

i. 1-Year neurotoxicity in rats. No observed adverse effect level (NOAEL) 60 ppm (2.6/3.4 mg/kg bwt/day M/F).

ii. 1-Year dog dietary. NOAEL 120 ppm (4.0/4.5 mg/kg bwt/day M/F).

iii. 24-Month rat dietary. NOAEL for chronic effects 60 ppm (2.9/3.6 mg/kg bwt/day M/F and NOAEL for oncogenic effects 600 ppm (31/37 mg/kg bwt/day M/F).

iv. 18-Month mouse dietary - NOAEL for chronic effects 20 ppm (2.8/3.7 mg/kg bwt/day M/F and NOEL for Oncogenic Effects 240 ppm (34.5/44.5 mg/kg bwt/day M/F).

6. *Animal metabolism.* A metabolism study was conducted in Sprague-Dawley rats at approximately 20 and 200 mg/kg bwt using radiolabeled chlorfenapyr. Approximately 65% of the administered dose was eliminated during the first 24 hours (62% in feces and 3% in urine) and by 48 hours following dosing, approximately 85% of the dose had been excreted (80% in feces and 5% in urine.) The absorbed chlorfenapyr-related residues were distributed throughout the body and detected in tissues and organs of all treatment groups. The principal route of elimination was via feces, mainly as unchanged parent plus minor N-dealkylated, debrominated, and hydroxylated oxidation products. The metabolic pathway of chlorfenapyr in the laying hen and the lactating goat was also similar to that in laboratory rats.

7. *Metabolite toxicology.* The parent molecule is the only moiety of toxicological significance in plant and animal commodities.

8. *Endocrine disruption.* Collective organ weights and histopathological findings from the 2-generation rat reproduction study, as well as from the subchronic and chronic toxicity studies in two or more animal species, demonstrate no apparent estrogenic effects or effects on the endocrine system. There is no information available which suggests that chlorfenapyr would be associated with endocrine effects.

#### C. Aggregate Exposure

1. *Dietary exposure.* Based on the completeness and reliability of the toxicity data and the exposure assessment conducted, BASF concludes that there is a reasonable certainty that no harm will result from aggregate exposure to chlorfenapyr, including all dietary exposure.

i. *Food.* There are currently no established U.S. permanent food tolerances for chlorfenapyr. There are two tolerance petitions pending at EPA; 0.5 ppm tolerance on imported citrus

and 1.5 ppm tolerance on greenhouse grown vegetable, fruiting, crop group 8. A dietary exposure estimate based on theoretical maximum residue contribution (TMRC) was conducted using the Dietary Exposure Evaluation Model (DEEM™). The TMRC is a "worst case" estimate for dietary exposure because it assumes that 100% of crop is treated and residues in the food are always found at the tolerance level. Additional assumptions used were all consumption of tomatoes-whole is from treated greenhouse grown tomatoes, greenhouse grown tomatoes are not processed, and all citrus juice in the U.S. is made from treated imported citrus pulp. Default processing factors were used to determine concentrations in processed fractions. The tolerance levels used in the dietary assessment were 0.5 ppm for citrus pulp, 1.5 ppm for vegetable, fruiting, group 8, and 0.01 ppm for all other crops.

a. *Acute exposure.* The acute RfD used for this evaluation was 0.45 mg/kg bwt calculated by applying the 100-fold safety factor to the NOEL from the acute neurotoxicity evaluation of chlorfenapyr. The acute exposure was evaluated at the 99.9<sup>th</sup> percentile. The most highly exposure sub-population was non-nursing infants (<1 yr old) which utilized 16.2% of the acute RfD. Therefore, based on the exposure assessment discussed above, BASF concludes there is a reasonable certainty that no harm will result from the acute dietary exposure to chlorfenapyr residues.

b. *Chronic exposure.* The chronic RfD used for this evaluation was 0.03 mg/kg bwt calculated by applying a 100-fold safety factor to the NOAEL from 1-year rat neurotoxicity study and the chronic feeding studies in the rat and mouse. The most highly exposure subpopulation was children 1–6 years of age which utilized 19.8% of the chronic RfD. Therefore, based on the exposure assessment discussed above, BASF concludes there is a reasonable certainty that no harm will result from the chronic dietary exposure to chlorfenapyr residues.

ii. *Drinking water.* There is no concern for exposure to residues of chlorfenapyr in drinking water based on the approved, pending and proposed directions for use and its physical and chemical properties. Approved uses in the U.S. include applications to ornamental plants inside greenhouses, to a narrow band of soil adjacent to buildings and to crack-and-crevice and spot treatments inside structures. A pending use expands greenhouse applications to vegetable, fruiting, crop group 8. The proposed use for food

handling areas is also applied as a crack-and-crevice and spot treatment inside structures. Chlorfenapyr has extremely low water solubility (120 ppb at 25 °C) and is also immobile in soil and does not leach because it is strongly adsorbed to all common soil types.

2. *Non-dietary exposure.* Non-dietary exposure to chlorfenapyr is expected to be negligible based on assessments made by EPA for the approved use on ornamentals grown in greenhouses, as a termiticide and for indoor applications for general pest control. These assessments were based on the physico-chemical characteristics of the compound, the intended use pattern, and available information concerning its environmental fate. The vapor pressure of chlorfenapyr is less than  $1 \times 10^{-7}$  mm of mercury (Hg); therefore, the potential for non-occupational exposure by inhalation is insignificant. These assessments also apply to the pending use on greenhouse grown vegetable, fruiting, crop group 8 and the proposed use in food handling areas.

#### D. Cumulative Effects

The pyrrole insecticides represent a new class of chemistry with a unique mechanism of action. No other data are available that indicate that any toxicological effects produced by chlorfenapyr would be cumulative with those of any other compound.

The parent molecule, chlorfenapyr is a pro-insecticide that is converted to the active form, CL 303,268, via rapid metabolism by mixed function oxidases (MFOs). The active form uncouples oxidative phosphorylation in the insect mitochondria by disrupting the proton gradient across the mitochondrial membrane. The production of ATP is inhibited resulting in the cessation of all cellular functions. Because of this unique mechanism of action, it is highly unlikely, that toxic effects produced by chlorfenapyr would be cumulative with those of any other pesticide chemical.

In mammals, there is a lower titer of MFOs, and chlorfenapyr is metabolized by different pathways (including dehalogenation, oxidation and ring hydroxylation) to other polar metabolites without any significant accumulation of the potent uncoupler, CL 303,268. In the rat, approximately 85% of the administered dose is excreted in the feces within 48 hours, thereby reducing the levels of chlorfenapyr and CL 303,268 that are capable of reaching the mitochondria. This differential metabolism of chlorfenapyr to CL 303,268 in insects versus to other polar metabolites in mammals is responsible for the selective insect toxicity of the pyrroles.