

dams were substantially elevated at these dose levels. Elevated tyrosine levels are known to cause kidney toxicity.

4. *Subchronic toxicity.* The subchronic toxicity of BAS 670 H was investigated in 90-day feeding studies in rats, mice and dogs, and in a 28-day dermal administration study in rats. Several supplemental short-term mechanistic studies in rats and mice were performed to elucidate the mode of action. Generally, very mild toxicity was observed in mice and dogs at high doses. In a combined neurotoxicity 90-day feeding study in rats, no signs of neurotoxicity were observed. Effects were seen in the pancreas, eye, kidney, liver, and thyroid gland. The target organs are identical with those in the chronic feeding studies with rats.

Two modes of action have been elucidated for BAS 670 H by short-term mechanistic studies, one leading to effects on eyes, kidney and liver, and a second leading to effects at the thyroid: BAS 670 H causes elevated tyrosine levels by HPPD inhibition accounting for effects on eye, liver and kidney. The mouse is the accepted model for this tyrosine level elevations, and a NOAEL of 1.2 mg/kg bwt/day was established for tyrosine elevation in mice. Other mechanistic studies demonstrated an impairment of pituitary-thyroid hormone levels by enhancing the hepatic clearance of thyroid hormones. The NOAEL for interference with thyroid hormones was 0.4 mg/kg bwt/day. The NOAEL for effects on the exocrine pancreas in rats was 1.1 mg/kg bwt/day. Similar effects were seen in the 28-day dermal study with rats; the NOAEL was 100 mg/kg bwt/day.

5. *Chronic toxicity.* The chronic toxicity and oncogenicity studies with BAS 670 H include two 12-month feeding studies with dogs, an 18-month mouse feeding study, a 12-month rat chronic feeding study and a 24-month rat oncogenicity study. In the chronic dog study, mild reductions of the body weight were observed at high doses. The NOAEL was 100 ppm (2.9 and 3.1 mg/kg bwt/day in males and females respectively).

In the 18-month chronic feeding study in mice, increased liver weights were seen at high doses. The NOAEL was 80 ppm (19 and 26 mg/kg bwt/day in males and females respectively). BAS 670 H was not carcinogenic to mice. In the chronic feeding studies in rats, the main target organs were eye, liver, kidney, thyroid gland, and pancreas. The same organs were affected in the subchronic studies. Short-term mechanistic studies demonstrated that BAS 670 H causes elevated tyrosine

levels by HPPD inhibition accounting for effects on the eye, liver and kidney. The mouse is the accepted model for this tyrosine level elevation, and a NOAEL of 1.2 mg/kg bwt/day was established for tyrosine elevation in mice. The NOAEL for effects on the exocrine pancreas in rats 6 ppm in both genders (0.4 and 0.5 mg/kg bwt/day in males and females respectively). At the end of the 24-month oncogenicity study, there was a slight but significant increase in benign thyroid adenomas in both genders. The thyroid was the only organ affected and the increase of the adenomas was significant only at the highest dose tested, while considerable general toxicity was already seen at 20-times lower doses. The mechanism of thyroid tumor formation by BAS 670 H was thoroughly investigated in short-term mechanistic studies. An enhanced hepatic clearance of thyroid hormones impairs pituitary-thyroid hormone levels leading to hypertrophy, hyperplasia and ultimately neoplasia. There is general agreement, that this mechanism is well understood in rodents and is of minor relevance to humans. A clear NOAEL of 0.4 mg/kg bwt/day was demonstrated for effects on thyroid hormone levels. A threshold (non-linear) cancer assessment is proposed and a cancer classification as "not likely to be a human carcinogen."

6. *Animal metabolism.* In the rat metabolism studies, the majority of the residue was excreted within 48 hours from both males and females. In all matrices investigated unchanged parent is the main component. Degradation starts with hydroxylation of the oxazole ring. The identified metabolites from both pyrazole ring label and phenyl ring label studies are reported. Goat and hen metabolism studies were conducted with feeding levels of about 10 ppm. In the goat, the majority of the applied dose was excreted. Non-metabolized BAS 670H was the major radioactive residue, and M670H02, formed from hydroxylation at the 4-position of the isoxazole ring, was the only significant metabolite formed. In poultry BAS 670 F was also rapidly excreted. Residues in liver consisted mainly of BAS 670H, and the only significant metabolite in poultry was again M670H02. The significant metabolite M670H02 was found in the rat metabolism study.

7. *Metabolite toxicology.* Toxicity of the metabolites of BAS 670 H with potential exposure to humans was concurrently evaluated during toxicity testing of the parent, because both plant and animal metabolites are formed during the course of toxicity testing. Both plant and animal metabolites are considered not of toxicological concern.

Some testing was conducted on the anaerobic aquatic metabolite, 670M10. The results as given below show no toxicological concern:

- Bacterial reverse mutation test (Ames): No effect = negative.
- Mammalian somatic cell gene mutation test (MNT): No effect = negative.
- Cytogenetic study *in vivo* (mouse HPRT): No effect = negative.
- 28-Day feeding study (rat): NOAEL 1,197 mg/kg bwt/day and 1,304 mg/kg bwt/day (male and female, respectively).

8. *Endocrine disruption.* BAS 670 H has been shown to alter thyroid hormone levels in rats as also observed with other 4-hydroxyphenylpyruvate dioxygenase enzyme inhibitor active ingredients. However, there have been no effects noted on sexual or other hormones in numerous subchronic and chronic toxicity studies with multiple species.

#### C. Aggregate Exposure

1. *Dietary exposure.* A chronic population adjusted dose (cPAD) of 0.00044 mg/kg/day is proposed. This cPAD is based on a lowest observed adverse effect level (LOAEL) of 0.4 mg/kg/day for pup renal pelvis dilation in the 2-generation rat reproduction study with an extra 3X uncertainty factor for using the LOAEL (rather than a NOAEL) plus a 3X Food Quality Protection Act (FQPA) factor on top of the standard 100X uncertainty factor. So the total uncertainty factor is 900 ( $3 \times 3 \times 100$ ), and the cPAD is calculated as  $0.4/900 = 0.00044$ .

An acute dietary population adjusted dose (aPAD) is proposed as 0.0013 mg/kg/day. This aPAD is based upon a NOAEL of 0.4 mg/kg/day obtained in the rat thyroid hormone study and a 3X FQPA uncertainty factor on top of the standard 100 ( $0.4/300 = 0.0013$ ).

BAS 670 H has been shown to be non-carcinogenic in mice, but was associated with an increase in thyroid follicular cell tumors at high doses in the rat. These tumors have been shown to develop by a non-genotoxic mode of action, in fact they were the consequence of induced changes of thyroid hormone levels. Therefore BAS 670 H should be classified as "not likely to be a human carcinogen."

i. *Food.* Exposure estimates were compared against the cPAD and aPAD of 0.0013 mg/kg bwt/day and 0.004 mg/kg bwt/day, respectively. Results of the chronic dietary exposure assessments demonstrated that even with the worst-case assumptions (residues at tolerance level and 100% crop treated), the estimated chronic dietary exposure was