THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 18 March 2003

TOXICOLOGY

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Describe how cytochrome P450 CYP enzyme induction and inhibition can modify endocrine function with examples of phenotypic alterations.

2. Outline the mechanisms for the development of drug-induced phospholipidosis in the rat and dog and discuss its relevance for man.

3. "Non-rodent toxicology studies provide little added value to the safety evaluation of pharmaceuticals". Discuss this statement and give criteria for non-rodent species selection.

4. Discuss, with examples, the biochemical reasons for species differences in toxicity.

5. Compare and contrast the use of *in vitro* and *in vivo* assessments of genotoxicity and discuss their advantages and disadvantages.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 18 March 2003

TOXICOLOGY (Option d)

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Discuss the mechanisms by which conjugation of drugs or xenobiotics with reduced glutathione can result in either an increase or decrease in toxicity, illustrate your answer with selected examples.

2. Excitotoxicity refers to the ability of glutamate and related excitatory amino acids to destroy neurons, discuss current concepts on the mechanisms underlying this process.

3. Write short notes on the following:
   (a) T max and AUC,
   (b) Urinary and biliary clearance and half-life,
   (c) Tissue distribution.

4. Discuss the proposed mechanisms of porphyria by the following chemicals: lead hexachlorobenzene griseofulvin

5. Discuss the biochemical basis for the adverse effects of the fibrate class of hypolipidaemic drugs.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2002

TOXICOLOGY

First Paper

Candidates must answer FOUR questions ONLY

Time allowed – THREE HOURS

1. Discuss potential difficulties in the safety assessment of recombinant human proteins to be used for long term therapy.

2. Discus the use of transgenic and gene knockout mouse models in carcinogenicity testing. Emphasise limitations and benefits.

3. Describe how potential effects on the eye can be monitored during the safety assessment of a new agro-chemical.

4. Give a critical account of the techniques available for detecting abnormalities in rat foetuses. Comment on the relevance of such observations for human risk assessment.

5. Recent changes have been made in the guidance given by regulatory authorities for the assessment of the immune system in repeat dose toxicity studies. Briefly outline the nature of the changes and then discuss what benefits you believe they can bring to pre-clinical safety evaluation.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2002

TOXICOLOGY

(histopathology and comparative pathology with special reference to toxicology)

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed – THREE HOURS

1. For any *three* of the following compare and contrast the following pairs of chemicals in their effects on biological tissue:
   (a) Organic and inorganic mercury salts,
   (b) Triethyl and trimethyl tin compounds,
   (c) Chloroform and carbon tetrachloride,
   (d) D-limonene and hexachlorobutadiene,
   (e) Paraquat and diquat.

2. Discuss the mechanism of induction of "light hydrocarbon nephropathy" and its risk assessment for human exposure.

3. Discuss the effects of spontaneous lesions on the interpretation of animal toxicity studies.

4. Rats in the high dose group of a 28-day dietary toxicity study on a pesticide have been noted to be mildly ataxic and show reduced muscle tone in the hind limbs. What pathology techniques could be employed to investigate this condition?

5. Describe how the rat nasal cavity should be prepared for histological assessment following inhalation exposure of xenobiotics. Survey the toxicological lesions that might be encountered in the nasal cavities of rats on inhalation studies with chemicals.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 1998

TOXICOLOGY

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Discuss the relative merits and limitations of *in vitro* tests in toxicological investigations.

2. Describe immunotoxicity testing, including comment on the predictive value of the various tests employed.

3. Outline the appropriate studies for reproductive toxicity testing of new psychotropic agents which have potential target effects on the testes.

4. Write short notes on the following:

   (i) cytochrome P-450 family
   (ii) area under the curve
   (iii) genetic polymorphism
   (iv) Syrian Hamster Embryo (SHE) cell assay
   (v) telomerase.

5. Discuss the possible predictive role of 90 day rodent toxicity tests in assessing likely non-genotoxic carcinogens. How can existing protocols for such tests be improved for this purpose?

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 1998

TOXICOLOGY

(histopathology and comparative pathology with special reference to toxicology)

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Analyse causes and consequences of hepatomegaly in rodents.

2. Discuss the mechanisms of tumour dissemination.

3. Write short notes on the following:

   (i) eosinophil leucocytes
   (ii) $P53^{+/-}$ hemizygous mice
   (iii) collagen type IV
   (iv) dystrophic calcification
   (v) immunohistochemical markers for cell proliferation.

4. Write short notes on the toxicological aspects of

   (i) apoptosis
   (ii) carcinoid tumours
   (iii) alpha-2 microglobulin
   (iv) osteoporosis
   (v) glioma.

5. Describe acute and chronic effects of oestrogen treatment at toxic doses in laboratory animals.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

April 1997

TOXICOLOGY

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Describe how xenobiotics may adversely affect the cardiovascular system in animal toxicity studies. What principles would you use in the assessment of their relevance for humans?

2. To what extent can whole animal toxicity studies predict adverse effects of xenobiotics in humans? Provide examples that illustrate the relationship between toxicity in particular organs or organ systems in animals and specific adverse effects in humans.

3. Write short notes on:

   a) the use of polymerase chain reaction in diagnosis

   b) skeletal muscle atrophy

   c) criteria for maximum tolerated dose (MTD) determination

   d) criteria for group sizes in regulatory toxicity studies

4. Outline the principal steps in *in vitro* toxicity test method validation and identify the performance criteria which need to be met before a test could be accepted for regulatory purposes.

5. Discuss the main issues in the safety assessment of biotechnology derived protein pharmaceuticals.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

April 1997

TOXICOLOGY
(histopathology and comparative pathology with special reference to toxicology)

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Describe the principal pathological alterations that can be produced in the liver through the administration of xenobiotics and the mechanisms by which they occur.

2. Discuss the histopathological implications of the use of transgenic animal models in chemical safety evaluation.

3. Compare and contrast mammary tumours in rats and mice.

4. Critically analyse the pathomechanism and human relevance of chemically induced rodent carcinoid tumours. Propose appropriate clinical investigations to verify the safety of such drugs.

5. Give an account, with examples, of drug and chemical testicular toxicity.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 1995

TOXICOLOGY

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. AB12345 is a racemate in early development and intended for the treatment of diabetes mellitus. Discuss the issues associated with an intention to develop a single isomer. Describe on what basis a decision could be taken to develop one of its two isomers.

2. Outline the value and practicability of using results from non-clinical safety evaluation to guide monitoring for adverse effects in humans for

   a) a compound to be used as a fire-retardant on children's pyjamas;

   b) a medicine for chronic use.

3. Devise a minimum battery of genotoxicity assays, justifying your choice of assays in drug development, with particular reference to the detection of genotoxic carcinogens.

4. Write short notes on <u>three</u> of the following

   a) Cytochrome P450

   b) testicular interstitial cell tumours in rats

   c) occupational exposure levels

   d) allergic contact responses

   e) volume of distribution.

5. Discuss issues associated with animal welfare in regulatory toxicology.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 1995

TOXICOLOGY

(histopathology and comparative pathology with special reference to toxicology)

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Define in detail what "SPF-status" means for laboratory rodents. What are the histopathological features associated with SPF status which distinguish such animals from those of 'conventional' status? Discuss, with examples, the advantages and disadvantages of using SPF animals in chronic toxicity testing compared to animals of conventional status.

2. Explain in detail how the pathologist can contribute to understanding the mechanism of bladder tumour formation in rats in a 2-year oncogenicity study of high doses of a simple aliphatic acid salt. How might the various findings be related to risk assessment of the substance for man?

3. Write short notes on **three** of the following:

   a) pathological techniques appropriate for investigation of a peripheral neuropathy;

   b) relative value of histochemical and immunocytochemical techniques for the identification of pituitary cell types in carcinogenicity testing;

   c) the toxicologically useful information that can be obtained by study of the femur of the rat in a standard 180-day toxicity test;

   d) the pathological findings in drug-induced nephropathies and their causes. Give examples.

4. How can the pathologist quantify toxic effects in a named organ? Explain the value and weakness of each technique and give illustrative examples.

5. There is an unusually high incidence of bronchitis amongst workers manufacturing a new antipsychotic drug. Two have died from pneumonia. What toxic actions might cause such an effect? As the manufacturer's Chief Pathologist, describe what diagnostic and confirmatory findings you would look for in what types of toxicity tests. What histopathological findings would you anticipate in the autopsies on the workers who died?

THE ROYAL COLLEGE OF PATHOLOGISTS

Final MRCPath/Part 1 Examination

March 1994

TOXICOLOGY

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. "There is a place for primate studies in safety evaluation". Discuss.

2. Describe methods used to evaluate developmental landmarks, behaviour and learning in young rodents. What are the principal strengths and weaknesses of the methods with respect to extrapolation of the results to man?

3. What toxicological data should be collected and how should it be used to set safe limits for the initial human exposures to a new drug?

4. "The distinction between genotoxic and non-genotoxic carcinogens is purely an operational convenience". Discuss with examples.

5. Write short notes on the following:

   a) the definition of clearance, volume of distribution and half-life

   b) implications of genetic polymorphism in drug metabolism

   c) clinical implications of the induction of mixed-function oxidase activity in animal studies.

THE ROYAL COLLEGE OF PATHOLOGISTS

Final MRCPath/Part 1 Examination

March 1994

TOXICOLOGY
(Histopathology)

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. What contribution can pathology make to the immunological assessment of a compound? Illustrate your answer with examples.

2. Define the term cirrhosis. Describe its pathology and systemic effects. Give examples of how it can be induced.

3. How could you investigate the induction of large bowel epithelial hyperplasia in the rodent with the aim of assessing its risk to man?

4. Describe in detail the histology and functions of the cells of the CNS and PNS. How would you detect a mild demyelinating lesion in the CNS and PNS *in vivo* and *in vitro*?

5. Write short notes on the following:

   a) the main processing problems when preparing HE sections and their causes

   b) the effects of enhanced hepatic metabolism on the thyroid in the rat

   c) drug induced pathology of the gall bladder

   d) phaeochromocytomas in the rat.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 1993

TOXICOLOGY

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. A drug is found to be positive in an Ames test. How will this affect its clinical development?

2. Animal teratogens are human teratogens. Discuss.

3. The top dose in a carcinogenicity bioassay should be the maximum tolerated dose. Is this paradigm relevant to risk assessment?

4. Within 5 years the use of *in vitro* tests will replace the need for animals in toxicity studies. Discuss.

5. A xenobiotic belongs to a class of compounds known to affect olfactory, auditory and visual senses. What tests would you recommend to investigate these possibilities?

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 1993

TOXICOLOGY
(Histopathology)

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Discuss the causes and significance of hepatomegaly in laboratory rodents.

2. In a preliminary toxicity study of an industrial chemical agent, rats treated with high dosages developed unsteady gait. How would you characterise the toxicity profile of such a compound?

3. Describe the lesions and complications encountered in laboratory animals given high doses of a corticosteroid compound.

4. Classify the renal tumours encountered in laboratory rodents and describe their characteristics enabling differential diagnosis.

5. Discuss the relative merits and limitations of using Sprague-Dawley rats and Fischers 344 rats in carcinogenicity studies.

THE ROYAL COLLEGE OF PATHOLOGISTS

Final/Part 1 Examination

March 1992

TOXICOLOGY

First Paper

Candidates MUST attempt FOUR questions

Time allowed - THREE HOURS

1. Outline the principles of Good Laboratory Practice. Discuss with examples, as appropriate, the view that "Good Laboratory Practice inhibits good science".

2. Discuss factors vital to the design and running of a rodent facility to conduct long-term toxicity and carcinogenicity studies. Take account of scientific, practical, safety and ethical considerations.

3. Describe, with examples, how *in vitro* studies contribute to knowledge in toxicology.

4. Describe how you would investigate a new chemical for nephrotoxicity.

5. A chemical has induced hepatocellular carcinoma and adenoma in a rat two-year study. Discuss how you would assess the significance of this finding for human exposure including any additional studies that you might conduct.