

day for males and females. Using an uncertainty factor of 100, the RfD is calculated to be 0.05 mg/kg/day. Based on the acute toxicity data, BASF believes that BAS 510 F does not pose any acute dietary risks.

BAS 510 F was shown to be non-carcinogenic in mice and dogs. There was a slight increase in thyroid follicular cell adenomas at the high dose in both sexes in the rat. A threshold-based mode of action for these tumors based on the EPA publication "Assessment of Thyroid Follicular Cell Tumors" (EPA/630/R-97/002, March, 1998) has been proposed. BASF believes the data to support this proposed mode of action are strong, and that the thyroid tumors seen in the rat following BAS 510 F exposure have a threshold. In addition, a battery of genotoxicity studies demonstrated that BAS 510 F has no genotoxic or clastogenic potential. Therefore, BASF believes that the threshold approach to regulating BAS 510 F is appropriate. Also, it should be noted that, while the Agency has in the past considered tumors of this type to be potential human carcinogens, the European Union has published a policy which considers these tumor types, when they occur at low incidence rates in the rat, to not be relevant to man. The publication: "European Commission, European Chemicals Bureau, ECBI/49/99 Add. 1 Rev. 2; Draft Summary Record, Commission Group of Specialized Experts in the Fields of Carcinogenicity, Mutagenicity and Reprotoxicity, Meeting at Arona, 12 September 1999." Therefore, BASF believes that these tumors are not likely relevant to humans and, if these tumors are to be considered relevant to humans, the threshold approach to cancer risk assessment is appropriate.

6. *Animal metabolism.* In the rat, the predominant route of excretion of BAS 510 F is fecal with urinary excretion being minor. The half-life of BAS 510 F is less than 24 hours. Saturation of absorption appears to be occurring at the high dose level. BAS 510 F is rapidly and intensively metabolized to a large number of biotransformation products. The hydroxylation of the diphenyl moiety was the quantitatively most important pathway. Second most important was the substitution of the Cl of the 2-chloropyridine part against SH by conjugation with glutathione. No major differences were observed with regard to label, sex, and dose level. In hens and goats the residues of concern were determined to be parent, the hydroxylated metabolite M510F01 (2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl)nicotinamide), and the glucuronic acid of the metabolite M510F02.

7. *Metabolite toxicology.* No additional studies were required for metabolite toxicology.

8. *Endocrine disruption.* No specific tests have been conducted with BAS 510 F to determine whether the chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects. However, there were no significant findings in other relevant toxicity studies (i.e., subchronic and chronic toxicity, teratology and multi-generation reproductive studies) which would suggest that BAS 510 F produces endocrine-related effects.

#### C. Aggregate Exposure

1. *Dietary exposure—i. Food.* A chronic dietary exposure analysis was conducted for BAS 510 F including crops which are target uses as well as inadvertent residues in rotational crops. The analysis assumed 100% of the crops were treated, default processing factors (even though much lower experimentally-derived processing factors are available), and used the tolerance value for residues. Even with these worst-case assumptions, it was determined that the Theoretical Maximum Residue Contribution (TMRC) was only 30.1% of the RfD dose for the U.S. population and 62.5% for children 1–6 years (the highest exposed age-related subpopulation). Based on the toxicology results, an acute dietary risk assessment for BAS 510 F is most likely not required, but if so only for children 1–6 years. For dietary exposure estimation, 100% crop treated and tolerance values for residues were used. The resulting acute exposure prediction for children 1–6 years (the highest exposed age-related subpopulation) resulted in an acceptable 8.8% of the acute reference dose at the 95th percentile. If a more realistic scenario were used assuming percent crop treated and the range of residues, a much lower exposure would be obtained.

ii. *Drinking water.* Estimates of ground water and surface water levels were determined using Screening Concentrations in Ground Water (SCI-GROW) and First Index Reservoir Screening Tools (FIRST) models, respectively. Using SCI-GROW to estimate chronic exposure to BAS 510 F from drinking water, drinking water consumption utilizes 0.15% of the RfD for the U.S. population and 0.044% for children ages 1–6. Using FIRST to estimate chronic exposure to BAS 510 F from drinking water, drinking water consumption utilizes 0.08% of the RfD for the U.S. population and 0.24% of the RfD for children ages 1–6.

2. *Non-dietary exposure.* BAS 510 F is not currently planned for residential uses. Thus, residential exposure is not aggregated into the risk assessment.

#### D. Cumulative Effects

Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." BAS 510 F is a foliar fungicide chemically belonging to the carboxin class of fungicides. BAS 510 F acts in the fungal cell by inhibiting of mitochondrial respiration through inhibition of the succinate-ubiquinone oxidase reductase system in Complex II of the mitochondrial electron transport chain. BAS 510 F shares this mode of action with only one other currently registered U.S. pesticide carboxin. EPA is currently developing methodology to perform cumulative risk assessments. At this time, there is no available data to determine whether BAS 510 F has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, BAS 510 F does not appear to produce a toxic metabolite produced by other substances.

#### E. Safety Determination

1. *U.S. population.* Using the conservative exposure assumptions described above and based on the completeness and the reliability of the toxicity data, BASF has estimated that aggregate exposure to BAS 510 F will utilize 30.2% of the RfD for the US population. For the highest exposed age-related subpopulation (children 1-6 years), the maximum aggregate exposure is predicted to be 62.8% of the reference dose. BASF concludes that there is a reasonable certainty that no harm will result from the aggregate exposure to residues of BAS 510 F, including anticipated dietary and drinking water exposures and non-occupational exposures.

2. *Developmental toxicity in the rat.* A developmental study was conducted via oral gavage in rats with dosages of 0, 100, 300, and 1,000 mg/kg bwt/day with a maternal and developmental no observed adverse effect level (NOAEL) of 1,000 mg/kg. No evidence of developmental toxicity was observed up to the highest dose tested.

3. *Developmental toxicity in the rabbit.* A developmental study was