

multigeneration study, resulted in an increased incidence of hepatic centrilobular hypertrophy — a parameter which could not have been detected in the DNT study as liver histopathology on parental animals was not performed in the DNT study.

4. *Subchronic toxicity.* The subchronic toxicity of BAS 510 F was investigated in 90-day feeding studies with rats, mice and dogs, and in a 28-day dermal administration study in rats. A 90-day neurotoxicity study in rats was also performed. Generally, mild toxicity was observed. At high dose levels (doses above the LOAELs) in feeding studies, all three species displayed alterations in various clinical chemistry parameters. These clinical chemistry alterations were likely secondary to general toxicity. Statistically significant increased absolute and relative thyroid weights were observed in male rats only at doses at and above the LOAEL. Increased absolute and relative liver weights were observed in both sexes at doses above the LOAEL in rats and dogs. Increased absolute and relative liver weights were seen in both sexes of the mouse at lower doses. However, the increases in liver weights at these lower doses in the mouse were not deemed to be compound related due to the unusually low concurrent control liver weight values. At doses above the LOAELs, liver weight increases were supported by histopathology alterations in the rat and mouse, but not in the dog. Overall, only mild toxicity was observed in oral subchronic testing.

In the 28-day repeat dose dermal study, no systemic effects were noted up to the highest dose tested of 1,000 mg/kg/day.

In a 90-day rat neurotoxicity study, there was no mortality, signs of clinical toxicity, or adverse effects on food consumption or body weight at any dose level in either sex. No signs of neurotoxicity were observed during clinical observations, functional observation batteries, or motor activity measurements of neuropathology. Therefore, there were no selective neurotoxic effects. Adverse effects were not seen even at the highest dose level tested. A LOAEL was not found and the NOAEL is the highest tested of 15,000 ppm (1,050 mg/kg/day in males; 1,272 mg/kg/day in females).

5. *Chronic toxicity.* Based on review of the available data, the Reference Dose (RfD) for BAS 510 F will be based on a 24-month feeding study in rats with a threshold No-Effect Level (NOEL) of 5 mg/kg/day. Using an uncertainty factor of 100, the RfD is calculated to be 0.05 mg/kg/day. The 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 2000 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 Reference Dose (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 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 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 with regard to label, sex, and dose level.

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.

9. *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