



## 9.0 CONTINUATION SHEET

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### Continuation of 2.1

As reproductive findings are a trigger for reporting preliminary toxicity findings, the following data is being reported.

In this study, vacuolation and hypertrophy/activation of the Leydig cells was found in the testes of males which received 630 or 2000 ppm BAJ 2740. Additionally, degeneration and/or immaturity of the testicular germinal epithelium occurred in males of the intermediate- and high-dose groups. Secondary to the testicular alterations, oligospermia and aspermia of the epididymides, and prostatic immaturity were found in males dosed with 630 or 2000 ppm BAJ 2740... Evaluation of these findings, however, should be performed when all study data is available and the final report is generated.

#### Discussion of Reported Effects

A subchronic feeding toxicity study was performed in dogs with concentrations of 0, 200, 630, and 2000 ppm in the diet. In this study, histopathological examination revealed treatment-related findings in the liver after 2000 ppm (cytoplasmic changes, periportal infiltrates, slight single cell necroses), in kidneys after 2000 ppm (dilation of proximal tubules), in adrenal glands in all dose groups (cytoplasmic vacuolation of the cortex, mononuclear cell infiltration), and in the thymus after 2000 ppm (mild cortical atrophy).

Also evidence of effects on the male reproductive system (testes, epididymides, and prostate) were found: Vacuolation and hypertrophy/activation of the Leydig cells was found in the testes of males which received 630 or 2000 ppm BAJ 2740. Additionally, degeneration and/or immaturity of the testicular germinal epithelium occurred in males of the intermediate and high dose group. Secondary to the testicular alterations, oligospermia and aspermia of the epididymides, and prostatic immaturity were found in males dosed with 630 or 2000 ppm BAJ 2740. The no-(adverse)-effect-level for male sexual organs was established at 200 ppm. A no-(adverse)-effect-level was not established with respect to the adrenal glands.

## STATUS OF PROJECT: BAJ 2740

### Project Management Toxicology

Results of a subchronic feeding study in dogs (T 4061566) (14 weeks)

Dose (ppm)	BW/FC	Clin. signs	Clinical chemistry/hematology	Organ weights	Histology
200	-	-	ECOD, ALD ↑ (m/f) EROD ↑ (f)	-	Adrenal cortex: cytoplasm. vacuolation (m/f)
630	BW: (↓) (m/f)	-	AST/ALT/AP/GLDH ↑ (f), Chol (↓) ECOD, ALD ↑ (m/f), EROD ↑ (f)	Liver: ↑ (m/f) Adrenals: ↑ (f) Pituitary: ↑ (f)*	Adrenal cortex: cytoplasm. vacuolation (m/f) Testes: hypertrophy and vacuolation of Leydig cells, immature germinal epithel. Epididymides: aspermia, oligospermia Prostate: immature
2000	BW: ↓ (m/f)	-	AST/ALT/AP/GLDH ↑ (m/f), Chol ↓ (m/f) ECOD, ALD ↑ (m/f) EROD ↑ (f) T4 ↓ (m/f)	Liver: ↑ (m/f) Adrenals: ↑ (f) Pituitary: ↑ (f)* Kidneys: ↑ (m/f)	Liver: cytoplasmic change, single cell necroses, inflammat. infiltration Kidneys: dilat. of prox. tubule Thymus: cortical atrophy Adrenal cortex: cytoplasm. vacuolation (m/f) Testes: hypertrophy and vacuolation of Leydig cells, immature germinal epithel. Epididymides: aspermia, oligospermia Prostate: immature

n = 4/dose/sex

\* only slight differences, but dose-related in females