



The Royal College of Pathologists

Pathology: the science behind the cure

Part 1 examination

Toxicology: First paper (General Toxicology)

Tuesday 23 March 2010

Candidates must answer ALL questions

Time allowed: 3 hours

1. Analytical Toxicology
 - a. Name two types of specimen/sample that can be taken from a living person to permit the analysis of a potential drug overdose.
 - b. Name two plasma measures that you could use to diagnose end stage kidney failure in a living patient.
 - c. Name two organs that might be affected when increases in plasma aspartate aminotransferase are seen following administration of a drug.
 - d. Name one additional enzyme change for each organ that you would need to distinguish between toxicity in the organs identified in 1c.

2. Biochemical Toxicology
 - a. Define the terms pharmacokinetics and pharmacodynamics.
 - b. Name two of the processes that determine the pharmacokinetics of a compound entering the body.
 - c. Name two phase 1 metabolic reactions.
 - d. Name two ways in which the half life of a drug can be significantly increased over that predicted.

3. Occupational Toxicology

- a. Define the terms AOEL and TWA.
- b. Name two routes of exposure through which a crop sprayer is exposed during the preparation and spraying of a pesticide on farmland.
- c. What is the occupational disease associated with slate quarrying and which underlying element is responsible for the toxicity?
- d. What is the target organ for 3c and what is the main diagnostic marker to establish the development of disease?

4. Genetic Toxicology

- a. Name two types of *in vitro* assay for the detection of genotoxicity.
- b. Why is the S9 component added to *in vitro* genotoxicity assays and what is its major component?
- c. Name two commercially available tools for the theoretical evaluation of structure activity relationships for genotoxic potential.
- d. Give two reasons why a DNA reactive chemical may not be carcinogenic in a two-year study in rodents?

5. Medical Toxicology

- a. What is the pharmacologic target molecule for organophosphorus pesticide poisoning?
- b. Name an antidote that can be given to counter organophosphorus toxicity.
- c. Organophosphorus pesticide poisoning, induces a number of symptoms for which the acronym “SLUD” has been used. Define SLUD.
- d. Name one other class of pesticides that also target the same pharmacological molecule.

6. Mechanistic Toxicology/Basic Physiology

- a. What effect does hyperventilation have on the blood and why?
- b. Name two features that determine why the herbicide paraquat induces toxicity in the lungs.
- c. Name the specific cell type in the lung that is thought to be the most sensitive target cell for paraquat toxicity.
- d. Name an antidote that has been used in cases of oral paraquat poisoning.

7. Safety Pharmacology

- a. What does the charcoal feeding assay assess?
- b. What is the end point measured in the assay?
- c. What is the significance of a decrease in the parameter measured by the charcoal test?
- d. What effect would the administration of morphine be expected to have on this parameter?

8. Immunotoxicology

- a. What is the end point measured in the “local lymph node assay”?
- b. What specific immunologic potential would a chemical possess that was shown to be positive in the LLNA assay?
- c. What are CD4+ve lymphocytes and CD8 +ve lymphocytes also referred to as?
- d. Name the type of allergic reaction that CD4 and CD8 positive cells are involved in.

9. Reproductive/Developmental Toxicology

- a. Name the cell in the testes responsible for the production of testosterone.
- b. Name two testicular toxic chemicals.
- c. Why should chemicals that cause liver damage, such as ethanol, induce testicular atrophy?
- d. What is the pharmacological mechanism of action of triazole fungicides in inducing reproductive toxicity?

10. Toxicological Pathology

- a. What does a compound-related increase in extramedullary haematopoiesis in the spleen suggest?
- b. Name two **morphological** features that define an apoptotic cell.
- c. Name two methods that can be used to assess bone marrow toxicity.
- d. Name two, non-drug-induced, pathologies that can be induced by gavage dosing of a drug.

11. General Toxicology

- a. Define the term MTD and give an end-point that can be used to set the MTD.
- b. Define the term REACH.
- c. Give two reasons why the intra-peritoneal dosing route can be problematic for chronic studies.
- d. Provide three routes for the excretion of a lipophilic chemical.

12. Pharmaceutical Toxicology

- a. Define the term “polypharmacy” and name a possible problem of this approach.
- b. Name two undesirable consequences of taking two drugs at the same time.
- c. The anti-tuberculosis drug isoniazid has been associated with liver and neurotoxicity when given to certain groups of patients. Name the underlying pharmacological cause of isoniazid toxicity.
- d. Name two additional complications of continual intravenous infusion as a route of administration of a drug in rodents over that seen with other routes of administration.

13. Molecular Toxicology

- a. Define the term microRNAs and describe how these might be used as biomarkers of tissue damage.
- b. Name two diseases where release of microRNA into the plasma can be diagnostic.
- c. Name two different technologies that can be used to measure changes in specific protein levels in the liver.
- d. Name two cell markers that can be used to identify apoptotic cells by flow cytometry.

14. Environmental Toxicology

- a. Name two test species systems that can be used for the assessment of chemicals in water.
- b. Name two ways in which pollution from a factory can enter the household water supply.
- c. Define the terms “bioaccumulation” and “biomagnifications”
- d. Provide one example of a chemical that undergoes bioaccumulation and one that undergoes biomagnifications.

15. Risk Assessment

- a. Describe two features that are required in the risk assessment process.
- b. What safety (uncertainty) factors would you apply to a LOAEL for a rodent carcinogenic pesticide used for apples, that is negative in genotoxicity assays and that has been demonstrated to show a thresholded mechanism, in order to derive an “acceptable daily intake” for fruit?
- c. What two additional measures would you need to assess whether your calculated ADI adequately protected the exposed population from harm?
- d. What two measures might you put in place if the measured exposure in 15c exceeds the ADI?



The Royal College of **Pathologists**

Pathology: the science behind the cure

Part 1 examination

Toxicology: First paper (General Toxicology)

Tuesday 24 March 2009

*Candidates must answer **ALL** questions*

Time allowed: 3 hours

16. Analytical Toxicology

- a. Imatinib, a specific tyrosine kinase inhibitor, has been shown to be associated with elevations in plasma troponin T. What target organ for toxicity is this indicating?
- b. Name two “specific” serum/plasma markers to measure kidney damage induced by a nephrotoxin in a dog study?
- c. Name two enzymes that can be monitored in plasma to assess hepatotoxicity?
- d. Name two protein markers that could be measured in the plasma to assess the response of fever?

17. Biochemical Toxicology

- a. The organophosphorus pesticide, parathion, is twice as toxic in male rats as in female rats. Name two reasons why this might be?
- b. Name two enzyme systems involved with anti-oxidant activity?
- c. Peroxisomal proliferation in rodents is associated with the induction of a number of enzymes. Name two hepatic enzymes affected by a drug/chemical of the peroxisome proliferator class?
- d. Name two phase two enzymic reactions?

18. Occupational Toxicology.

- a. What carcinogenic chemical precursor was found to be associated with the production of polyvinylchloride and what was the characteristic cancer, and the organ in which it occurred, that was induced by high level exposure to the chemical?
- b. What enzyme is responsible for the metabolism and activation of the chemical precursor of polyvinylchloride, and what is the immediate chemical product of this metabolism.
- c. Which organ is affected by occupational exposure to cotton dust and name the disease?
- d. What type of hypersensitivity reaction is involved in the pathogenesis of cotton dust disease and which cells would you expect to be involved in the reaction?

19. Genetic Toxicology

- a. Define the terms clastogenesis and aneuploidy?
- b. What is the organism used in the Ames test, what amino acid does the organism require in the absence of induced mutations, and what genetic lesion does the test assess?
- c. Excessive frying of food has been linked with the production of mutagenic chemicals. Name two such chemicals (abbreviations will suffice!) and describe from which source in the food they are thought to be derived?
- d. Define the term “the SHE assay” and the end point that it induces?

20. Pharmaceutical Toxicology

- a. Give two purposes of phase 1 clinical trials?
- b. Give two common reasons for drugs that enter phase 1 trials not being progressed into phase 2?
- c. Give two reasons why a drug may be more toxic in a sick patient than in a normal healthy volunteer?
- d. In 2004 Merck voluntarily withdrew the cyclo-oxygenase inhibitor drug, VIOXX, from sale. Why was this action taken?

21. Mechanistic Toxicology/Basic Physiology

- a. Name two roles that the lungs play in the control of homeostasis?
- b. Name two features that determine the pulmonary toxicity of the herbicide Paraquat?
- c. Which active transport system does Paraquat hijack in effecting its toxicity?
- d. End-stage kidney failure is frequently associated with anaemia. What is the basis for this effect?

22. Safety Pharmacology

- a. What adverse drug reaction is the clinical use of cisapride associated with and what is the biochemical basis for the interaction between Ketoconazole and cisapride that results in an increased risk of the ADR?
- b. What effect would an overdose of an Angiotensin II receptor antagonist be expected to have on heart rate and why?
- c. Name two parameters that can be performed *in vivo*, in an intact animal, to assess the potential effect of a drug on the cardiovascular system?
- d. Give two reasons why the hERG assay may not be associated with QT prolongation?

23. Immunotoxicology

- a. Chronic stress can be accompanied by immunosuppression and infection. What is the basis for this outcome?
- b. Which ICH guideline provides recommendations on the preclinical testing of drugs showing potential immunotoxicity?
- c. Name two indications from standard one month rodent studies that can lead to the need to undertake additional specific immunotoxicity investigations?
- d. The term “enhanced histopathology” has been recommended for a more thorough evaluation of the immune organs (not mentioned in guideline). What would this mean for an evaluation of the spleen?

24. Reproductive/Developmental Toxicology

- a. Certain phthalates are known reproductive toxicants. Name two reproductive endpoints affected by administration of phthalate esters?
- b. Name two types of testicular cells, which are specifically affected by low testosterone levels and what is the effect?
- c. What is the mechanism of action of cadmium in inducing testicular atrophy?
- d. Name a potential plasma biomarker of testicular toxicity?

25. Toxicological Pathology

- a. Name two transgenic mouse models that have been proposed as a replacement for the classical two-year lifetime mouse carcinogenicity bioassay?
- b. In tumour nomenclature, what names are given to malignant tumours of the following tissues: striated muscle, lymphatics & CNS glial cells?
- c. What chemical agent is involved in ragwort poisoning, which organ is typically affected by ragwort poisoning and what is the pathology?
- d. Name two special stains that could be used to assess fibrosis in the liver?

26. General Toxicology

- a. Name two adverse effects resulting from an intravenously administered drug given to rats via the tail vein that would be a consequence of dose route rather than any effect of the dosed chemical?
- b. Name the single most common cause of early, non-neoplastic, deaths in male Sprague-Dawley rats on a dietary administered, lifetime carcinogenicity study?
- c. Name two factors that affect the early onset of the disease mentioned in 11b above?
- d. Define the term MTD and give an example of an effect that could determine an MTD?

27. Medical Toxicology

- a. What is the main target organ for overdosing with paracetamol (acetaminophen)?
- b. What is the metabolite thought to be responsible for the hepatotoxicity?
- c. What is the initial molecular target for the reactive metabolite generated from paracetamol, what is the effect on this molecule and what chemical reaction takes place between the reactive metabolite and the molecular target?
- d. Name two antidotes that are available to treat cases of paracetamol overdose and how are they thought to work?

28. Molecular Toxicology

- a. What molecule is the Affimetrix gene chip microarray used to study in toxicology?
- b. What alternative methodologies can be used to study the same molecular changes?
- c. Name two ways of assessing the proliferation rate of cells?
- d. Define the term SNP and give one consequence of a SNP?

29. Environmental Toxicology

- a. Name the agent involved in the Seveso incident in 1976 and what was the first, the most obvious, and the most characteristic feature of acute human exposure?
- b. Which cytochromes P450 are associated with the metabolism of this chemical and which nuclear receptor is the chemical a ligand for?
- c. Name two target organs affected by exposure to the Seveso chemical?
- d. Name two types of toxic end point affected by exposure to the Seveso toxin?

30. Risk Assessment

- a. Define hazard and risk?
- b. Name two types of data obtained from an animal bioassay that can help in the risk assessment process?
- c. Name two possible exposure routes by which an individual may contact a pesticide residue?
- d. Define the therapeutic index (TI) for a drug?

End of paper



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?