



The Royal College of Pathologists

Part 1 examination

Toxicology: First Paper (General Toxicology)

Tuesday 18 March 2008

Candidates must attempt to answer all questions

Time allowed: 3 hours

1. Analytical Toxicology
 - a. What is the likely clinical significance of elevated plasma/serum γ -glutamyltransferase?
 - b. Name two “specific” serum/plasma markers to measure if cholestasis was suspected in a dog study?
 - c. What acute effect would giving a high dose mineralocorticoid drug, such as fludrocortisone acetate, have on the plasma?
 - d. Name two of the available methodologies for measuring protein in urine?

2. Biochemical Toxicology
 - a. What is the basis for inter-individual variation in the rate of metabolism of debrisoquine?
 - b. Name two common classes of drugs for which variation in metabolism from this cause may result in an adverse therapeutic response?
 - c. What important drug metabolising enzyme does the Ah receptor upregulate?
 - d. Name two important environmental chemicals that are ligands for the Ah receptor?

3. Occupational Toxicology

- a. What lifestyle factors have been shown to be important in the development of cancer due to asbestos exposure?
- b. What tumour is most pathognomonic for prior exposure to crocidolite asbestos? .
- c. What physicochemical feature of the asbestos fibre is thought to be a risk factor in determining its fibrogenic potential?
- d. What two roles do macrophages play in the pathogenesis of asbestosis?

4. Genetic Toxicology

- a. Why is induced rat liver S9 added to the Ames assay?
- b. Why are Aroclor 1254, or a combination of sodium phenobarbitone and β -naphthoflavone, used to induce the rat liver prior to the preparation of S9?
- c. Identify a key limitation of conventional S9 based activation systems in mirroring in vivo metabolism?
- d. Give an example of a chemical requiring metabolic activation in order to be positive in such an assay?

5. Medical Toxicology

- a. Explain why a recent case of addiction to 'Nurofen Plus' (an Ibuprofen/ codeine formulation) resulted in the death of the affected individual?
- b. Why should this combination be addictive?
- c. Name two target organs affected by non-steroidal anti-inflammatories (NSAIDs)?
- d. What is the pharmacological target for the NSAID's?

6. Mechanistic Toxicology/Basic Physiology

- a. Name three roles that the kidney plays in the control of homeostasis?
- b. What is the mechanistic basis for the toxicity of the industrial intermediate, hexachlorobutadiene, to the kidney?
- c. Name three target organ changes induced by chronic, high level, stress in animals?
- d. What is the biochemical aetiology of hepatic encephalopathy and name a xenobiotic that can cause the disease?

7. Safety Pharmacology

- a. What does the hERG assay assess?
- b. What is the significance of a positive result in the hERG assay? .
- c. What is the significance of QT prolongation in a drug intended as an anti-inflammatory for general useage?
- d. Name two preclinical assays that can be used to assess cardiac arrhythmias of drugs?

8. Immunotoxicology

- a. Name three specific changes that you would expect following chronic administration of an immunosuppressive agent?
- b. Which immunoglobulin class is ubiquitously involved in type 1 anaphylactic hypersensitivity reactions?
- c. Name two *in vivo* assays that are used to detect chemicals having delayed type (cell mediated) hypersensitivity reactions?
- d. Name two immune function assays that could be used to confirm an immunosuppressive effect of a potential drug?

9. Reproductive/Developmental Toxicology

- a. Define the term “endocrine disruptor”?
- b. Name two environmental oestrogens?
- c. How are endocrine disrupters thought to work at the molecular level?
- d. Give a single example of a biological outcome from exposure to an endocrine disruptor?

10. Toxicological Pathology

- a. Name a chemical that induces light hydrocarbon nephropathy in the rat?
- b. Describe the three, cardinal, morphological, features of light hydrocarbon nephropathy?
- c. Describe three features that determine the development of light hydrocarbon nephropathy in the kidney?
- d. What are the long-term consequences of light hydrocarbon nephropathy?

11. General Toxicology

- a. Excluding micro-dosing studies, what is the minimum duration of a preclinical animal study required for a single dose administration of a drug to human volunteers in the EU?
- b. Delayed neuropathy, resulting from exposure to certain organophosphorus compounds, is induced by the inhibition of which enzyme?
- c. Name three factors that affect the toxicity of a drug given to an animal?
- d. Define, AUC, C_{max}, T_{1/2} for a compound given to a subject?

12. Pharmaceutical Toxicology

- a. List two causes of unexpected 'adverse drug reactions'.
- b. Name two causes of drug resistance during cancer chemotherapy?
- c. What is the molecular target for the statin group of chemicals, and toxicity in which target tissues caused the withdrawal of the statin, Baycol (cerivastatin), from the market?
- d. What was the major safety concern associated with the clinical use of the specific Cox 2 inhibitor, Vioxx (rofecoxib), which caused its removal from the market?

13. Molecular Toxicology

- a. Describe three molecular probes that can be used to assess the apoptotic index of cells in culture?
- b. Name two different technologies that can be used with the above probes to study apoptotic rates in cells in culture?
- c. Describe the role of the “apoptosome” in apoptosis?
- d. Define the term “oncoprotein” and name an oncogene that has been responsible for the development of a cancer?

14. Environmental Toxicology

- a. Name the agent responsible for Minimata Disease?
- b. How was man exposed to mercury at Minimata?
- c. Name one target organ for toxicity with this agent?
- d. What was the source of the Iraq outbreak of poisoning with the same toxic agent in 1971?

15. Risk Assessment

- a. Define the term “no adverse effect level”?
- b. From where is the 100 fold safety (uncertainty) factor derived?
- c. Define the term “acceptable daily intake” or ADI in the context of pesticide regulation for food contamination?
- d. Give two measures that are generally needed to calculate the ADI?



The Royal College of Pathologists

Part 1 examination

**Toxicology: Second Paper
(Biochemical Toxicology Subspecialty)**

Tuesday 18 March 2008

Candidates must attempt to answer FOUR questions ONLY

Time allowed – three hours

1. Describe the expected toxicological/pharmacological effects of a prospective new mixed PPAR α /PPAR γ agonist in terms of its molecular, cellular, tissue and whole body effects both preclinically and in man?
2. Kidney pathology is associated with chronic overdose with certain non-steroidal anti-inflammatory drugs (NSAIDs). Explain the relationship between NSAIDs and kidney damage, the proposed pharmacological/biochemical mechanisms behind the effect, and the likely urinary, and plasma, biomarkers that could be monitored to detect the effect?
3. Describe the importance of genetic polymorphisms in drug metabolism, giving specific examples of drugs affected by this phenomenon?

Please turn over for Questions 4 & 5

4. Describe the biological purpose of phase 2 xenobiotic metabolism, the differing enzymic reactions that can take place and giving specific chemical examples of each type and the enzymes, and cofactors, involved where possible?

5. Describe the differing routes, the characteristics that determine whether a chemical will be excreted via a defined route, and the physiological processes in the organs involved, by which a chemical toxin may be excreted from the body? Provide an example of a chemical excreted by each route?



The Royal College of Pathologists

Part 1 examination

**Toxicology: Second Paper
(Toxicologic Pathology Subspecialty)**

Tuesday 18 March 2008

Candidates must attempt to answer FOUR questions ONLY

Time allowed – three hours

1. A novel pesticide has been shown to induce a small, but significantly increased, incidence of uterine sarcomas, of mixed morphology, in mice at the top dose level only. No increased incidence was observed in rats. Describe the questions that you would pose and how you would approach evaluating the relevance of this finding to man and the risk assessment process required?
2. Describe how transgenic mouse models can be used to identify genotoxic and non-genotoxic carcinogens, explaining how the genetic changes accelerate the carcinogenic process and the factors that are important in design of such studies?
3. Describe the cardinal pathological features of “light hydrocarbon nephropathy”, explain the underlying mechanism for the induction of the nephropathy and describe how you would prove that a small, but statistically increased, incidence of kidney tumours in a rat study was due to this proposed mechanism?

Please turn over for Questions 4 & 5

4. Describe the features and tissues/organs affected by an immunosuppressive agent and describe what biomarkers of immunosuppression and the methodology that might be used, to evaluate such an agent?

5. Discuss the causes and significance of drug-induced hepatomegaly in a 1 month rodent study, the mechanisms involved and describe how you would address the possible significance of the effect to man illustrating your answer with selected chemical examples?



THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 14 March 2006

TOXICOLOGY

First Paper

Answer FOUR questions ONLY
Time allowed – THREE HOURS

1. Write short notes on any FOUR of the topics a) to f) below (suggested length half-page per answer).
 - a) Organophosphorus-induced delayed type neurotoxicity
 - b) The comet assay
 - c) α -2u globulin nephropathy
 - d) The respiratory toxicity of asbestos
 - e) Minamata disease
 - f) Balkan nephropathy
2. Explain why the toxicity of a metabolically-activated chemical, as assessed in an *in vitro* hepatocyte system, may differ from that shown observed in the liver during an *in vivo* oral gavage study in the rat.
3. Describe the effects of administration of a PPAR α agonist to a rat. Describe the downstream sequence of changes following interaction of the agonist with its respective receptor and how you might monitor these using current molecular biology methodologies.

Please turn over for Questions 4, 5 and 6

4. Describe and discuss the approaches available for the identification, characterisation and assessment of skin and respiratory chemical allergens.

5. Describe and discuss the mechanisms by which chemical exposure can lead to thyroid gland hypertrophy, hyperplasia and cancer. Use specific chemical examples to illustrate your answer.

6. A chemical accident has occurred in which 20,000 litres of benzene has been spilled onto the motorway.
 - a) What biological samples would you take from individuals exposed to the spillage?
 - b) What biomarkers would you measure to assess any acute organ toxicity and why?
 - c) What follow up medical investigations would you recommend?
 - d) What information would you need to manage the risks associated with the incident?



THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 15 March 2005

TOXICOLOGY

First Paper (General Toxicology)

Candidates must answer **FOUR** questions **ONLY**

Time allowed - three hours

1. “The skin is an important organ in determining the toxicity of topically applied chemicals”. Describe the structure of the skin and discuss this statement.

2. Write short notes (maximum half a page) on **four** of the following:
 - (a) In relation to chemical exposures define the terms ‘hazard’ and ‘risk’ and explain the differences between the two terms.

 - (b) Explain the principles of ‘dose-response’ and its importance for toxicology

 - (c) Define ‘enterohepatic’ circulation and its importance in toxicology illustrating your answer with some specific chemical examples

 - (d) Define the importance of the formation of acyl glucuronides in toxicology and illustrate your answer with specific chemical/drug examples

 - (e) Loss of contraceptive protection in epileptic women

Please turn over for questions 3, 4 and 5

3. Define the concept of the '3Rs'. Describe the considerations that need to be accounted for in using results from an *in vitro* human hepatocyte system and where, and with what reservations, results from this study might this be used to predict subsequent studies in man.
4. 'Initiation and promotion' are important concepts in the theory of chemical carcinogenesis. Differentiate initiation from promotion and illustrate how this hypothesis has been explored using a defined *in vivo* model system. What are the limitations of the two-stage hypothesis in explaining the carcinogenic process?
5. Metabolism studies on a novel chemical have shown that no parent compound could be detected in the blood at any time following oral administration. Discuss what could have happened to the chemical, the organs and the metabolic and kinetic processes that might have caused this.