human health risks of this compound have already been published in the Federal Register for public notice and comment. They are listed below:

- Three “Notices of Filing” of petitions for tolerances on the following commodities: cottonseed (62 FR 5399, February 5, 1997); citrus (63 FR 14926, March 27, 1998); and milk, milkfat, meat, meat fat and meat byproducts derived from use of chlorfenapyr ear tags on beef and dairy cattle (63 FR 52260, September 30, 1998). These documents, required by the Food Quality Protection Act (FQPA), were prepared by American Cyanamid, the registrant.

- A time-limited tolerance (62 FR 44565, August 22, 1997) established for emergency use on cotton. This document set forth EPA's human health risk assessment on cotton.

Thus, the public has had ample opportunities to comment on the human health risk assessment for this compound.

However, no similar presentation has been made to the public of the ecological risks or the benefits of this use. EPA believes the ecological risks and the benefits of this use are both significant, and they are discussed in detail in this summary. This compound clearly helps contain the pest pressures faced by the American cotton producer. Chlorfenapyr use on cotton plainly provides the cotton grower with an effective tool to control several important cotton pests. At the same time, significant and somewhat unusual ecological risks are presented by its use, as set forth below:

- This is the first member of the pyrrole chemical class for which registration has been sought. The Agency’s knowledge of this chemical class is limited to what has been

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presented in support of registration of chlorfenapyr. In addition, the Agency has no prior experience in regulating pyrroles, which it can transfer to regulation of chlorfenapyr.

- This is a persistent compound. If applied to the same fields for many consecutive years, the Agency expects it will build up to levels that likely present reproductive risks to birds. Since it will be applied as a foliar spray, the Agency expects that the area containing residues will, in time, extend beyond the boundaries of the treated field. Further, even if use were discontinued after a number of years of application, the Agency expects that a significant amount of time will pass before residue levels drop to levels that are below levels of concern.

Thus, the risk assessment and conclusions raised by chlorfenapyr use present special issues for pesticide regulation. At the same time, major benefits to the American cotton grower can be expected from its use. With these facts at hand, EPA must weigh these risks and benefits before making a regulatory decision. EPA is taking the unusual step of soliciting public comment on the implications of both benefit and ecological risk assessments as they pertain to the regulatory process for this compound because of the specific facts and circumstances of this case. EPA believes that both the ecological risks and the benefits of this use are significant, and warrant this approach.

Specifically, the Agency is requesting comments on the following issues:

A. Before making its regulatory decision, is there any additional information the Agency should consider that it currently has not?

B. Are the assessment characterizations of the ecological risks and the economic benefits associated with the proposed use of chlorfenapyr on cotton scientifically sound? Or do they require additional considerations or analysis? What, if anything, else should the Agency consider or change in the assessments before rendering its decision?

C. Are there mitigation measures other than those proposed by the registrant and considered by the Agency (Sec. III.B.5.) that may help to reduce the exposure and thus ecological risk?

The outline of the remainder of this document is as follows:

I. Regulatory Setting.

A. Application for Registration. On December 9, 1994, EPA received an application from American Cyanamid Company for registration of the new chemical chlorfenapyr (Pirate®, Alert®) to control a number of pests of cotton. As noted above, EPA published a Notice of Filing of a pesticide petition proposing tolerances for residues of chlorfenapyr on cottonseed and animal commodities used for food. Comments received in response to this notice supported registration, and raised no substantive issues.

EPA completed a human health risk assessment in March, 1997. This assessment reviewed the toxicology and residue data submitted by the company to determine if the cotton use posed a risk to human health. The assessment concluded that the cotton use did not pose human health risks that were at levels of concern.

The ecological risk assessment completed in January, 1997, raised a number of concerns about this compound. Discussions with the registrant began in January, 1997, to determine if the company and the Agency could agree on terms of registration. These discussions concluded in May, 1997. EPA and the registrant disagreed on the results of the environmental risk assessment. At that time, EPA did not reach a decision to register chlorfenapyr on cotton. The registrant volunteered to submit additional data to refine the ecological exposure assessment for this compound. To meet growers' needs for the 1997 and 1998 crop years, EPA issued emergency exemptions (Sec. 18s) which authorized limited chlorfenapyr use.

Between August, 1997, and May, 1998, the registrant submitted additional ecological exposure data to the Agency. In October, 1997, the registrant convened an expert panel to review the data submitted and the risk assessment. The findings of this expert panel were also submitted to EPA for review. In August, 1998, EPA completed a refined ecological risk assessment and continued discussions with American Cyanamid on the risk assessment and the risk-benefit determination to address ecological and environmental concerns.

B. Other U.S. regulatory activity.

1. Other U.S. chlorfenapyr registrations pending. Several other applications for registration for chlorfenapyr under Sec. 3 of FIFRA are pending at EPA. They are listed below (starred uses have related food tolerance petitions pending under the Federal Food, Drug, and Cosmetic Act (FFDCA)):
Greenhouse Ornamentals, Citrus*, Vegetables* (cabbage, broccoli, head lettuce, leaf lettuce, potatoes, and fruiting vegetables, including tomatoes, peppers, eggplant...), Cattle eartags*, Termites, Cockroaches, Ants, Imported Fire Ants in Nursery stock, Mole crickets in Turf. In addition, an import tolerance petition for imported citrus is pending.

2. Experimental Use Permits. The following experimental use permits have also been issued for this compound: cotton, greenhouse ornamentals, oranges and lemons, lettuce, cabbage, tomatoes, cattle eartags, and termites.

3. Emergency Exemptions (Section 18s). Under Sec. 18 of FIFRA, EPA may grant to States exemptions from the requirements for registration for emergency uses, as long as progress is being made towards registration. Accordingly, States have requested that chlorfenapyr be made available for use on cotton to control the beet armyworm and resistant tobacco budworm, for the past five, and four years, respectively.

In 1994, requests received from Alabama, Georgia, Louisiana, and Mississippi for control of the beet armyworm were all denied, because EPA could not make the finding that the benefits outweighed the risk of unreasonable adverse effects on the environment. Exemptions were, however, issued for another material, tebufenozide, to Alabama and Mississippi for control of beet armyworm.

In 1995, requests for this use on cotton were again received from Alabama, Georgia, Louisiana, Mississippi, and Tennessee and were initially denied. The use was now also being requested for control of another pest, the pesticide-resistant tobacco budworm. However, the states presented further arguments supporting the existence of emergency conditions, and the exemptions were eventually issued to these states, with the exception of Tennessee. Exemptions for this use were also issued to Arkansas, Florida, and Texas in 1995 (for a total of seven states). The Agency imposed risk mitigating measures and also required monitoring for wildlife mortality.

In 1996, 1997, and 1998 exemptions for the use of chlorfenapyr on cotton were granted to the same states listed above (Tennessee did not apply for a Sec. 18 in 1997), and also to South Carolina. In 1997 and 1998, an exemption was also issued to the state of California for use of chlorfenapyr on cotton to control spider mites. Additionally, in 1998, several states, plus North Carolina and Oklahoma for the first time, requested use due to unusually severe pressure from beet armyworm.

In 1995 - 1997, the following acreages were treated, with the percentage of total cotton acreage planted in the U.S. given also: **1995** (228,568 acres, 1.3% total planted); **1996** (426,990 acres, 2.9% total planted); **1997** (134,104 to 223,337 acres, 1 to 1.7% total planted).

C. International Regulatory Activity. Chlorfenapyr is registered in 31 countries. It is registered on cotton in the following countries: Australia, Azerbaijan, Bolivia, Brazil, Egypt, Guatemala, Honduras, Kazakhstan, Mexico, Nicaragua, South Africa, Turkey, Turkmenistan, Uzbekistan, Zambia, and Zimbabwe. It is registered for uses other than cotton in the following countries: Argentina, Australia, Azerbaijan, Brazil, Chile, China (PRC), Columbia, Costa Rica, Egypt, Guatemala, Honduras, Indonesia, Israel, Japan, Kazakhstan, Kenya, Korea, Mexico, Nicaragua, South Africa, Taiwan, Tanzania, Thailand, Turkey, Turkemenistan, Uganda, United Arab Emirates, Uzbekistan, Vietnam, Zambia, and Zimbabwe.

Applications for registration on cotton are under review in the European Union (Greece, and Spain). Application for registration for uses other than cotton are under review in the following countries: Canada, Costa Rica, European Union (Belgium, France, Greece, Italy and Spain), Indonesia, Pakistan, and Taiwan.

II. Summary of Human Health Risk. EPA has completed a human health assessment for chlorfenapyr. A time limited tolerance (62 FR 44565, dated August 22, 1997), which expires July 31, 1999, has been established for residues of chlorfenapyr on cottonseed and animal products to be used for food resulting from the emergency uses authorized under Sec. 18. (In addition, the tolerances cover residues in animal products used for food resulting from the experimental use in cattle eartags). The human health risk assessment for cotton was summarized and presented for public notice and comment in connection with the establishment of the time limited tolerance on cottonseed. One comment (from American Cyanamid) was received during the comment period. It disputed a number of points in the human health risk assessment. The Agency has not developed a point-by-point response to these comments.

However, since that time, the Agency has completed a second human health risk assessment for chlorfenapyr use on a second crop (citrus) for which American Cyanamid has applied for registration. In this risk assessment the Agency refined its estimates of risk to human health for use on both cotton and citrus and found they were not at levels of concern. Because it reflects the Agency's current thinking on the human health risk picture for this compound, and because its risk estimates include exposure to residues on cottonseed, a summary of the citrus risk assessment is presented here. For a more detailed discussion, consult the citrus and cotton human health risk assessments accompanying this summary.

A. Hazard Assessment. The toxicology data base is complete. However, because of concerns about some nervous system effects seen in submitted studies, the registrant is required to submit a developmental neurotoxicity study. The results of the hazard assessment are summarized below.

1. Chronic Exposure. Chlorfenapyr has not been found to be carcinogenic. For other chronic effects, a Reference Dose (RfD) has been established at 0.003 mg/kg/day based on the No Observed Adverse Effect Level (NOAEL) in the 1-year rat neurotoxicity study of 2.6 mg/kg/day. The effects observed at the lowest observed adverse effect level (LOAEL) of 13.6 mg/kg/day (300 ppm) were decreased body weight gains and brain lesions (vacuolation). An uncertainty factor (UF) of 1000 was applied to account for interspecies extrapolation, intraspecies variability and the additional FQPA (Food Quality Protection Act) Factor of 10. The FQPA factor has been retained because chlorfenapyr has produced central nervous system (CNS) lesions in several studies in both rats and mice. It will be reevaluated after the developmental neurotoxicity study has been submitted.

2. Acute dietary exposure and short- and intermediate-term dermal and inhalation effects. The no observed adverse effect level from the acute neurotoxicity study in rats was determined to be 45 mg/kg for acute dietary risk assessments. The lowest observed adverse effect level was 90 mg/kg based on lethargy in males. An uncertainty factor (UF) of 1000 is based on 100 to account for interspecies extrapolation and intraspecies variability plus the 10-fold FQPA Factor described above.

The no observed adverse effect level from the 28-day dermal toxicity study of 100 mg/kg/day for short- and intermediate-term occupational or residential risk assessments is based on increased cholesterol, relative liver weights and cytoplasmic vacuolation of the liver in male and females rabbits at the lowest observed adverse effect level of 400 mg/kg. An UF of 1000 is considered appropriate for this chemical for the reasons discussed above.

B. Exposure Assessment. The residue chemistry data base is adequate to estimate dietary exposure for use on cotton. However, six additional field trials are required for cotton gin by-products (cotton gin trash). No residential exposure is expected from the cotton use. Standard exposure analyses were used to estimate occupational exposure.

C. Risk Assessment.

1. Summary. A chronic dietary exposure analysis was performed using anticipated residue values (derived from averages of field trial results). The chronic analysis showed that exposure for non-nursing infants less than 1 year old (the subgroup with the highest exposure) would be 26% of the RfD, while the exposure for the general U.S. population would be 12% of the RfD. Based on the chronic dietary (food) exposure and using default body weights and water consumption figures, chronic levels of concern (LOC) for drinking water were calculated. The combined exposure of chronic dietary and drinking water exposure to chlorfenapyr use would be no greater than 100% of the RfD for children or the general U.S. population.

Based on the existing toxicological database for chlorfenapyr, the level of concern has been established at Margins of Exposure (MOEs) below 1000. For use of chlorfenapyr, acute dietary MOEs ranged from 4,500 to 9,000. MOEs for short- and intermediate term occupational risk range exceed 1000. Potential residues in drinking water are not above levels of concern. Occupational MOEs were not at levels of concern. Therefore the MOEs for the use of chlorfenapyr are above the level of concern for all exposure scenarios.

2. FQPA findings. As required by FQPA, EPA has made a determination of safety for the U.S. Population, Infants, and Children and has concluded that there is a reasonable certainty that no harm will result to infants and children from chronic aggregate exposure to chlorfenapyr residues. EPA relied on the following information to reach this conclusion: The percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of chlorfenapyr ranges from 5 percent for nursing infants less than one year old, up to 26 percent non-nursing infants less than one year old. Despite the potential for exposure to chlorfenapyr in drinking water, EPA does not expect the chronic aggregate exposure to exceed 100% of the RfD. Since there are no residential uses of chlorfenapyr, no chronic residential exposure is anticipated.

EPA has further concluded that there is a reasonable certainty that no harm will result to infants and children from acute aggregate exposure to chlorfenapyr residues. The acute dietary (food only) MOE for females 13+ years old (accounts for both maternal and fetal exposure) is 4500. This risk assessment assumed 100% crop treated for all treated crops consumed, resulting in a significant over-estimate of dietary exposure. Despite the potential for exposure to chlorfenapyr in drinking water, EPA does not expect the acute aggregate exposure to exceed the level of concern. The large acute dietary MOE calculated for females 13+ years old provides assurance that there is a reasonable certainty of no harm for both females 13+ years and the pre-natal development of infants.

For chlorfenapyr, acceptable prenatal toxicity studies in rats and rabbits have been submitted to the Agency. There are no data gaps for the assessment of the effects of chlorfenapyr following *in utero* exposure. However, a developmental neurotoxicity study has been requested. An acceptable reproductive toxicity study in rats with chlorfenapyr is also available. There are no data gaps for the assessment of the effects of chlorfenapyr to young animals following early postnatal exposure.

The existing data demonstrated no indication of increased sensitivity of rats and/or rabbits to in utero exposure to chlorfenapyr. The no observed adverse effect levels for maternal toxicity (in the existing developmental studies) were always less than or equal to the no observed adverse effect levels for fetal toxicity. The existing data demonstrated no indication of increased sensitivity of rats and/or rabbits to early post natal exposure to chlorfenapyr. The no observed adverse effect levels for systemic toxicity was always less than the no observed adverse effect levels for reproductive toxicity. However, since this chemical has a demonstrated potential for central nervous system lesions, EPA determined that there was inadequate evidence to be sure that increased sensitivity to infants or children did not exist.

EPA determined that for chlorfenapyr, the additional 10-fold FQPA Factor for the protection of infants and children should be retained for lack of understanding of the cause, and possible further unknown neurotoxicity with regard to the developing young. EPA considered that "unusual toxic properties raise concerns regarding the adequacy of the standard (i.e., 100-fold) margin/factor." EPA has required that a developmental neurotoxicity study be conducted based upon the effects of a spongyform myelopathy and/or vacuolation seen in the brain and spinal cord of treated rats and mice.

III. Summary of Ecological Risk Assessment

A. Background. Since 1994, EPA has conducted several increasingly refined assessments of the risks to terrestrial and aquatic organisms resulting from chlorfenapyr use on cotton. Extensive data provided by American Cyanamid have been central to allowing EPA to move from generalized assumptions that are part of the screening level assessment to more complex and realistic assessments of ecological risks associated with this use.

B. Current Risk Assessment. The current risk assessment builds upon previous EPA risk assessments for this chemical and use site, but incorporates important changes in chlorfenapyr labeling, additional toxicological data (avian, aquatic, and benthic (sediment dwelling) invertebrates), and refinements to the exposure modeling. The following discussion focuses on chronic avian exposures for specific bird species known to occur in cotton fields on the basis of measured pesticide residues in dietary items, and presents those levels of exposure over time. For acute avian effects, and effects on other terrestrial and aquatic organisms, consult EPA's ecological risk assessment accompanying this summary.

1. Hazard Identification. Chlorfenapyr is a member of the chemical family "pyrroles" and it is the first pyrrole submitted for U.S. registration. Chlorfenapyr has a unique mode of action. It is a pro-insecticide that is converted (or metabolized) to the active form by mixed function oxidases (MFOs) in the target pest. The active form acts on the mitochondria and uncouples oxidative phosphorylation which stops the production of ATP, the primary source of cellular energy. This action causes cell death, and ultimately, death of the target organism, the insect. However, the process interrupted is a process common to all living organisms, and so is of concern for non-target organisms.

It appears that various species metabolize chlorfenapyr differently. For example, it appears that insects are more efficient in converting chlorfenapyr to its active form (and thus are more susceptible) than are vertebrate species. Data supplied by American Cyanamid for rats, goats, and poultry indicate that the active form is produced in all these species. However, there are differences in sensitivity to chlorfenapyr between mammals and birds. One possible explanation for this difference comes from metabolism data that show the active form is metabolized in mammals to compounds which are more water soluble (or excretable in urine), but in birds less of these soluble metabolites of the active form are found. This information does not suggest chlorfenapyr is not excreted from poultry, merely that the pathways for metabolism and elimination from the body may differ between mammals and birds. This explanation for differences in toxicity is tentative, as specific metabolic rates have not researched for different species.

EPA uses ecological toxicology studies on select species to identify the toxicity to nontarget organisms, for example, birds. Because of the persistence of chlorfenapyr, repeat applications, and evidence that it can be found in avian food items, the Agency required chronic toxicity studies for this compound. In a chronic toxicity study for birds, over a period of 22 weeks, the test species is subjected to continuous exposure to a pesticide at predetermined test levels, before and during its breeding season. The following biological effects (endpoints) are measured: eggs laid, eggs cracked, eggs set, viable embryos, live 3-week embryos, normal hatchlings, 14-day-old survivors, weights of 14 day old survivors, egg shell thickness, total food consumption, and initial and final body weights by sex. These measures are statistically analyzed to determine the level of exposure at which no adverse effects were observed (NOAEC, or no observed adverse effect concentration) , and the threshold level at which adverse effects are observed (the LOAEC, or lowest observed adverse effect concentration).

For chlorfenapyr, in a chronic reproductive study using mallard ducks (the most sensitive species tested), four groups of birds were fed chlorfenapyr at concentrations of 0 (control group), 0.5, 1.5 and 2.5 ppm respectively in their diet. The no observed adverse effect concentration was identified as 0.5 ppm and is the value to be used in the risk assessment. The lowest observed adverse effect level for systemic effects was 1.5 ppm for reduced body weight in adult females. The lowest observed adverse effect concentration for reproductive effects was 2.5 ppm. At that level, there were significant differences in 2.5 ppm group compared to the control group: total number of eggs laid (-41%), the number of eggs set (-42%) the number of viable embryos (immediately after laying) (-44%), the number of viable embryos at 21 days of age (just prior to hatch) (-33%), the number of normal hatchlings (-56%), the number of hatchlings surviving 14 days (-56%), and a decrease in body weight of adult males and females (males: -14%; females: -15%). The data upon which these results are based are presented in table 1.

Table 1. Study of Chronic Reproduction in the Mallard: Mean (Average) Values for Specified Biological Effects (Endpoints) by Treatment Group

Biological Effect (Endpoint)	**Control Group**	**0.5 ppm Group**	**1.5 ppm Group**	**2.5 ppm Group**
Eggs laid	50.75	49.25	35.28	30.13
Eggs set	47.31	44.75	31.86	27.38
Viable embryos	39.56	40.38	27.21	22.18
Live 3-week embryos	30.06	38.75	26.21	20.00
Normal hatchlings	33.00	31.88	21.14	14.50
14-day-old survivors	32.88	31.75	21.07	14.43
Final weight of males (grams)	1251.00	1207.44	1144.81	1072.06
Final weight of females (grams)	1155.75	1124.13	977.64	983.4

Unlike human health assessments, EPA does not use uncertainty factors to account for intraspecies or interspecies differences in sensitivity. It is possible that there is a bird species that was not tested that is more sensitive than the mallard duck.

2. Environmental Fate.

a. Persistence/Rate of Degradation. Chlorfenapyr's persistence is typified by a laboratory aerobic soil metabolism half-life of 1.4 years [standard upper 90% confidence limit based on five soils, excluding a previous, anomalous, 3.8 year value] and its observed, comparable field dissipation "half-life" of 1.3 years [standard upper 90% confidence limit based on five small-plot cotton studies in four cotton states]. Chlorfenapyr was essentially stable to laboratory hydrolysis and anaerobic soil metabolism.

b. Degradates. Because of the persistence of the parent compound and relatively short study durations, only small amounts of structurally similar metabolites or degradates, some of which exhibit ecotoxicity, were identified in soil in field or lab studies. Concentrations of these, when detected, were typically a few percent each or less of the applied chlorfenapyr. In general, transformation products appear to approximate or exceed the persistence of the parent. Neither mineralization (carbon dioxide evolution) nor volatilization were significant in laboratory studies, and were not monitored in the field.

c. Accumulation in the Physical Environment. Because of chlorfenapyr's persistence, uniform annual use in a given area would result in significant build-up in environmental compartments. Using chlorfenapyr's estimated half-life of 1.4 years, and assuming repeated annual applications, the compound is expected to build up to a level in the environment of 2.5 times the annual application rate (converted to parts per million (ppm)). Note that this assumes that 100% of the amount applied ultimately reaches the soil.

3. Exposure Characterization. The characterization of exposure is the area of the risk assessment that has been most substantially refined over the course of the chlorfenapyr review. An initial risk assessment used a screening-level exposure scenario commonly used in all EPA terrestrial exposure assessments. This standardized approach relies on pesticide residue data for wildlife food items and food item surrogates generated from numerous field studies and summarized by Hoerger and Kenaga (1972) and modified by Fletcher et al. (1994) [see risk assessment for references]. It allows for a calculation of potential residue values on/in wildlife food and feed. It results in a single maximum residue concentration. The screening approach considered upper bound estimates of exposure to residues in wildlife food items (95^{th} percentile). The screening assessment did not account for degradation/dissipation of chlorfenapyr residues in wildlife food items.

With the primary ecological risk focused on chlorfenapyr's persistence and avian reproduction effects, EPA risk assessors proceeded with additional exposure analyses. The next level of analysis substituted the "typical" (50^{th} percentile) values for the upper bound value. The results still substantially exceeded levels of concern.

The analysis was further refined as follows: Although chlorfenapyr is a persistent compound, EPA expected that some level of dilution/dissipation could occur in the environment. Therefore, an exposure characterization that would provide for some assumed level of dilution/dissipation was tested. A “ubiquitous soil model” was devised as an exposure scenario in an effort to account for field dilution/dissipation of chlorfenapyr residues. This model accounted for dilution and dissipation by assuming that the avian diet was contaminated at a level that was equal to that accumulated in soil. The level was assumed to be equivalent to the application amount of pesticide evenly dispersed in a 15 cm depth of soil plus residual carryover (based on a range of half-lives in soil) from previous years of application (present years application + previous accumulated value/15 cm soil). This resulted in exposure values in the range of 0.7-1.4 ppm in the avian diet. These exposure values were then compared to the reproduction toxicity threshold. Again, the results substantially exceeded levels of concern. American Cyanamid suggested that the exposure values still substantially overestimated true wildlife exposure in the field. Accordingly, they undertook studies to better estimate chlorfenapyr persistence in soil and residues in wildlife food items.

American Cyanamid has provided actual residue data for chlorfenapyr in avian food items, including weed seeds, weed seed heads, and insects (both adults and larvae). These measured residues in avian food items were an important component of the exposure estimation models used in the current EPA risk assessment.

Although the residue studies were designed to run 28 days, some of the data on the different components of the avian diet were collected for shorter time periods. Therefore, risk calculations were made only for the time periods where complete and comparable data on avian diet residues were available, in most cases, 14 days. The Agency used no extrapolations.

Food intake rates were calculated for bird species known to be in cotton fields (on the basis of registrant-supplied avian census data). The mixtures of food items comprising the diet were species-specific. Exposures were calculated based on caloric intake necessary for normal avian activity. Acute avian exposures were based on an assumption that 100 % of the diet for short periods of time could originate from treated cotton fields. However, calculated exposures for assessment of reproduction risks assumed either 100 % or 10 % of the avian diet originating from the fields. The 10 % assumption was based on the frequency of observations of birds in cotton fields from census data on sites across the Cotton Belt region of the United States.

4. Risk Conclusions. EPA uses risk quotients (RQs) to measure risk. A risk quotient compares the level of exposure (generally the levels of pesticide residue in the diet) to the critical toxicity concentration (the highest concentration at which toxicity does not occur -- the "no observed adverse effect concentration" (NOAEC) set forth in the hazard identification). This is expressed as set forth below:

$$RQ = \frac{\text{exposure level}}{\text{toxicological endpoint NOAEC}}$$

Risk quotients are then compared to EPA's established Levels of Concern (LOCs). These levels of concern are critical values indicating potential risk to nontarget organisms, such as birds.

When risk quotients exceed the levels of concern, the potential exists for risk to nontarget organisms. More specifically, the criteria indicate whether a pesticide, when used as directed, has the potential to cause adverse effects to nontarget organisms. For birds, the level of concern for chronic effects is equal to or greater than "1". This means that the level of pesticide residues that the birds are consuming is equal to or greater than the level at which no effects were observed.

For chlorfenapyr, the no observed adverse effect concentration from the mallard duck reproduction study (0.5 mg/kg) was compared to exposures resulting from residues in the estimated diets of several species of birds known to inhabit cotton fields. Sample results of the risk assessment for uses of chlorfenapyr on cotton are presented below using two of these species.

Table 2. An Example of Avian Species Risk Quotients assuming 100% cotton field use): White-Eyed Vireo

Days After 1st Treatment	Reproduction. RQ (using 0.2 lb ai/A x 2 applications)
0.1	52.77
3.1	16.80
7	9.03
7.1	67.60
14	20.53

Table 3. An Example of Avian Species Risk Quotients assuming 100% cotton field use: Mourning Dove

Days After 1st Treatment	Reproduction. RQ (using 0.2 lb ai/A x 2 applications)
0.1	21.43
3.1	7.50
7	5.66
7.1	32.58
14	14.45

Tables 2 and 3 show that dietary residues associated with an application rate typical for beet armyworm present a substantial risk to avian species for the impairment of successful reproduction. Predicted dietary exposure levels (based on measured residues in avian food items) for all application rates exceed the threshold for reproductive effects for all of the species selected to represent avian receptors in cotton fields by factors up to 68. These exposure estimates were based on measured data for 14 days (the limit of the measured data available to the Agency from field studies with applications typical for certain cotton pests). However, the rates of decline for chlorfenapyr in bird food items suggest that, for application rates typical for pests in cotton, the dietary exposure may exceed toxicological thresholds for birds for up to five weeks after initial chlorfenapyr application. Even when assumed use of cotton fields by wildlife is reduced to below those demonstrated from cotton field data (i.e., an assumption of 10% of diet originating from cotton fields), risks to reproduction still exceed levels of concern in many instances, as shown in tables 4 and 5.

Timing of chlorfenapyr applications to the cotton crop coincide with the reproductive window of most of the more than 50 species of birds that the registrant reports to be associated with cotton fields. Many of the bird species included in this risk assessment, which are representatives of the species found in cotton fields, are presently exhibiting downward population trends in cotton-growing states. Further impairment of reproduction and increased individual mortality would further stress populations of these species in one or more cotton-growing states.

Table 4. An Example of Avian Species Risk Quotients assuming 10% cotton field use): White-Eyed Vireo

Days After 1st Treatment	Reproduction. RQ (using 0.2 lb ai/A x 2 applications)
0.1	5.28
3.1	1.68
7	0.90
7.1	6.76
14	2.05

Table 5. An Example of Avian Species Risk Quotients assuming 10% cotton field use: Mourning Dove

Days After 1st Treatment	Reproduction. RQ (using 0.2 lb ai/A x 2 applications)
0.1	2.14

Days After 1st Treatment	Reproduction. RQ (using 0.2 lb ai/A x 2 applications)
3.1	0.75
7	0.57
7.1	3.26
14	1.45

Concerns for acute avian exposure and acute and chronic exposures for certain aquatic, sediment dwelling, estuarine, and marine organisms are not included in this summary, but remain a concern to EPA. Consult the risk assessment for a detailed discussion.

The current avian risk assessment conclusions are consistent with the findings of previous EPA risk assessments for chlorfenapyr use on cotton. However, the confidence of the present avian risk findings is greater than in previous assessments because of the following factors:

- use of measured residue values in seeds, insects, and forage
- assessment of risks to specific species known to occur in cotton fields, including species-specific considerations of life history information, dietary preferences, and metabolic requirements
- incorporation of information specific to the use of cotton fields as a food resource by wildlife
- identification of conservative and less than conservative assumptions incorporated in the assessment. These assumptions are discussed below.

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Like previous risk assessments, the current risk assessment incorporates some exposure parameter values and assumptions that may be biased toward the "upper bound" or overestimates of risk. These factors are listed below:

- Maximum lepidopteran larvae residues used in exposure (however, not the highest possible insect residues from available information)
- 100% of diet from cotton field
- Use of seed residue data as surrogate for fruit residues (consistent with other EPA exposure assessment approaches, no data on weed fruits available).

On the other hand, the current risk assessment includes factors that are more realistic or may underestimate risk. They are listed below:

- An assumption of only 10% of diet from field still poses reproduction risks

- Use of composite weed seed residues for exposure (no accounting for acute effects associated with hot-spots)

- No adjustment of toxicity endpoints for potentially sensitive nestlings

- No adjustment of toxicity endpoints for inter-species differences in sensitivity

- Use of mean biological parameters in exposure models (body weights, metabolic requirements, food intake rates)

- No quantitation of dietary exposure from soil invertebrates in the diet

- No quantitation of other exposure routes (dermal, inhalation, drinking water)

- No quantitation of the contributions of multiple year residues to exposure (single season exposure only)

- No quantitation of additional toxicological risks from biologically active metabolites known to occur in soil and in insects.

5. Mitigation Measures. The registrant has proposed the following risk mitigation measures:

- Restricted use Pesticide. The registrant has proposed that the product be "Restricted Use" due to aquatic and avian concerns. As a restricted use product, it could be applied only by certified applicators.

- Drift and runoff hazard statements. To limit drift and runoff to water bodies, the user is directed to avoid inadvertent application to water.

- Bee statement. Since this product is toxic to bees, the user is directed to take measures to avoid exposing bees.

- Endangered Species. The user is directed to avoid use in areas where threatened or endangered species are likely to be, and to notify authorities and American Cyanamid if adverse environmental effects are observed.

- Economic thresholds. The proposed label states that application should not begin until target pest populations have reached local economic threshold levels. The user should consult with the Cooperative Extension Service or crop advisor to determine recognized local economic threshold levels. The directions for use for beet armyworm specify applications only after an economic threshold, such as 5 active "hits" per 100 row feet, is met. For tobacco budworm, higher rates should be used only when pest pressure is heavy or large larvae (greater than 1/4 inch) predominate.

- Resistance and Pest Management statement. Directions are included to use in a pest management program which coordinates different chemistry classes of insecticides in spray schedules, provides thorough coverage of targeted crops and pests, uses proper chemical rates per label directions, and monitors pest populations.

- Pests. The proposed label (dated 12/97) for states other than California and Arizona lists four species of spider mites, beet armyworm and tobacco budworm and cotton bollworm. Loopers and other armyworms are listed as secondary, not primary, pests (if the are present in the field at time of application for control of tobacco budworm and cotton bollworm, they also will be controlled). The label for use in California and Arizona is similar.

Most of the proposed measures are designed to mitigate or reduce direct acute concerns associated with chlorfenapyr use, although they may also affect chronic concerns. The Agency considered these mitigation measures in its ecological risk assessment. The Agency believes that the field residue data show that these mitigation measures still yield dietary exposure estimates that exceed chronic toxicity thresholds for birds. In addition, the nature of the concern -- chronic reproductive effects combined with the persistence of chlorfenapyr -- make this a difficult problem to mitigate. Based on the Agency's analyses, the Agency believes the above mitigation measures will have only a limited effect on the risks posed by chlorfenapyr.

IV. Benefits Assessment. As noted above, chlorfenapyr is a member of a new class of chemicals, the pyrroles, and has a unique mode of action for control of target insect pests. The Agency has been evaluating the value of chlorfenapyr for the control of cotton pests since 1994 when the initial Section 18's were submitted by several cotton states to control beet armyworm (and later, resistant tobacco budworm and spider mites in California). The qualitative analyses of this active ingredient have shown that it has its greatest efficacy and benefits against beet armyworm, and may have an important place in the late season control of one or more spider mite species attacking cotton in California. However, the benefits of the compound against resistant tobacco budworm, non-resistant tobacco budworm, bollworm and spider mites outside of California are not as great because the Agency believes adequate alternatives exist for these pests.

A. Beet armyworm. For beet armyworm control, chlorfenapyr is one of the most effective materials available. The beet armyworm is a very erratic pest, generally most severe following mild winters and summers with above average temperature and below average rainfall. It has a history of causing sporadic, but large losses (Table 6). In 1995, the year that Sec. 18s were approved late, losses were large, and for a number of producers, they were catastrophic. Thus, the beet armyworm's ability to damage bolls and strip a cotton field of foliage, and thereby wipe out a crop for an individual producer, is well documented.

Table 6. Losses in Cotton from Beet Armyworm

Year	Infested Acres (mil)	Treated acres (mil)	Bales lost* (000)
1991	2.3	0.5	3.7
1992	2.5	0.3	0.7
1993	3.5	1.7	9.5
1994	2.1	0.4	9.0
1995	6.8	2.6	368.1
1996	2.3	0.3	22.2
1997	2.0	0.5	14.7

*1 bale = 500 lbs.

The other effective compound registered against beet armyworm is spinosad (Tracer®). EPA believes that since beet armyworm has a well-documented capacity to develop resistance to pesticides, it is important that there be more than one alternative to control it. In addition, there are four compounds for which registration applications are pending or which are registered to control beet armyworm on other crops. These compounds may be considered for Sec. 18s in 1999.

The Agency is also aware that the need for chlorfenapyr to control this pest is increased by the initiation of boll weevil eradication programs in several mid-South states. During the start-up years of a boll weevil eradication program, multiple insecticide applications reduce parasites and predators which can result in more severe beet armyworm outbreaks than might happen in the absence of the program. However, the Agency is very supportive of the boll weevil eradication program because once eradicated, the number of insecticide applications per acre, per growing season is reduced. Reduction of pesticide usage also saves growers money. For these reasons, the Agency believes there is a very high benefit at this time for chlorfenapyr use against beet armyworm.

B. Spider mites on cotton in California. Spider Mites are a serious problem in California because, like the beet armyworm, they are erratic and cause serious economic losses on a variable number of acres annually. California has a well established IPM (integrated pest management) program and uses the chemicals that are least disruptive to the beneficial insects that attack cotton pests. The major active ingredients used are dicofol, propargite and abamectin. One or more species of spider mites in California have developed resistance to all of these materials. For these reasons, the Agency believes there is a high benefit at this time for chlorfenapyr use for spider mite control in California only.

C. Spider mites outside of California. The Agency realizes that in hot dry years such as 1998, the twospotted spider mite can cause losses outside of California. There are a number of alternatives available to control spider mites, including some that cannot be used in California because of the potential disruption of their IPM program. (IPM for cotton outside of California and Arizona is currently more limited, because of the greater diversity and likelihood of higher populations of species in the arthropod pest complex, including boll weevil). Although there seems to be a question of the availability of some of these materials in cotton areas outside of California, that lack of availability is not known to be caused by the basic producer. Further, in an emergency, it is possible that a Section 18 could be considered for unusually severe infestations. For these reasons, the Agency believes there is significantly lower benefit to chlorfenapyr use against spider mites outside of California.

D. Resistant tobacco budworm, non-resistant tobacco budworm and bollworm. The Agency is aware that resistant tobacco budworm has been a serious concern to cotton growers, primarily in the Mid South and parts of Texas, since the late 80's. At the time of the initial Section 18's, chlorfenapyr was the only effective alternative to the three phase resistance management program used in the Mid South to preserve the remaining efficacy of the synthetic pyrethroids. However, in the last few years, Bt cotton and spinosad have been registered and both of these are very effective against resistant tobacco budworm. Even though these new alternatives were registered, EPA continued to make chlorfenapyr available under Sec. 18. because spinosad's availability to growers was limited. Currently, there are two unregistered active ingredients that have good efficacy against the resistant tobacco budworm. Both of these are in expedited review, having passed the Agency's reduced risk screen for new active ingredients. They should be registered in mid to late 1999. In the event that a serious situation occurs next season, there is still the option of applying for a Section 18 to use chlorfenapyr against this pest. In the case of non-resistant populations of the tobacco budworm and the bollworm, the Agency believes that there are many effective alternatives to chlorfenapyr available to control these pests. For these reasons, EPA believes the benefits case for chlorfenapyr against resistant tobacco budworm, non-resistant tobacco budworm, and bollworm are not as high as they are for beet armyworm or spider mites in California.

Refer to Table 7 for a listing of the current status of registered alternatives and those in the pipeline for a registration decision, some within a year or less. Note that some registered alternatives are identified as being in the pipeline for a reregistration eligibility decision (RED). In the reregistration process, as required by FIFRA, the Agency reviews the human health and ecological risk and benefits of compounds registered before 1984. If ecological or human health risks are at levels of concern and exceed the benefits of use, mitigation measures and/or regulatory action may be required when the RED is issued.

Table 7. Alternatives to Control Certain Pests in Cotton

Pest	Effective Alternatives	Comments
Beet Armyworm		
Registered	Spinosad (Tracer®) • appears to be at least as good as chlorfenapyr • broader efficacy • has had problems with availability since it was registered. It is expected to be widely available in 1999.	

Pest	Effective Alternatives	Comments
In the Pipeline	Tebufenozide (Confirm®) • less effective than chlorfenapyr • works best at lower populations of beet armyworm • registration decision expected winter 1998-99. • has been issued under Sec. 18 for use on cotton Compound A • passed reduced risk screen • may not be as effective as chlorfenapyr • registration decision expected late summer 1999. Compound B • second generation to another compound effective against beet armyworm • passed reduced risk screen • not as effective as chlorfenapyr • registration decision expected by fall 1999. Compound C • not a reduced risk compound • tolerance petition and application expected to be submitted spring 1999 for cotton • effective on beet armyworm on vegetables; registrant states that it is effective for cotton as well (no known data in public literature).	Chlorfenapyr (Pirate®) • as a Sec. 18, it has become the standard treatment • very effective against beet armyworm • Important role in boll weevil eradication.
Spider Mites (CA only, Twospotted, Pacific, Carmine, and Strawberry)		
Registered	dicofol (Kelthane®) • varying degrees of resistance • in RED pipeline • specific to spider mites • has environmental risk concerns propargite (Comite®) • varying degrees of resistance • in RED pipeline • specific to spider mites • has risk concerns abamectin (Zephyr®) • varying degrees of resistance • not specific to spider mites	Use of OPs not normally recommended because of negative impacts on IPM program.

Pest	Effective Alternatives	Comments
In the Pipeline	Compound D • early season only • primarily an ovicide • not reduced risk • not scheduled for a registration decision • has been issued for Sec. 18s on cotton	
Spider Mites (all other states)		
Registered	dicofol (Kelthane®) • in RED pipeline • specific to mites • has environmental risk concerns propargite (Comite®) • in RED pipeline • specific to mites • has risk concerns abamectin (Zephyr®) • not specific to mites OPs including chlorpyrifios (Lorsban®) and profenophos (Curacron®) • broad efficacy bifenthrin (Capture®), a synthetic pyrethroid	Indication of availability problems for dicofol, propargite and abamectin. Spider mite problem not of the same magnitude as CA but there appears to be localized outbreaks annually. They can be serious in broader areas during very hot, dry years.
In the Pipeline	Compound D: • early season only • primarily an ovicide • not reduced risk • not scheduled for a registration decision • has been issued for Sec. 18s on cotton	
Resistant Tobacco Budworm		

Pest	Effective Alternatives	Comments
Registered	Bt Cotton • reduced risk • effective and the standard. • however, non-Bt Cotton refuges (4 or 25%) required. • Bt Cotton varieties not always adapted to all growing areas spinosad (Tracer®) is the standard on conventional cotton • reduced risk • equal to or more effective than chlorfenapyr • has had problems with availability since it was registered. • It is expected to be widely available next year	
In the Pipeline	Compound A • Reduced risk • may not be as effective as spinosad Compound B • Reduced risk • may not be as effective as spinosad	
Non-Resistant Tobacco Budworm		
Registered	synthetic pyrethroids, including cypermethrin (Ammo®), esfenvalerate (Asana®), cyfluthrin (Baythroid®), tralomethrin (Scout®), deltamethrin (Decis®), zeta-cypermethrin (Fury®), lambda-cyahalothrin (Karate®), bifenthrin (Capture®) OPs including sulprofos (Bolstar®), and profenofos (Curacron®) carbamates including thiodicarb (Larvin®) spinosad (Tracer®) Bt Cotton Bt foliar applications in early season on non-Bt cotton.	Three-phase program for control of non-resistant tobacco budworm strategy would specify the use of OPs and carbamates or foliar Bt (on non Bt Cotton) early, synthetic pyrethroids midseason, and OPs and/or carbamates late season

Pest	Effective Alternatives	Comments
In the Pipeline	Compound A • reduced risk • may not be as effective as spinosad Compound B • reduced risk • may not be as effective as spinosad	

V. Risk Benefit Determination. FIFRA Sec. 3.C.(5) provides that "the Administrator shall register a pesticide if the administrator determines that, [among other things]... it will perform its intended function without unreasonable adverse effects on the environment...". Unreasonable adverse effects are defined as "(1) any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide." (As noted above, the Administrator may also conditionally register a pesticide under certain circumstances. Consult FIFRA for additional information about conditional registration). In this section, EPA will set forth some considerations for making a risk benefit determination for this compound.

The Agency has been evaluating the risks and benefits of chlorfenapyr for the control of cotton pests since 1994, when several cotton States submitted the initial Section 18's. The qualitative analyses of this active ingredient have shown that it has its greatest efficacy and benefits against beet armyworm, and may have an important place in the control of one or more spider mite species attacking cotton in California. However, the Agency is concerned about chlorfenapyr's potential for adverse ecological effects (especially on bird reproduction) and build-up in the environment because of its persistence. For these reasons, EPA is also concerned about any use that would permit applications repeated annually on the same acreage.

The Agency appreciates the need for the nation's cotton growers to remain competitive in an international market. This includes having a diverse arsenal of active ingredients to control important cotton pests, in order to obtain high yields of quality fiber as economically as possible, consistent with the FIFRA standard to avoid unreasonable risk to the environment. In addition, chlorfenapyr is registered in other countries for use on cotton, among other crops. EPA recognizes that U.S. growers would like to use the same pesticide available to their competitors in the world market. However, under FIFRA, the Agency also has the responsibility to protect the environment.

For beet armyworm control, chlorfenapyr is one of the most effective materials available, the other being spinosad (Tracer®), which has been registered as a reduced risk compound. It is also important to note that for beet armyworm, the likelihood that chlorfenapyr will be applied to cotton acres on two or more successive years is relatively small, because the pest is sporadic, and because an effective alternative is available. The Agency is also aware that the need for chlorfenapyr to control this pest is increased by the initiation of boll weevil eradication programs in several Mid South states, for the reasons outlined in the section on benefits. For these reasons, the strongest case that the benefits of chlorfenapyr outweigh its risks may be made for use against the beet armyworm.

Spider mites on cotton in California are also a serious problem because, like the beet armyworm, they are erratic and cause serious economic losses on a variable number of acres annually. California has a well established IPM program and uses the chemicals that are least disruptive to the beneficial insects that attack cotton pests. One or more species of spider mites in California have developed resistance to all of the materials used in the IPM program. For spider mites in California, the case for benefits outweighing risks is not as strong as the case for beet armyworm. The Agency's chief concern is the possibility of repeat annual applications, allowing the compound to build up in the environment, thus increasing the severity of the impacts on birds (and other species).

For spider mites outside of California, the Agency recognizes that in some local areas, the twospotted spider mite can cause losses, and this concern has been discussed in the section on benefits. Should there be a serious outbreak, it is possible that a Section 18 could be considered in future years. Thus, at the present time, the Agency believes, for spider mites outside of California, the risks outweigh the benefits for the following reasons: several effective alternatives are available, and the probability of repeated annual applications for several pest species will cause increased build-up of chlorfenapyr in the environment, increasing the severity of the impacts on birds (and other species).

The Agency is aware that the resistant tobacco budworm has been a serious concern to cotton growers, primarily in the Mid South and parts of Texas, since the late 80's. The benefits of chlorfenapyr use has been discussed above, in the section on benefits. Thus, for resistant tobacco budworm, EPA believes the risks outweigh the benefits for the following reasons: effective alternatives are available and new chemicals are in the pipeline for registration and/or are potentially available under Sec. 18. In addition, registration of chlorfenapyr on this pest will likely result in the application of this material on the same cotton acres year after year, at an application rate higher than for spider mites or beet armyworm. These circumstances would cause a greater build-up of the compound in the environment, resulting in more severe impacts on birds (and other species).

For non-resistant populations of the tobacco budworm and the bollworm, the Agency believes that there are many effective alternatives to chlorfenapyr available to control these pests. Thus, for these pests, the benefits of registration are minimal and the risks greatly outweigh them.

VI. Issues. EPA has set forth its understanding of the risk/benefit case for chlorfenapyr use on cotton, and invites the public to comment on the general policy issues set forth below:

A. Before making its regulatory decision, is there any additional information the Agency should consider that it currently has not?

B. Are the assessment characterizations of the ecological risks and the economic benefits associated with the proposed use of chlorfenapyr on cotton scientifically sound? Or do they require additional considerations or analysis? What, if anything, else should the Agency consider or change in the assessments before rendering its decision?

C. Are there mitigation measures other than those already considered by the Agency (Sec. III.B.5.) that may help to reduce the exposure and thus ecological risk?