

following are summaries of chronic toxicity studies submitted to EPA.

The chronic toxicity/oncogenicity studies with BAS 510 F include a 12-month feeding study with Beagle dogs, an 18-month B63CF1 mouse feeding study, a 24-month Wistar rat chronic feeding study and a 24-month Wistar rat oncogenicity study.

At the highest dose tested in dogs, effects observed consisted primarily of increased liver and thyroid weights and some serum clinical chemistry changes. The NOAEL was 800 ppm (21.8 mg/kg bw males; 22.1 mg/kg bw females).

Decreased body weights were seen in males in the mouse chronic study at doses of 400 ppm and above. Decreased female body weight was seen at doses of 2,000 ppm and above. The target organ in this study was the liver. In both the rat chronic and oncogenicity studies, the highest dose tested of 15,000 ppm exceeded a maximum tolerated dose (MTD) and was discontinued after 17 months. Effects observed at the next highest dose of 2,500 ppm primarily centered around the thyroid and liver.

Overall, mild toxicity was observed with chronic exposure to BAS 510 F. No evidence of treatment-induced oncogenicity was observed in the mouse or dog studies. A slight increase in thyroid follicular cell adenomas was seen in both sexes at the high dose when the data from both rat bioassays are combined.

A mode of action (MOA) for the thyroid follicular cell adenomas has been proposed. This MOA is based on the EPA publication "Assessment of Thyroid Follicular Cell Tumors," March 1998, EPA/630/R-97/002. This document describes the criteria which must be met in order for a compound to be considered under the MOA described in that publication. BASF Corporation believes that BAS 510 F has met the cited criteria.

6. *Threshold effects.* Based on a review of the available chronic toxicity data, BASF believes EPA will establish the RfD for BAS 510 F at 0.05 mg/kg/day. This RfD for BAS 510 F is based on the 2-year chronic and 2-year oncogenicity studies in rats with a threshold average NOEL of 5 mg/kg/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 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 MOA 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 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, 1 – 2 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.

7. *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. In hens and goats the residues of concern were determined to be parent, the hydroxylated metabolite M510 F01 (2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl)nicotinamide), and the glucuronic acid of the metabolite M510 F02.

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

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 to include the proposed uses of apples and hops. The dietary exposure included prior tolerances for beet root, root vegetables, tuberous and corm vegetables, bulb vegetables, leafy vegetables, head and stem brassica, leafy brassica greens, legume vegetables, fruiting vegetables, cucurbit vegetables, stonefruit, berries, tree nuts, pistachios, cereal grains, mint, grapes, raisins, strawberries, peanut, peanut meal, peanut oil, cotton seed, soybean seed, canola, flax seed and sunflower seed in addition to the new tolerances for apples and hops. 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. The one exception to the use of defaults was for the apple processing, where an average calculated processing factor of 0.09 was used for apple juice. For apple juice concentrate, the juice factor of 0.09 was adjusted by the ratio of the default concentrate (3.9) and default juice (1.3) processing factors, which led to an estimated processing factor of 0.27 for apple juice concentrate. Even with these worst-case assumptions, it was determined that the Theoretical Maximum Residue Contribution (TMRC) was only 34.0% of the reference dose for the U.S. population and 77.1% 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 non-nursing infants <1 year old. For dietary exposure estimation, 100% crop treated and tolerance values for residues were used. The resulting acute exposure prediction for non-nursing infants (the highest exposed age-related subpopulation) resulted in an acceptable 10.6% 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 and surface water levels were determined using SCIGROW and FIRST models, respectively. The drinking water level of concerns (DWLOCs) for chronic exposure are obtained by subtracting the chronic dietary food. This is outlined in the following table.