Laboratory Animal Paper - Sample Long Answer Question

A variety of mechanisms may result in reduced fertility rates in rat reproductive toxicity studies. For each of the mechanisms listed below, describe and explain the effects including where appropriate the hormone levels, organ weights, estrous cycles, and microscopic findings (or lack of) observed in male and female reproductive tissues during the pathological evaluation.

Stress/decreased food consumption in males and females (15 marks).

Hyperprolactinaemia in females (6 marks)

Androgen (testosterone, DHT) agonists in males and females (comment on any distinctive effects of dose level) (16 marks)

Model answers and marks awarded.

Stress/decreased food consumption (15 marks).

Stress activates the HPA axis (for example, glucocorticoid/epinephrine levels are raised). Activation of the hypothalamus-pituitary-adrenal axis results in a reduction in gonadotrophic hormone (LH, FSH) release from the pituitary (1). In females this results in cycle cessation (1) or cycle asynchrony (1). There is atrophy of the reproductive tract with reduced uterus weight (1) and microscopically decreased height of the endometrium (1), reduced thickness of the myometrium (1) and thinning of the vaginal epithelium (1). In the ovaries, lower weight (1), decreased number and size of corpora lutea (1) and interstitial glands of the ovary may change from their normal phenotype to become small spindle-shaped cells with dark elongated nuclei (1). In males, the reduction in gonadotrophic hormones (GnRH, LH) leads to a reduction in testosterone production in Leydig cells (1) and the lower testosterone levels leads to lower weight of accessory sex glands (1) but is usually not sufficiently reduced to affect spermatogenesis so testis weights are normal (1) and there are no microscopic changes in the germinal epithelium (1). Epididymis weights may be reduced slightly (1).

Hyperprolactinaemia (6 marks)

Hyperplasia (1) and increased secretion (1) in the mammary gland. There is persistent diestrus evident in the reproductive tract (1) with mucification of the vaginal epithelium (1) and persistent (1) hypertrophic (1) corpora lutea.

Androgen agonists (comment on any distinctive effects of dose level) (16 marks)

Trophic effects on accessory sex glands (prostate/seminal vesicle) via androgen receptors (1) leads to higher weight (1) through increased secretion and hyperplasia (1). Increased negative feedback on the hypothalamus-pituitary-gonadal axis leads to decreased luteinizing hormone (1). In males, decreased LH stimulation of Leydig cell steroidogenesis leads to localized reduction in testosterone levels (1) impairing spermatogenesis, evident microscopically as degeneration of spermatocytes and spermatids (1), with retention of spermatids (1). Higher doses of an androgen agonist may overcome this localized effect on testosterone levels, leading to an inverse dose relationship (2). Atrophy of Leydig cells is not apparent microscopically unless effect (decreased LH) is severe so typically only seen at high dose if at all (1). Testis and epididymis weights are lower (1), the latter mainly due to reduced sperm evident microscopically (1). In females, disruption of LH reduces cycling leading to persistent diestrus (1), vaginal mucification (1), uterine hyperplasia/hypertrophy (1) and the mammary gland acquires a male-like phenotype (1).