MODULAR TRAINING PROGRAMME IN APPLIED TOXICOLOGY

Module Descriptions

The Modular Training Programme in Applied Toxicology comprises the following eight core modules and a number of supplementary modules:

Core Modules

1. Carcinogenicity and Mutagenicity
2. Principles of Experimental Toxicology and Risk Assessment
3. Principles of Toxicological Pathology
4. Reproductive Toxicology
5. Target Organ Toxicology – Systems I: Liver, Kidney, Gastro-intestinal Tract and Skin
6. Target Organ Toxicology – Systems II: CNS, PNS, Endocrine and Musculo-skeletal Systems
7. Target Organ Toxicology – Systems III: Cardiorespiratory and Haematopoietic Systems
8. Toxicokinetics and Metabolism

Supplementary Modules

1. Alternatives Methodologies to the Use of Animals in Toxicology
2. Bioinformatics and ‘-omics’
3. Biologics
4. Biomarkers
5. Dermal Toxicology
6. Design of in vivo Studies*
7. Ecotoxicology
8. Experimental Inhalation Toxicology*
9. Food Chemical Safety Evaluation
10. Haematology and Clinical Biochemistry*
11. Immuno-toxicology
12. Occupational Toxicology (including REACH implementation and legislation)
13. Paediatric Toxicology
14. Pathology of the Endocrine System
15. Plant Protection Products and Plant Biotechnology
16. Safety Assessment of Pharmaceutical Agents
17. Safety Pharmacology in Pre-clinical Research and Development
18. Techniques in Safety Assessment

The University of Surrey also offers modular training programmes in Genetic Toxicology, Pharmaceutical Medicine and Clinical Pharmacology. Courses offered by all these programmes can be taken as supplementary modules to the Modular Training Programme in Applied Toxicology. However, a maximum of two modules only from these programmes may be chosen; all other modules must be selected from the relevant MSc itself.

* sponsored by the BBSRC
CARCINOGENICITY AND MUTAGENICITY
Core Module
Credit Weighting:  15 (equivalent to 7.5 ECTS credits)
Module Organiser: Dr S C Price, Faculty of Health and Medical Sciences

It was established in the early 1900's that the administration of certain chemicals could result in cancers in laboratory animals. Earlier epidemiological studies had shown that some human cancers were influenced by environmental factors. In modern times, there has been considerable concern about the potential for some natural and synthetic chemicals to cause human cancer and stringent regulations cover the manufacture and use of such chemicals. Fortunately, the aetiology of human cancers is much better understood now than it was earlier in the century and sophisticated test batteries and research methods have been developed for the study of mutagenesis and carcinogenesis.

Learning Outcomes:
On the successful completion of this module the student should be able to assess carcinogenicity study reports in the context of overall toxicological evaluation. This will require:

- an understanding of the aetiology of cancer;
- an understanding of the processes involved in mutation, DNA repair and carcinogenesis;
- an understanding of the significance of non-genotoxic carcinogens versus genotoxic carcinogens;
- an understanding of the basis of carcinogenicity screening procedures and their limitations;
- a knowledge of the basic pathology of cancer;
- the ability to integrate knowledge of mutagenesis, carcinogenesis, biochemistry and epidemiology into the process of risk assessment.

Pre-course Reading:

Module content:
- Cancer, mutation and gene structure
- Mutagenicity testing in vitro
- Mutagenicity testing in vivo
- Human monitoring
- The need and rationale for carcinogenicity testing
- The pathogenesis of cancer
- Theories of growth control and carcinogenesis
- Initiation and promotion – skin
- Cancer epidemiology
- Structure-activity relationships and carcinogenesis
- Human oncogenes and human cancer
- DNA repair
- Mutagenicity testing – structure-activity relationships
- Testing procedures and protocols
- Neoplasia by non-genotoxic agents – the kidney
- Neoplasia by genotoxic and non-genotoxic agents
- Initiation and promotion – bladder
- Classification and morphology of tumours
- Risk assessment – statistics/mathematical models/extrapolation to man
Many toxicity testing procedures are based on general principles established for a broad spectrum of chemicals. However, there is an increasing need for a more rational approach to toxicity testing of chemicals and drugs not only to ensure safety, but also to make the process of safety assessment cost-effective. This module aims to take a critical approach to the conduct and interpretation of toxicity studies emphasising the need to employ a flexible approach in order to maximise understanding of the underlying mechanisms of toxicity and their relevance to human risk assessment.

Learning Outcomes:

On successful completion of this module, participants should:

- have a good overview of modern experimental toxicology and risk assessment;
- understand the limitations and advantages of toxicity testing protocols;
- be able to integrate the contribution of toxicity testing and its role in human risk assessment;
- have a good appreciation of the management of chemical safety evaluation.

Pre-course Reading:

- Illing, Paul (2001) *Toxicity and Risk*
- Woolley, Adam (2003) *A Guide to Practical Toxicology*

Module content:

- History and philosophy of toxicological evaluation
- The rationale for acute toxicity testing: the limitation of currently accepted methods
- The rationale for sub-acute and chronic toxicity testing
- Carcinogenicity testing
- The role of mutagenicity testing
- Basic requirements for toxicological evaluation
- The rationale for reproductive toxicity testing
- The role of biochemical, metabolic and toxicokinetic studies in the evaluation of toxic hazard and risk
- Evaluation of immunotoxicity
- Integration of toxicological studies with technical development of industrial chemicals
- Integration of toxicological studies with technical development of pesticides
- Integration of toxicological studies with technical development of drugs
- Environmental aspects of risk assessment
- Risk assessment for food contaminants
- Mathematical models in risk assessment
- Occupational risk assessment
- International guidelines on toxicological evaluation
Histopathology plays a central part in toxicological evaluation. Although most major studies employ an experienced pathologist, it is necessary for all toxicologists to appreciate the basic principles of pathology. This module aims to introduce the principles of pathology, including the preparation and examination of tissues from toxicity studies.

**Learning Outcomes:**

On successful completion of the module, participants should understand basic pathological findings in a broader context which will assist them in communicating with specialist pathologists. They will:

- know and understand the themes and major causes and processes in pathology;
- have a knowledge of the biochemical bases of pathological change;
- appreciate the major microscopic changes associated with toxicity at the cellular and tissue level;
- be able to integrate the role of histopathology within the context of toxicity studies.

**Pre-course Reading:**

- Turton, J. and Hooson, J. (1998) *Target Organ Pathology: A Basic Text*
- Grasso, Paul (2002) *Essentials of Pathology for Toxicologists*

**Module content:**

- Themes, causes and processes in pathology
- Causes of pathological changes
- Chemical mediators of inflammation
- Acute and chronic inflammation
- Disorders of the immune response
- Disorders of tissue growth - hypertrophy, dysplasia and neoplasia
- Tissue restoration and repair
- Cell necrosis and degeneration
- Thrombosis and embolism; their origins and consequences
- New techniques used in histology and electron microscopy
- Cell organelles and their response to toxic agents
Reproductive toxicology studies assumed increasing importance following the thalidomide disaster of the 1960's and detailed reproductive toxicity studies are now a routine part of toxicity screening. Such studies may screen the effects of germ cell and pre-natal exposure on several generations of animals. In recent years, behavioural effects have attracted increasing interest. In addition, in vitro screening systems are now being applied to complement conventional approaches.

**Learning Outcomes:**

On successful completion of this module, the participant should have an understanding of a broad spectrum of topics on reproductive toxicology using a multidisciplinary approach to risk assessment. The student will:

- acquire a basic understanding of the processes of spermatogenesis, oogenesis, fertilisation and organogenesis in the mammal;
- obtain knowledge of the major mechanisms of reproductive toxicity;
- understand the basic strategies for screening for reproductive toxicity;
- understand the significance of species differences and any limitations of animal tests for reproductive toxicity;
- acquire a perspective on the use of in vitro screening systems for reproductive toxicity.

**Pre-course Reading:**

- Teratology Primer (2005)

**Module content:**

- Principles of reproductive toxicology
- Principles of pharmacokinetics
- Timing of pregnancies (mouse, rat, rabbit)
- Timing of pregnancies (monkey)
- Embryology I: from the zygote to organogenesis
- Genetic defects
- Morphology of the male and female reproductive systems
- Spermatogenesis and oogenesis
- Studies on male fertility
- Multigeneration studies
- Embryology II: organogenesis
- Visceral evaluations
- Behavioural toxicology
- Embryology III: the fetal period
- Perinatal development of enzyme systems
- Legal requirements for reproductive toxicology testing
- Whole-embryo culture
- Limb-bud culture
- Other in vitro systems
- Significance and limitations of in vitro systems
TARGET ORGAN TOXICOLOGY

Although the principles of toxicology can be applied broadly to many organ systems, an understanding of the toxicology of individual organ systems is necessary for accurate risk assessment. The Target Organ Toxicology modules examine the pathology, anatomy, physiology and toxicology of the liver, kidney, gastrointestinal tract, skin, central and peripheral nervous system, endocrine organs, musculo-skeletal system, cardiorespiratory system and haematopoietic system. These modules also take examples of compounds from the literature that result in toxic effects on such organs.

On successful completion of the modules relating to the various Target Organ Systems, the student should be able to understand and define mechanisms of action of substances on target systems to enable interpretation of data from effects observed in these systems.

The Target Organ Toxicology modules are core modules of the Modular Training Programme in Applied Toxicology. They comprise:

- Target Organ Toxicology – Systems I: Liver, Kidney, Gastro-intestinal Tract and Skin
- Target Organ Toxicology – Systems II: CNS, PNS, Endocrine and Musculo-skeletal Systems
- Target Organ Toxicology – Systems III: Cardiorespiratory and Haematopoietic Systems
Learning Outcomes:

On successful completion of this module, participants should:

- have a basic understanding of the physiology and anatomy of the liver, kidney, gastrointestinal tract and skin;
- understand the basis for the major toxicities described for compounds that affect the liver, kidneys, gastrointestinal tract and skin;
- understand the basic pathological and biochemical changes associated with such toxicity;
- be able to integrate the significance of liver, kidney, gastrointestinal tract and skin toxicity observed in animal testing in the context of human risk assessment;
- be able to identify the major testing strategies for examining toxicity to the liver, kidneys, gastrointestinal tract or skin.

Pre-course Reading:


Module content:

LIVER

- Structure and functions
- Xenobiotic metabolism
- Acute pathological changes
- Mechanisms of acute hepatotoxicity
- Adaptive and toxic changes in the liver of rodents
- Chronic hepatotoxicity, repair, cirrhosis
- Hepatocarcinogenesis
- Assessment of hepatic function and damage in animal species
- Cholestasis
GASTROINTESTINAL TRACT

- Structure
- Regulation of secretions
- NSAIDS and ulcer formation
- The rodent forestomach
- Toxicology of the caecum
- Acute and chronic toxicity of the glandular stomach and intestines
- Hypersensitivity, Peyer's patches and the gastric immune system
- Carcinogenesis in the glandular stomach and intestine
- Carcinogenesis in the pancreas

KIDNEY

- Structure of the mammalian kidney
- Functions of the mammalian kidney
- Assessment of renal function and damage in animal species
- Nephrotoxins I - the tubule
- Nephrotoxins II - glomerulus and papilla
- Secondary effects of kidney failure

SKIN

- Normal skin structure and function
- Absorption of compounds into and across skin
- Chemically-induced skin damage, irritation and repair
- Sensitisation and hypersensitivity reactions
- UV-induced skin damage and photosensitisation.
TARGET ORGAN TOXICOLOGY – Systems II:
CNS, PNS, Endocrine and Musculo-Skeletal Systems
Core Module
Credit Weighting: 15 (equivalent to 7.5 ECTS credits)
Module Advisers: Dr S C Price, Faculty of Health and Medical Sciences
Professor G Pilkington, University of Portsmouth

Learning Outcomes:

On successful completion of this module, participants should:

- have a basic understanding of the physiology of the CNS, PNS, endocrine and musculo-skeletal systems;
- understand the basis for the major toxicities described for compounds that affect the CNS, PNS, endocrine or musculo-skeletal systems;
- understand the basic pathological and biochemical changes associated with such toxicity;
- be able to integrate the significance of CNS, PNS, endocrine and musculo-skeletal toxicity observed in animal testing in the context of human risk assessment;
- be able to identify the major testing strategies for examining toxicity to the CNS, PNS, endocrine and musculo-skeletal systems.

Pre-course Reading:


Module content

NERVOUS SYSTEM

- Introduction to the gross anatomy and histology of the CNS and PNS;
- Basic neurophysiology;
- Basic neuropharmacology;
- Selective vulnerability by area and cell type;
- Behavioural changes in animals;
- Behavioural toxicity of antidepressants;
- General toxicological principles. Acute and chronic toxicity of organophosphates and carbamates;
- Delayed neuropathy by organophosphates;
- Neuronal necrosis and water disposition: organotins and organoleads;
- Physiological aspects of neurotoxicity in man and animals;
- Neurotoxic chemicals including pesticides;
- Brain tumours;
- Toxicology of the eye;
- Toxicology of the ear;
- Neurotoxic effects of metals.
ENDOCRINE SYSTEM

- Introduction to the endocrine system;
- Toxicology of the hypothalamo-pituitary axis;
- Adrenocortical toxicology
- Toxicology of the thyroid;
- General endocrine interactions;
- Endocrine tumours;
- Neuroendocrine effects of alcohol.

MUSCULO-SKELETAL SYSTEM

- Bone as a target organ;
- Effects of metals on bone;
- Structure and biochemistry of muscle;
- Chemically-induced myopathies.
**TARGET ORGAN TOXICOLOGY – Systems III:**
Cardiorespiratory and Haematopoietic Systems
Core Module
Credit Weighting: 15 (equivalent to 7.5 ECTS credits)
Module Advisers: Dr S C Price, Faculty of Health and Medical Sciences
Dr C Hardy, Huntingdon Life Sciences

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**Learning Outcomes:**

On successful completion of this module, participants should:

- have a basic understanding of the histology, physiology and anatomy/histology of the cardiorespiratory and haematopoietic systems;
- understand the basis for the major toxicities described for compounds that affect the cardiorespiratory and haematopoietic systems;
- understand the basic pathological biochemical changes associated with such toxicity;
- be able to integrate the significance of toxicity to the cardiorespiratory and haematopoietic systems observed in animal testing in the context of human risk assessment;
- be able to identify the major testing strategies for examining toxicity to the cardiorespiratory and haematopoietic systems.

**Pre-course Reading:**


**Module content:**

- Anatomy and physiology of the cardiovascular system;
- Direct-acting cardiotoxicants and angiototoxicants;
- Secondary effects on the cardiovascular system;
- Measurement of cardiovascular function;
- Structure and histopathology of the upper respiratory tract;
- Structure and physiology of the lung;
- Introduction to inhalation toxicology;
- Pulmonary function assessment;
- Toxicology of the lung;
- Biochemistry and physiology of haematopoiesis;
- Introduction to practical haematology;
- Naturally occurring haematological disorders in animals;
- Anaemias caused by chemicals;
- Biochemistry of platelets;
- Chemically-induced disorders of blood coagulation;
- Effects of chemicals on leucocytes.
A good knowledge of the principles of xenobiotic metabolism is central to toxicology because many compounds undergo enzymic metabolism to form toxic metabolites. Similarly, many toxicants are inactivated by the action of xenobiotic metabolizing enzymes. Toxicokinetics is the study of the rates of absorption, distribution, metabolism and excretion of toxicants and is central to an understanding of the exposure of target tissues to toxicants. This module focuses on toxicokinetics and xenobiotic metabolism with particular emphasis on risk assessment.

**Learning Outcomes:**

Upon successful completion of the module, participants will be able to critically evaluate the data in the context of toxicological evaluation. They will:

- understand the major pathways of xenobiotic metabolism in mammals;
- appreciate the significance of metabolism in toxicology;
- appreciate the major species differences in metabolism and their significance for toxicity testing;
- understand the principles of toxicokinetics;
- be able to integrate knowledge of kinetics, dynamics and metabolism in the study of toxicity.

**Pre-course Reading:**

- Gibson, G. and Skett, P. (2001) *Introduction to Drug Metabolism*
- Clark, B. and Smith, D., (2001) *An Introduction to Pharmacokinetics*

**Module content:**

- Overview: lung, oral and intestinal absorption;
- Metabolism - Phase I and II;
- Skin absorption and metabolism;
- Stereoselectivity in drug metabolism and toxicology;
- Enzymology and molecular biology;
- Distribution and excretion;
- Toxicodynamic effects, reactive molecules and dose-response curves;
- Basic xenobiotic metabolism and the implications for drug development;
- Techniques for measuring xenobiotics;
- Plasma monitoring for therapeutic optimisation;
- Basic pharmacokinetics;
- Bioavailability;
- Interspecies comparison in drug metabolism and toxicokinetics;
- Extrapolation of data from animals to man;
- Pharmacokinetic modelling.
This module endeavours to make students aware of the current use of animals in toxicology and the possibilities for the refinement, reduction and replacement of the use of animals.

**Learning Outcomes:**

On successful completion of this module, participants will appreciate fully the role and limitations of alternatives to animals in chemical safety evaluation and risk assessment, and investigations of mechanisms of toxicity. They will:

- understand the advantages and limitations of alternative methods in chemical safety evaluation for product development;
- understand the principles of risk assessment.

**Pre-course Reading:**

- Reducing the Use of Laboratory Animals in Biomedical Research: Problems and Possible Solutions. ECVAM Workshop Report 29, *ATLA* 26, 283-301, 1998

**Module content:**

- Advantages and limitations of alternatives to animals
- Validation of alternative tests
- Cytotoxicity testing
- Xenobiotic metabolism studies
- Biokinetic modelling
- Quantitative structure activity relationships
- Mutagenicity testing
- Hepatotoxicity
- Nephrotoxicity
- Neurotoxicity
- Teratogenicity
- Testicular toxicity
- Lung toxicity
- Cardiotoxicity
- Immunotoxicity
- Eye irritation
- Skin penetration and irritation
- Transgenic cell lines
The ability to access, organise and analyse large amounts of information from disparate sources will become a key competency for biological and clinical scientists. An appreciation of bioinformatics and its associated tools is a starting point for developing a working knowledge of the areas. *Perhaps someday all things biological will be classified and jammed into an enormous database — leading to some hypothetical metadiscipline called biomics.*


**Learning Outcomes:**

On successful completion of the module, participants should understand concepts in molecular biology and bioinformatics which will assist them in communicating with specialists. Participants should:

- have an appreciation of molecular biological/omics concepts underlying the collection of bioinformatic data;
- have a knowledge of the databases available for “-omic” data and their management;
- have an understanding of the bioinformatic tools available for interrogating and integrating data from a range of sources;
- have an awareness of how this information can be used in the investigation of chemical safety;
- have an overview of the future impact of bioinformatics on applied toxicology.

**Pre-course Reading:**


**Module content:**

- Genomics, transcriptomics, proteomics, metabolomics and the other “-omics”
- The “-omics”: their relationships and the data universe
- Data management of “-omics” data
- Bioinformatic tools for the “-omics”
- Qualitative bioinformatic tools
- Annotation
- Quantitative bioinformatic tools
- Bioinformatics and/or statistical approaches to molecular biology data
- Data mining
- Multivariate methods: cluster analysis, PCA and more advanced approaches
- Epidemiological and experimental approaches
- Molecular epidemiology
• Complex diseases and multifactorial mechanisms
• Genes, environments and their interactions
• The inter-relationship between the “-omics” and biomarkers (of exposure, susceptibility and disease progression) and their links with surrogate measures
• The development of a predictive biology and system biology
• In silico biology
• The refinement of dose-response relationships
• The role of biomarkers/biomics in mechanism-based risk assessment
• Case studies and examples
• Tutorials on bioinformatic and statistical tools
• Demonstration of selected “-omics” and bioinformatic tools by system developers (e.g. Ciphergen, Affymetrix etc)
BIOLOGICS
Supplementary Module
Credit Weighting: 15 (equivalent to 7.5 ECTS credits)
Module Adviser: Dr Lee Coney, Huntingdon Life Sciences
Dr Maggie Dempster, GlaxoSmithKline

Biologics are the “new” medicines. This is an evolving innovative field and offers the potential for many therapies, the most promising of which include those using recombinant DNA technologies. However new technologies are not without their problems. A sound understanding of these products is needed and, although safety considerations are needed throughout the life cycle, conventional approaches are not always appropriate due to the unique nature of biologics. This module will take the participant through the background to the introduction to biologics, the drug development programme and, through case studies, discuss on a case by case basis the pros and cons of these new therapies.

Learning Outcomes:
On successful completion of this module, participants will:

• be aware of the current regulations dictating how biologics are used;
• be able to make a judgement of the animal species to be used, and why;
• appreciate the problem areas in relation to generating relevant data to communicate the hazards and risks associated with the product;
• understand the objectives underlying the preclinical development programme;
• be able to make a reasoned judgement of other alternative methods to be used when no relevant species exists;
• be aware of the consequences of immunomodulation.

Pre-course Reading:

Module content:

• Overview of types of biomarkers; historical perspective and product class overview
• Product classes: monoclonal antibodies; recombinant proteins; vaccines; cell therapy; nucleic acids
• Regulatory background: ICH S6, FDA, EMEA, FTIM, MABEL
• Manufacturing / comparability: GMP issues, biosafety / adventitious agents, QC issues
• Chemistry / bioanalytics: pharmacokinetics, pharmacodynamics, immunogenicity
• Safety assessment considerations: general toxicity, reproductive toxicity, carcinogenicity, safety pharmacology
• First Time in Man Current Regulatory Background
• CMC Safety Issues – Manufacturing / Comparability / Relative Potency
• Species / Dose Selection / Immunogenicity / Immunotoxicity
• TGN1412 Case Study and MABEL Concept
• Immunomodulatory Drugs
• Alternative technologies
• The safety assessment of vaccines
• The safety assessment of novel product types (fragments, conjugates, pegylated, novel scaffolds etc.)
• The safety assessment of Stem Cell Therapy products
• The safety assessment of Gene Therapy products
• The safety assessment of oligonucleotide products
• The safety assessment of Biosimilars
Biomarkers are involved with many, if not all, aspects of toxicology. Thus, biomarkers not only have a role in the safety evaluation of all chemicals and epidemiological studies in relation to environmental and occupational exposure but also in risk assessment. Knowledge of biomarker types and applications will broaden the appreciation and understanding of these areas of toxicology. This module will also interrelate with many of the other modules.

**Learning Outcomes:**

On successful completion of this module, participants will:

- understand the major types of biomarkers with specific examples;
- appreciate the role of biomarkers in safety evaluation, risk assessment and epidemiological studies;
- gain knowledge of the techniques by which certain biomarkers may be determined;
- understand the principles of bioinformatics/chemometrics in relation to biomarkers and pattern recognition;
- be able to integrate knowledge of effects on various biomarkers.

**Pre-course Reading:**


**Module content:**

- Overview of types of biomarkers
- Specific biomarkers of exposure
- Specific biomarkers of response-organ toxicity
- Specific biomarkers of response-metabolic/physiological dysfunction
- Specific biomarkers of susceptibility
- Novel biomarkers: breath analysis, metabonomics, genomics, proteomics
- Pattern recognition, bioinformatics/chemometrics
- Biomarkers of disease
- Biomarkers of efficacy
- Use of biomarkers in risk assessment
- Biomarkers of immunotoxic effects
- Case studies on specific biomarkers for phospholipidosis; peroxisome proliferation; DNA damage; endocrine disruptors; testicular damage; liver dysfunction.
This unique course is designed to provide a fundamental understanding of the principles and practices of skin toxicology. It is intended to allow delegates to gain an understanding of the principles required to interpret issues associated with skin toxicity. The course will also look at the regulatory aspects of topical product assessment. Due to the continual importance of alternative methods in toxicology testing, this course will look in detail at the principles and measurement of skin absorption both in vivo and in vitro and will consider the development of in vitro replacements and future EU initiatives in the use of these alternatives. Great emphasis has been placed on developing in vitro tests to replace laboratory animal-based skin safety assessments. The EU policy to abolish animal testing for cosmetics and fragrances has provided significant impetus for the development of in vitro replacements and future EU initiatives such as REACH may also necessitate extensive use of in vitro alternatives. A number of replacement techniques for identifying corrosive or irritant substances have been validated by ECVAM.

**Learning Outcomes:**

On successful completion of the module, participants should:

- appreciate the general role of skin at the organism level;
- be able to identify a basic range of common skin disorders from clinical or histological observations;
- understand the morphological changes associated with maintenance of normal skin barrier function;
- be aware of the molecular mechanisms involved with barrier homeostasis;
- understand transdermal routes of entry in relation to the anatomical features of the stratum corneum and appendages, and review species differences;
- be able to assess the specific techniques used for in vivo percutaneous absorption measurements;
- have an overview of photo-irritants and photo-sensitising agents;
- appreciate the clinical applications of phototoxic substances;
- be aware of the UK and related guidelines on cosmetic testing policy;
- understand the need for in vitro alternatives, their validation and the future of these test systems.

**Pre-course Reading**


**Module content:**

- Anatomy, biochemistry, skin surface microflora, common pathologies
- Principles of diffusion and thermodynamics
- Factors affecting skin absorption
- Measurement of percutaneous absorption
- Occupational and common skin disorders
- Phototoxicity
- Instrumentation for measuring skin toxicity
- Regulatory aspects of skin toxicology
- Reduction, refinement and replacement of animal testing
- Transdermal drug delivery
- Topical formulation development and bioequivalence
DESIGN OF \textit{IN VIVO} STUDIES
Supplementary Module
Credit Weighting:  15 (equivalent to 7.5 ECTS credits)
Module Organiser: Dr S C Price, Faculty of Health and Medical Sciences

Poor experimental design is not only costly but morally repugnant because animals will have been subjected to experimental procedures for no benefit to human health or to better understanding of how xenobiotics affect living creatures. The aim of this module is to make participants aware of the need for careful planning at all phases of an \textit{in vivo} toxicology study. It is recognised that in many studies the scientists responsible are constrained by the requirements of the regulatory authorities and that these may differ from one jurisdiction to another. It is hoped that the learning outcome will be a decrease in the number of studies where poor planning results in data which cannot be interpreted or is unacceptable to the relevant authorities.

\textbf{Learning Outcomes:}

On the successful completion of this module, the student will:

\begin{itemize}
  \item be aware of the need for careful planning at all phases of an \textit{in vivo} toxicology study.
  \item be able to reduce the number of studies whose poor planning means that no useful results are obtained, and hence reduce the number of animals required.
\end{itemize}

\textbf{Pre-course Reading}

\begin{itemize}
  \item Ballantyne, B., Marrs, T. and Syversen, T., (2000) \textit{General and Applied Toxicology}
  \item Nohynek, G. (2002) \textit{Presentation of Toxicology Results}
\end{itemize}

\textbf{Module content:}

\begin{itemize}
  \item The role of regulatory guidelines in the EU and constituent countries, and the USA
  \item Alternatives to the use of living animals
  \item Choice of species, strain and sex
  \item Animal welfare legislation in EU and USA
  \item Statistical considerations in study design
  \item Record keeping from protocol to report
  \item Choice of measurements and preservation of specimens
  \item The roles of clinical biochemistry, urinalysis, haematology, histopathology and electron microscopy
  \item Special consideration in studies using very young or ageing animals
  \item Tests required for assessing the safety of industrial chemicals, food components and contaminants
  \item Pesticides and pharmaceutical agents
  \item Multi-generational studies
  \item Assessment of the toxicity of mixtures.
\end{itemize}
To obtain greater understanding of the ways in which chemical substances may cause harm to the environment and to a variety of vertebrate species, and to examine how results obtained under laboratory conditions, and from field studies and model systems, may be extrapolated to assessing the impact of chemicals on ecosystems.

**Learning Outcomes:**
Upon successful completion of this module, participants will:

- have an overview of chemical (pollutant) behaviour in the environment leading to adsorption, bioaccumulation, dispersal and degradation;
- have an insight into the importance of biological processes for the maintenance of environmental and human health (including detoxification processes);
- have an insight into how the integrity of biological systems are maintained and how human activity (especially release of toxins) affects these systems and their functions;
- have an insight into how biological systems at different levels of biological integration (from gene to ecosystem) can be used as bioindicators of environmental health;
- be able to evaluate the effect of different remediation technologies on ecosystem function.

**Pre-course Reading**

**Module content**
- Ecology and population dynamics
- The philosophy and rationale of ecotoxicology
- Principles of chemical distribution in the environment
- Biotic degradation
- Effects of toxicants on micro-organisms: bacteria and algae
- Monitoring of background data
- Principles of evaluation of toxic effect
- Difficulties in ecological risk assessment with particular emphasis on avian toxicology
- Assessment of aquatic toxicology - fresh water systems
- Legislation and ecotoxicology
- Strategies for ecological risk assessment
- Bioconcentration and bioaccumulation of organic pollutants
- Effects of pesticides upon terrestrial ecosystems
- Assessment of effects on terrestrial organisms - beneficial insects
- Effects on terrestrial organisms - plants
- Approaches to model aquatic ecosystems
- Modelling in ecotoxicology
- Assessment of marine ecosystems
- Environmental quality standards
- Bioremediation
- Future prospects - biodiversity, impact of biotechnology
Inhalation toxicology is an area of utmost importance in toxicology. It is often difficult to interpret data and thus make a judgement for extrapolation to man. Certain principles of toxicology are applicable to a large number of chemicals, and therefore an understanding of these principles is essential for the development of an insight into the subject. It is important to understand and define mechanisms of action of substances on the respiratory tract to enable interpretation of data from effects observed in these systems. The aim of this module is to make participants aware of practical methods of administration, common effects seen following administration, and problem-solving.

**Learning Outcomes:**
On successful completion of this module, participants should:
- have an understanding of the histology, physiology and anatomy of the respiratory tract;
- understand the basis for the major toxicities described for compounds that affect the respiratory system;
- understand the basic pathological and biochemical changes associated with such toxicity;
- be able to identify the major testing strategies for examining toxicity to the respiratory system;
- have an appreciation of how atmospheres are generated and monitored;
- have a knowledge of study design including species selection and dosimetry;
- have an understanding of the current regulations governing inhalation toxicology including the use of alternative methods where applicable;
- be able to integrate the significance of toxicity to the respiratory system observed in animal testing in the context of human risk assessment.

**Pre-course Reading:**

**Module content:**
- Normal structure and histopathology of the respiratory tract
- Generating atmospheres
- Monitoring atmospheres
- Vapour concentration
- Physicochemical properties of aerosols and particles
- Particle deposition
- Dosimetry
- Exposure systems
- Species selection
- Study design
- Regulations
- OECD guidelines
- Responses of the lower respiratory tract to compounds
- Responses of upper respiratory tract to agents
- Carcinogenicity
Major developments in food technology and in food regulations in recent years have led to significant changes in the way food safety is evaluated and monitored. This module presents a critical overview of the toxicology of foods and their ingredients.

Learning Outcomes:

On successful completion of this module, participants should:
- understand the relative risks from different classes of toxicants in food;
- be aware of current issues in food toxicology and safety assurance.

Pre-course Reading:


Module content:

- No observed effect levels (NOELS) and acceptable daily intakes (ADIs)
- Zero tolerance and the politics of food regulatory affairs
- Natural food toxicants
- Effects of thermal processing
- Preservatives
- Colorants
- Stabilisers
- Toxicology of major dietary constituents
- Food irradiation
- Impact of biotechnology and novel processes
- Low-calorie ingredients
- Toxicology of food packaging materials
- Food intolerance
- Alternatives to animal testing
- Allergenicity testing
- Future prospects
Haematological and clinical biochemical analyses are an important part of any toxicology study. Blood sampling during a study allows the monitoring of an animal’s general health and to track the course of any treatment-related effects without the necessity of sacrificing the animals. A clear understanding of the haematopoietic system, its structure and function, the variation between species, and an awareness of methods and the practical application of sampling and analyses are crucial to the planning of studies and the interpretation of results. This module will also allow interpretation of data in light of other information presented.

**Learning Outcomes:**

On successful completion of this module, participants should:

- be able to interpret data from preclinical toxicity studies and put them in context with historical control data;
- be able to identify the types of samples needed for each study;
- understand the limitations of the results obtained when extrapolating to man;
- understand the limitations of animal data, ie species and strain difference;
- be aware of the current methodologies available for analysis and their advantages and disadvantages;
- understand common effects seen during preclinical studies.

**Pre-course Reading:**

- Evans, G O (ed) (1996) *Animal Clinical Chemistry: A Primer for Toxicologists*
- Turton, J. and Hooson, J. (1998) *Target Organ Pathology: A Basic Text*

**Module content:**

- Regulatory perspective
- Structure and function of blood
- Coagulation
- Haematopoiesis
- Normal toxicological profile of clinical chemistry
- Measurements of haematological and clinical parameters
- Urinalysis
- Enzymology
- Causes of variation
- Common effects seen in studies, eg index of hepatotoxicity
- Spontaneous lesions
- Agents affecting blood
- Typical profile of toxic compounds
- Analysis and interpretation of data
- Extrapolation to man
- Practical demonstration
- Current methodologies available – advantages and disadvantages
- Future perspectives
An understanding of immunotoxicology is important for all areas of toxicology including consumer products, pharmaceuticals, agrochemicals, occupational exposure to chemicals and exposure to environmental pollutants. This module presents an overview of the types of reaction which occur with the immune system and the ways in which these are manifested in different tissues.

**Learning Outcomes:**

Upon successful completion of this module, participants should:

- understand the basic functioning of the components of the immune system and how they interact in immune defence;
- understand how toxic agents exert effects on the immune system and the basis of testing for immunotoxicity.

**Pre-course Reading**

- Descotes, J. (1999) *An Introduction to Immunotoxicology*

**Module content**

- Introduction to immunotoxicity
- Pathological evaluation of lymphoid tissue
- Immune function testing and host resistance assays
- Evaluation of immunotoxicity in humans
- Human immunotoxins
- Mechanisms of chemical-induced allergy
- Approaches to investigation of contact sensitisation
- Allergic contact dermatitis in man
- Food allergy
- Mechanisms of autoimmunity
- Complement activation in drug immunotoxicity
- Induced autoimmunity in man
- Drug-induced hepatitis
- Approaches to investigation of respiratory sensitisation
- Occupational respiratory allergy in man
- Asthma - aetiology and approaches to treatment
- Immunotoxicity of organotins
- Alternative methodologies
Exposure to chemicals is involved in all types of working environment. This module deals with the ways in which various types of chemical material and process may have adverse health effects on workers, and the regulatory measures enforced to protect against these effects. The aims of the course are:

- To provide an appreciation of the EU regulations relating to new and existing chemicals, and how these are applied within a member state (UK). In particular, the impact REACH has on the evaluation of chemical legislation.
- To provide an appreciation of regulatory measures to protect workers from harmful effects of chemical substances.
- To provide an understanding of how occupational exposure levels are established.
- To give an awareness of occupational hygiene measures of ensuring protection of workers from harmful effects of chemicals.
- To provide an appreciation of the varied nature of chemical exposure in the workplace.
- To give an introduction to the toxicological effects of a number of chemical agents and materials that are of current concern in the working environment.

**Learning Outcomes:**

On successful completion of this module, students should:

- have a good understanding of the different types of regulation related to industrial chemicals, and why they are required;
- have an understanding of the toxicological assessment involved in safe or acceptable levels of exposure to chemicals at work;
- have an understanding of the control measures employed to protect workers and to monitor their health;
- have an awareness of some of the major current issues in occupational toxicology.

**Pre-course Reading:**

- Illing, Paul (2001) *Toxicity and Risk: Content, Principles and Practice*
- Participants should also be familiar with the principles of occupational exposure limits as defined, for example, in the introductory section of the HSE EH40 documents, or they should refer to documentation available in their own country.
Module content

- Control of Substances Hazardous to Health (COSHH)
- EU chemicals directive
- Classification and labelling
- Establishment of occupational exposure levels
- Approaches to setting in-house exposure limits
- Basics of occupational hygiene
- Biomonitoring
- Dusts, aerosols and vapours
- Fibres
- Toxicology of silica
- Risk assessment for mixtures of chemicals
- Interactions of noise and chemical substances
- Occupational asthma
- Metals toxicology
- Dealing with an accidental chemical release.
Children’s health has received much attention by regulators, the scientific community and the public. This is not surprising as many drugs used to treat children have never been formally tested in paediatric clinical trials and are used “off label” at dose levels derived by adjustment from adult dose levels. Children are also a vulnerable group for environmental chemicals since they may display novel toxicities not observed in adults or may be more or less sensitive to known toxicities. There are a significant number of examples where drugs have produced markedly different results in the small child in comparison with adults, even when administered at similar mg/kg dose levels. Differences in toxicity findings between children and adults can often be explained by differences in drug metabolism and pharmaco/toxicokinetics or by potential effects on those organ systems which are still developing post-natally.

**Learning Outcomes:**

On successful completion of this module, participants should:

- understand and appreciate the legislation that is coming into force regarding paediatric medicines;
- investigate the potential effects of these drugs in juvenile animals compared to the adult animal;
- investigate the potential effects on development, evaluate species differences and then extrapolate the findings to man.

**Pre-course Reading:**

- Zoetis, Tracey and Hurttt, Mark E. Species Comparison of Anatomical and Functional Renal Development: Birth Defects research (Part B) 68:111-120.
• Development and reproductive Toxicology: A Practical Approach, second edition edited by Robin D. Hood, chapter 8, Nonclinical Juvenile Toxicity Testing

Module content:

• Introduction, history and justification
• Legislation: FDA/EPA
• Study designs: rodent/non-rodent
• Organ system development: critical periods and cross species comparison (CNS, liver, thyroid, kidney, skeletal, cardiovascular, immune system, gastrointestinal tract)
• Pharmacokinetics and drug metabolism: comparison of man>animal at stages through development
• Industrial perspective
• Clinical perspective
• Regulator’s approach.
The endocrine system is an important regulatory system and plays a major role in maintaining homeostasis. It is also a system that can be affected by many xenobiotics leading to major changes not only in the Endocrine System itself but many of the major target organs as well as the underlying control mechanisms. The system is also affected by species, sex, strain and age. It is often difficult to assess the toxicity because of the high spontaneous changes seen within experimental species.

Learning Outcomes:

On successful completion of the module, participants should:

- understand the general physiology and toxicology of the endocrine system;
- understand how all the systems interact with one another, ie feedback controls;
- appreciate the types of spontaneous lesions found;
- gain knowledge on interpreting findings;
- have a working knowledge of species differences;
- be able to identify common lesions seen in the endocrine system.

Pre-course Reading:


Module content:

- Endocrine physiology and toxicology
- Thyroid and parathyroid
- Pituitary
- Adrenal
- Pancreas
- Spontaneous pathologies of endocrine system
- Neuroendocrine system
- species differences including man
- Neoplasia
- Mechanistic data
- PPAR’s – targets for therapeutic agents
- Practical slide reading sessions
The continued increase in world population makes ever increasing demands on food supply. To meet this need, a considerable effort has gone into plant/crop protection, reducing wastage after harvesting and storage, and performing genetic changes to increase yield. Chemicals were used to improve the quality of the soil (fertiliser) and to reduce wastage by fungi and insect pests. Over the last 50 years, the use of chemicals to ensure the food supply has improved considerably by paying attention to efficacy and safety. Nowadays, plant protection products are directed to specific needs and are biodegradable - the former reduces the amount of chemicals needed and the latter ensures that pollution is kept to a minimum.

**Learning Outcomes:**

On successful completion of this module, participants should:

- understand the current regulations applicable to plant protection products;
- have a good overview of risk assessment;
- be able to define the hazards applicable to man, animals and the environment.

**Pre-course Reading:**

Due to the changing aspects of this area, up-to-date research papers/journals will be used as pre-course reading. There is no book that covers areas in detail. However, for areas such as risk assessment, the book used will be *A Guide to Practical Toxicology: Evaluation, Prediction and Risk* by Adam Woolley (2003).

**Module content:**

- Hazard assessment - defining the hazard to man, animals and environment
- Exposure assessment - the exposure chain from manufacture to disposal (OELs)
- Risk assessment
- Biotechnology: issues for consideration by the agrochemical industry
- Problem solving
- Major historical classes of materials
- Current regulations
SAFETY ASSESSMENT OF PHARMACEUTICAL AGENTS
Supplementary Module
Credit Weighting: 15 (equivalent to 7.5 ECTS credits)
Module Adviser: Dr S C Price, Faculty of Health and Medical Sciences

This module aims to give a greater understanding of the ways in which pharmacologically active substances may cause harm to human health, how these effects are investigated, and how results obtained in animals and healthy human volunteers are extrapolated to patients.

Learning Outcomes:
On successful completion of this module, participants should:

- understand the limitations and advantages of toxicity testing protocols;
- have an appreciation of the trends in drug development and toxicological interest;
- be able to integrate safety assessment and drug development/drug registration submissions;
- understand the underlying mechanisms of drug toxicity;
- have an overview of the impact of pharmacogenetics.

Pre-course Reading:


Module content

Issues in testing of pharmaceutical agents:
- dose selection, metabolism, pharmacokinetics, toxicokinetics, oncogenic potential, new in vivo models;
- study design - how data from animal studies is used to support clinical trials; types of tests required.

Strategies for drug safety evaluation:
- legislation; pre-clinical-testing; clinical trials; post-marketing surveillance; integration of safety assessment with drug development/drug registration submissions; veterinary medicines; specific drug classes; impact of pharmacogenetics.

Trends in drug development of toxicological interest:
- drug design; pharmaceutical agents produced by biotechnology; novel formulations.

Mechanisms of drug toxicity:
- exacerbation of pharmacological action; direct toxic effects; drug-drug and drug-nutrient interactions; idiosyncratic reactions; use of mechanistic data in risk assessment.

Future trends:
- new technologies; assessment of the environmental impact of drug production and use.
SAFETY PHARMACOLOGY IN PRE-CLINICAL RESEARCH AND DEVELOPMENT
Supplementary Module
Credit Weighting: 15 (equivalent to 7.5 ECTS credits)
Module Adviser: Dr Jean-Pierre Valentin, AstraZeneca

The integration of the basic sciences (pharmacology, toxicology, biochemistry and other sciences) in the search for potential pharmacodynamic liabilities of new pharmaceutical agents is an important component in the assessment of the potential risk for human exposure to any new agent. In addition, there is considerable concern about the potential adverse drug reactions which the standard toxicological test procedures do not aspire to recognise. Clinical experience indicates that these side-effects affect the function of major vital organs and are more frequent than the toxic reactions due to morphological and biochemical lesions. Therefore, to assure human safety, in vitro and in vivo safety pharmacology studies are a regulatory requirement for the start of clinical investigations world-wide. In the pharmaceutical industry, they should be conducted at any point from early discovery to post-marketing.

Learning Outcomes:

On successful completion of the module, participants should be able to:
• understand the common effects seen during pre-clinical studies;
• integrate knowledge of adverse effects on major vital functions in reference with chemical/pharmaceutical class of drugs;
• gain knowledge of all in vitro and in vivo techniques used in pre-clinical safety pharmacology studies;
• identify the most pertinent and reproducible testing strategies for examining putative adverse side effects induced by new chemicals, biologics, therapeutics;
• understand the major regulatory concepts (ICH Guidelines) of modern safety pharmacology;
• have an overview of the impact of safety pharmacology studies on the development phases of new drugs in order to assess the physiological benefit versus risk ratio before going to clinic.

Pre-course Reading:

References and reprints from Guidance documents (e.g. basics in cardiac and neuronal ion channels electrophysiology, cardio-respiratory and CNS pharmacology, Guidance for Industry – ICH-S7A & ICH-S7B).

Module content:

• Overview of cardiac electrophysiology and cardiovascular functions
• Overview of lung mechanics and ventilatory function
• Overview of neuro-electrophysiology and major CNS functions
• Overview of main adverse effects on vital functions: cardiovascular, respiratory and central nervous systems
• Overview of adverse effects on renal, gastrointestinal, liver functions
• Notion of risk assessment and numerous biomarkers used in Safety Pharmacology
• In vitro and in vivo pre-clinical strategies to identify drugs with potential to induce long QT syndrome
• Pre-clinical issues with drug-induced liver and/or renal injury
• Interest of magnetic resonance imaging in pharmaceutical safety assessment
• Pre-clinical issues with drug/biologic-induced immunogenicity and immunotoxicology
• Overview of new technologies (in silico, proteomics, genomics, metabonomics, toxicogenomics…) and how they are applied in Safety Pharmacology
• Notion of Good Laboratory Practices (GLP) and Good Scientific Practices (GSP) in the generation of reproducible results in in vitro and in vivo cardiovascular studies
• Regulatory aspects of Safety Pharmacology via guidelines from the International Conference on Harmonisation of Pharmaceuticals for Human Use (ICH-S7a and ICH-S7b)
• FDA submission standards for Safety Pharmacology studies (including oncologics, biologics, vaccines, monoclonal antibodies…).
Histological examination of tissues has always played a key role in toxicology. Increasingly, however, simple light microscopic examination of tissues is being supplemented by special techniques which now, for example, permit localisation of particular proteins and mRNA and are being extended to examine DNA in defined areas of the tissue. Familiarity with the scope of these techniques is essential for pathologists, especially toxicological pathologists whose aim is to understand the pathogenesis of lesions.

**Learning Outcomes:**

On successful completion of this module, participants should:

- understand the scope and limitations of techniques available to the toxicologist/pathologist;
- understand the scope and limitations of assessing pathological changes in a quantitative fashion;
- identify the types of statistical tests which can be used.

**Pre-course Reading:**

- Chayen, J. and Bitensky, L. (1991) *Practical Histochemistry*
- Crocker, J. (1994) *Molecular Biology in Histopathology*

*Although these books are dated, they give a good overview of “old” technologies. Current technologies will be covered in the lectures and through papers supplied by individual speakers.*

**Module content:**

- Image analysis
- Histochemical techniques
- Immunohistochemistry
- Training of experimental pathologists
- Quality control in pre-clinical studies
- Uses of confocal microscopes
- TEM and SEM
- Assessment of cell proliferation
- Assessment of apoptosis
- *In situ* hybridisation
- Imaging ions
- Analysis of DNA in microscopic lesions
- Statistical analysis of data