IPCS

Training Module No 1

CHEMICAL SAFETY

FUNDAMENTALS OF APPLIED TOXICOLOGY

The Nature of Chemical Hazards

Second (Revised) Edition, 1997

Produced under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation and the World Health Organization, and within the framework of the Inter-Organization Programme for the Sound Management of Chemicals

The International Programme on Chemical Safety (IPCS), established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessing the risk to human health and the environment from exposure to chemicals, through international peer-review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 United Nations Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

IPCS Training Module No. 1

Chemical Safety:

Fundamentals of Applied Toxicology:

The Nature of Chemical Hazards

Second (revised) edition 1997

The second (revised) edition is an updated and expanded version of the first edition (1992). In particular, the sections dealing with environmental toxicology have been expanded and now form Part B of the Module. The introductory material, human health and toxicology constitute Part A.

CONTENTS

INTRODUCTION

"Chemical Safety" is achieved by undertaking all activities involving chemicals in such a way as to ensure the safety of human health and the environment. It covers all chemicals, natural and man-made, and the full range of exposure situations from the natural presence of chemicals in the environment to their extraction or synthesis, industrial production, transport, use and disposal.

Chemical safety has many scientific and technical components. Among these are toxicology, ecotoxicology and the process of chemical risk assessment which requires a detailed knowledge of exposure and of biological effects. Countries need people with relevant knowledge and skills at various levels. Government agencies and industrial concerns need not only by professional toxicologists and ecotoxicologists, but also other experienced staff who understand the scientific basis for chemical safety and its implementation. For example, staff involved in the assessment of chemical risks to human health and the environment, in establishing and monitoring regulations, in public or occupational health or in environmental protection are crucial for chemical safety. To assist countries in organizing and running training activities the IPCS has developed this Module providing information on key components of chemical safety. The modular approach is intended to be flexible and suitable for students with a variety of educational and cultural backgrounds. The Module can be used for distance learning and course instruction or post-course reading and can be adapted to meet local needs. In the text provision is made for self-assessment of course attainment to reinforce learning and to indicate areas to the learner that need more attention.

This Module covers basic aspects of chemistry, health effects of chemicals and environmental toxicology and is intended as a primer for those needing a grounding in these chemical safety topics.

The Module was first prepared by **Dr J.H. Duffus**, The Edinburgh Centre for Toxicology, Heriot-Watt University, Edinburgh, Scotland and published in 1992. The toxicology and human health components of the Module were revised and updated by Dr Duffus in January 1995.

Section 1.3 Environmental Toxicology and Ecotoxicology was redrafted by **Mr M.L. Richardson**, The Birch Assessment Services for Information on Chemicals (BASIC), Rickmansworth, England, in 1994 and revised in 1996 as part of the second (revised) edition.

At the IPCS Central Unit Dr E. Smith was responsible for the technical development of the Module and Dr P.G. Jenkins advised on the editorial and publication aspects.

NOTES FOR STUDENTS

GUIDE TO USE OF THIS MODULE

This module is designed to be used either for independent study or as part of an organized course.

From this module, you can learn the fundamental knowledge necessary to ensure chemical safety.

You can only become fully competent by applying this knowledge to real problems under the supervision of someone with considerable experience.

Independent study requires organization.

1. Find a place where you can work without disturbance.

2. Set yourself a timetable with targets for completion of each section or otherwise defined unit of study

3. Ensure that you allocate time each day for your study so that you can work steadily through each module.

4. If you decide to spend a number of hours studying on any day, take 5-10 minute breaks approximately every half hour. You will find that this helps you to concentrate when you are studying and to remember more.

Look at the list of contents and the layout of the module. **Note particularly the Section 2 "Some Terms Used in Toxicology and Chemical Safety".** This is a guide to the language of toxicology and chemical safety. It defines many terms that may be new to you. It also explains more precisely some terms that you may think you know. **Particular attention should be given to the explanations of "risk" and "hazard", and associated terms such as "risk assessment", "risk evaluation", "absolute risk", and "relative risk".** Much confused thinking can be avoided if these terms are used in the sense described in this Section.

Note should also be taken of the terms relating to ecotoxicology.

Regard the module as a foundation on which to build. Write you own comments where appropriate in the text and make the text your own.

Add information that is relevant to your interests that you acquire from other sources such as television, radio, newspapers, lectures, textbooks, literature research and general conversation.

Write on the summary page notes relating to points of particular interest to yourself.

Highlight points that you think particularly important.

Mark points that you do not understand or even disagree with. Refer to these when you have a chance of discussion with a tutor, fellow student, or an expert in the field. **Do not hesitate to ask questions about any aspect of chemical safety that puzzles you. Tutors welcome questions as a sign of genuine interest and concern about chemical safety.**

SELF ASSESSMENT

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Text marked by asterisks is designed to help you judge your own progress.

You are asked questions or to carry out activities related to the content of the relevant module section.

Try these without further reference to the text. Then, if you have difficulty, look at the text and consult your tutor.

Do not hesitate to consult your tutor about problems. Your tutor is there to help you.

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Note well the objective given at the beginning of each section of the module and the summary at the end.

The objective indicates what you should be able to do if you have studied the module properly and the summary restates the main points covered in the module.

You will find that you can use the objective and summary to check your understanding of each section of the module and to guide your revision if you are preparing for an examination. If you add points to the summary immediately after learning the section, this will help you to memorise them and to recall them at a later date.

PART A: INTRODUCTORY MATERIAL, HUMAN HEALTH AND TOXICOLOGY

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1.1
THE PHYSICAL FORM OF CHEMICALS

OBJECTIVE

You should be aware of the different physical forms in which chemicals can exist and the significance of these forms for exposure and consequent effects of chemicals.

You should be aware of the constant movement of chemicals between physical forms and how this may influence exposure patterns.

MAJOR PHYSICAL FORMS

1. Solid

A large piece of solid material may cause you physical damage if it falls on you but usually presents no risk of poisoning since poisoning depends on uptake by the body.

Handling solids may result in contact dermatitis and sufficient absorption of molecules for other adverse effects to occur.

Grinding, abrasion or disintegration of a large piece of material may produce dusts. A dust is defined as a group of airborne solid particles ranging from 0.1 to 25 micrometers in diameter.

Dusts with an effective aerodynamic diameter of between 0.5 and 10 micrometres (the respirable fraction) can persist in the alveoli and respiratory bronchioles after deposition there.

Peak retention of dusts depends upon aerodynamic shape but seems to be mainly of those particles with an effective aerodynamic diameter of between 1 and 2 micrometers.

Note 1. The effective aerodynamic diameter is defined as the diameter in micrometres of a spherical particle of unit density which falls at the same speed as the particle under consideration.

Dusts of larger diameter than 10 micrometres either do not penetrate the lungs or lodge further up in the bronchioles and bronchi where cilia can return them to the oesophagus.

From the oesophagus dusts are excreted through the gut in the normal way and it is possible that particles entering the gut in this way may cause poisoning as though they had been ingested in the food.

Note 2. Dusts of effective aerodynamic diameter 10 micrometres or less may be referred to as PM10 dusts. There is evidence of a broad association between inhalation of PM10 dusts, irrespective of their precise chemistry, and respiratory disease.

A large proportion of dust breathed in will enter the gut; this dust may affect the gut directly by reacting with it chemically or indirectly from contamination with micro-organisms. Constituents of dust may be absorbed from the gut and cause systemic effects.

Physical irritation by dust particles or fibres can cause very serious adverse health effects (see Note 2 above) but most effects depend upon the solids being dissolved.

Special consideration should be given to asbestos fibres which may lodge in the lung and cause fibrosis and cancer even though they are insoluble and therefore not classical toxicants; similar care should also be taken with manmade mineral fibres.

2. Liquid

Liquids, like solids, can cause physical damage as well as poisoning.

Fluidity gives liquids mobility and this leads to problems of containment. Containment of liquids is made more difficult by their ready convertibility to aerosols and vapours.

Liquids can dissolve other substances and this may have a profound effect on the harm they can do to living organisms.

3. Gas

Gases can also cause either physical or chemical damage; for example, an inert gas could kill simply by displacing air.

In general, chemicals in the gas phase are at their most hazardous from the point of view of acute toxicity since the lungs have evolved to facilitate uptake of oxygen and absorb most gases readily.

In addition, absorbed gases enter the general blood circulation directly, unlike substances absorbed from the intestine, which are often transformed by the liver before entering the general circulation in the form of derivatives.

Some transformation to derivatives may occur in the lung and, as with transformations in the liver, the derivatives produced may be either more toxic or less toxic. Assessment of these transformations must be done on a case by case basis.

4. Vapour

Vapours are the gaseous form of substances which are normally in solid or liquid form at the existing temperature and pressure.

Vapours are in equilibrium with the solids or liquids from which they originate. The equilibrium changes with changes in temperature and pressure.

Vaporization increases with increase in temperature or with decrease in pressure. Substances with high vapour pressure and liquids with low boiling points vaporize (volatilize) readily.

MINOR PHYSICAL FORMS

Aerosols

An aerosol is suspension in a gas of liquid droplets or solid particles, ranging from 0.001 to about 100 micrometres effective aerodynamic diameter: mass concentrations may range from 10^{-9} to 10 g per cubic metre of gas.

Usually the size of the particles in an aerosol is sufficiently small to allow them to remain suspended for long enough to be widely dispersed.
Amongst aerosols, a distinction is made between dusts, fumes, smokes, and mists and fogs.

Dusts

Dusts are generally formed by disintegration processes, such as those involved in mining and ore treatment; examples are silica and asbestos dusts.

The nature of any dust is highly dependent on the process that produced it. Thus, altering the process may alter, for better or worse, the health hazard to workers and others exposed to the dust. For example, reducing the PM10 fraction in the air (see Note 2 above) will obviously be beneficial even if the total dust load stays the same.

Fumes

Fumes are solid particles formed by condensation from the gaseous or vapour phase.

Fumes usually result from chemical reactions such as oxidation or from sublimation or distillation processes followed by condensation; examples are oxides of iron and copper. Fumes may flocculate and coalesce

Fume particles are usually less than 1 micrometre in diameter and can be breathed into the alveoli but are usually breathed out again and so may be less of a hazard than larger particles in the PM10 fraction.

Smokes

Smokes result from the combustion of fossil fuels, asphaltic materials and wood. Smokes consist of soot, liquid droplets and, as in the case of wood and coal, a material-ash fraction.

Because smokes contain polycyclic aromatic hydrocarbons which have been identified as carcinogens, exposure to smoke is associated with increased risk of lung cancer and should be kept to a minimum.

Mists and fogs

Mists and fogs consist of suspended droplets formed by condensation of gas or vapour or by dispersal of liquid by splashing or foaming or by deliberate atomization. Examples are oil mists from cutting and grinding operations and pesticide mists from spraying operations.

Mists and fogs may dissolve gases and particles from the air and may carry harmful micro-organisms in suspension.

Note Well

Substances can change from one physical form to another depending upon the environmental conditions, especially temperature and pressure.

Light causing photochemical processes to occur can also cause large changes in the chemistry of exposed systems; so can ultraviolet radiation and X-rays.

Electromagnetic and electrostatic fields may affect the distribution of particulates and consequently both exposures and related chemical processes.

Thus, environmental conditions must be known before any hazard characterization or risk assessment is possible.

Most environmental samples will contain chemicals in a variety of states and these will determine the exposure conditions for people or other organisms at risk.

Radon is a naturally occurring radioactive gas which may complicate interpretation of epidemiological data relating to occurrence of cancers which may be due to mutagenic chemicals.

SUMMARY

Substances can exist in a number of different physical forms. These forms determine the availability of the substance to living organisms and hence to people at risk.

The physical forms also determine the likelihood of the substances being dispersed from the site of production and the route of dispersal.

The physical form of a substance depends upon the treatment it receives and the environmental conditions.

SELF ASSESSMENT QUESTIONS

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Without reference to the preceding text, list the physical forms in which substances can occur.

Draw a diagram showing how the physical forms are related and how substances may change from one form to another.

Check your answers by reference to the text.

Consult your tutor if necessary.

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1.2

HEALTH EFFECTS OF CHEMICALS

1.2.1 - DESCRIPTIVE TERMS USED ON LABELS AND OTHER INFORMATION SOURCES

OBJECTIVE

You should be aware of the health significance of the descriptive terms used on labels, in the general literature and in the information sources available to you.

Toxic substance (harmful substance)
A substance which can cause injury to living organisms as a result of physicochemical interactions.

Toxicity is:
1. Capacity to cause injury to a living organism defined with reference to the quantity of chemical administered or absorbed, the way in which the chemical is administered (inhalation, ingestion, topical application, injection) and distributed in time (single or repeated doses), the type and severity of injury, the time needed to produce the injury, the nature of the organism(s) affected and other relevant conditions.

2. Adverse effects of a chemical on a living organism defined with reference to the quantity of chemical administered or absorbed, the way in which the chemical is administered (inhalation, ingestion, topical application, injection) and distributed in time (single or repeated doses), the type and severity of injury, the time needed to produce the injury,the nature of the organism(s) affected, and other relevant conditions.

3. Measure of incompatibility of a substance with life: this quantity may be expressed in relation to the absolute value of median lethal dose (LD_{50}) or concentration (LC_{50}) (median lethal dose and concentration are discussed later).

The degree of toxicity produced by exposure to a given substance is usually directly proportional to the exposure concentration and to the exposure time; a possible exception to this general rule is immunotoxicity as reflected in hypersensitivity and other allergic reactions.

The relationship between severity of effect and exposure concentration and time is dependent upon the age and the underlying health of the person or organism at risk.

The embryo and the fetus in the womb may be particularly sensitive and so expectant mothers should be particularly careful to avoid exposure to potentially toxic substances.

Corrosive

Chemical causing a surface-destructive effect on contact; in toxicology, this normally means causing visible destruction of the skin or the lining of the respiratory tract or the gastrointestinal tract.

Irritant

A substance which can produce inflammation of skin and mucous membranes following immediate or prolonged contact.

Solubility is important in determining the site of irritant action in the respiratory and gastro-intestinal tracts.

Highly soluble substances such as ammonia and formaldehyde can rapidly affect the upper respiratory and/or gastro-intestinal tracts.

Substances of low solubility, such as phosgene and nitrogen dioxide, can affect the bronchi before irritation of the upper respiratory tract occurs.

Substances with extreme pH values will always act as irritants.

Asphyxiant

A substance which can deprive a living organism, its tissues and cells of oxygen or of the ability to use it.

An inert gas such as helium can dilute available oxygen below the level required to support life: carbon dioxide can have the same effect and this has led to death of workers in fermentation vessels.

A reactive gas such as hydrogen can react with oxygen making it unavailable but the main danger will be of explosion

Some substances, such as carbon monoxide, can inhibit oxygen transport in living organisms and thus deprive tissues of oxygen: others, such as hydrogen cyanide, inhibit oxygen utilization: both groups of chemicals are asphyxiants.

Primary anaesthetic

A substance such as ether which depresses central nervous system activity.

Systemic poison

A substance which affects organs or tissues in the body. For example:
Carbon tetrachloride affects the liver (hepatotoxicity).
Mercuric chloride affects the kidney (nephrotoxicity).
Carbon disulphide affects the nervous system (neurotoxicity).
Benzene affects bone marrow cells and hence the formation of white blood cells (haemopoietic toxicity or haematotoxicity).

Lung damaging agent

Any substance harming the lungs, including those which do not produce any immediate irritant reaction, such as dusts of asbestos which cause fibrosis.

Dusts in this group may become more dangerous if contaminated with bacterial allergens, fungal allergens, mycotoxins, or pollens.

Contamination of dusts with fungal spores can lead to fungal invasion of damaged lungs which is very difficult to treat: for example - farmers' lung.

Genotoxic agent

A substance which can damage the genetic material of an organism: such a substance may be mutagenic (see below) but not necessarily.

Mutagen

A substance which can cause mutations. A mutation is any relatively stable heritable change in the genetic material, DNA.

Many mutagenic substances can also cause cancer (carcinogens).

Carcinogen

A substance which can cause cancer. Cancer is the disease which results from the development of a malignant tumour and its invasive spread into surrounding tissues.

A tumour (neoplasm) is a growth of tissue forming an abnormal mass in the body.
A benign tumour is one which is localized and neither spreads nor causes cancer.
A malignant tumour is composed of cells which break off and spread throughout the body causing cancer. This process is called invasive spread or metastasis.

Embryotoxic agent

A substance with the potential to induce adverse effects in progeny during the first stage of pregnancy between conception and the fetal stage.

Teratogen

A substance which, at doses which have no effect on the mother can cause nonheritable birth defects. These defects may lead to miscarriage. After birth, the defects may be referred to as 'congenital defects'.

RISK AND SAFETY PHRASES

A widely used series of risk and safety phrases is shown in Tables 1.2.1.1 and 1.2.1.2.
The phrases are given on labels or in Material Safety Data Sheets and International Chemical Safety Cards, for example, as numbers preceded by R for risk and S for safety.

Table 1.2.1.1
Risk phrases used in the classification, packaging, labelling and provision of information on dangerous substances.

R1	Explosive when dry
R2	Risk of explosion by shock, friction fire or other sources of ignition
R3	Extreme risk of explosion by shock friction, fire or other sources of ignition
R4	Forms very sensitive explosive metallic compounds
R5	Heating may cause an explosion
R6	Explosive with or without contact with air
R7	May cause fire
R8	Contact with combustible material may cause fire
R9	Explosive when mixed with combustible material
R10	Flammable
R11	Highly flammable
R12	Extremely flammable
R13	Extremely flammable liquefied gas
R14	Reacts violently with water
R15	Contact with water liberates highly flammable gases

Table 1.2.1.1 (continued)

R16	Explosive when mixed with oxidising substances
R17	Spontaneously flammable in air
R18	In use, may form flammable/explosive vapour-air mixture
R19	May form explosive peroxides
R20	Harmful by inhalation
R21	Harmful in contact with skin
R22	Harmful if swallowed
R23	Toxic by inhalation
R24	Toxic in contact with skin
R25	Toxic if swallowed
R26	Very toxic by inhalation
R27	Very toxic in contact with skin
R28	Very toxic if swallowed
R29	Contact with water liberates toxic gas
R30	Can become highly flammable in use
R31	Contact with acids liberates toxic gas
R32	Contact with acids liberates very toxic gas
R33	Danger of cumulative effects
R34	Causes burns
R35	Causes severe burns
R36	Irritating to eyes
R37	Irritating to respiratory system
R38	Irritating to skin

Table 1.2.1.1 (continued)

R39	Danger of very serious irreversible effects
R40	Possible risk of irreversible effects
R41	Risk of serious damage to eyes
R42	May cause sensitisation by inhalation
R43	May cause sensitisation by skin contact
R44	Risk of explosion if heated under confinement
R45	May cause cancer
R46	May cause heritable genetic damage
R47	May cause birth defects
R48	Danger of serious damage to health by prolonged exposure
R49	May cause cancer by inhalation
R50	Very toxic to aquatic organisms
R51	Toxic to aquatic organisms
R52	Harmful to aquatic organisms
R53	May cause long-term adverse effects in the aquatic environment
R54	Toxic to flora
R55	Toxic to fauna
R56	Toxic to soil organisms
R57	Toxic to bees
R58	May cause long-term adverse effects in the environment
R59	Dangerous to the ozone layer
R60	May impair fertility
R61	May cause harm to the unborn child

Table 1.2.1.1 (continued)

R62	Possible risk of impaired fertility
R63	Possible risk of harm to the unborn child
R64	May cause harm to breastfed babies

Combination of risks

R14/15	Reacts violently with water, liberating highly flammable gases
R15/29	Contact with water liberates toxic, highly flammable gas
R20/21	Harmful by inhalation and in contact with skin
R20/21/22	Harmful by inhalation, in contact with skin and if swallowed
R20/22	Harmful by inhalation and if swallowed
R21/22	Harmful in contact with skin and if swallowed
R23/24	Toxic by inhalation and in contact with skin
R23/24/25	Toxic by inhalation, in contact with skin and if swallowed
R23/25	Toxic by inhalation and if swallowed
R24/25	Toxic in contact with skin and if swallowed
R26/27	Very toxic by inhalation and in contact with skin
R26/27/28	Very toxic by inhalation, in contact with skin and if swallowed
R26/28:	Very toxic by inhalation and if swallowed
R27/28	Very toxic in contact with skin and if swallowed
R36/37	Irritating to eyes and respiratory system
R36/37/38	Irritating to eyes, respiratory system and skin
R36/38	Irritating to eyes and skin
R37/38	Irritating to respiratory system and skin
R42/43	May cause sensitisation by inhalation and skin contact.

Table 1.2.1.1 (continued)

R48/20	Harmful: danger of serious damage to health by prolonged exposure
R48/20/21	Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with the skin
R48/20/21/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed
R48/20/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation, and if swallowed
R48/21	Harmful: danger of serious damage to health by prolonged exposure in contact with skin
R48/21/22	Harmful: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed
R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed
R48/23	Toxic: danger of serious damage to health by prolonged exposure through inhalation
R48/23/24	Toxic: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin
R48/23/24/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed
R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed
R48/24	Toxic: danger of serious damage to health by prolonged exposure in contact with skin
R48/24/25	Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed
R48/25	Toxic: danger of serious damage to health by prolonged exposure if swallowed
R50/53	Very toxic to aquatic organisms, may cause long term adverse effects in the aquatic environment

Table 1.2.1.1 (continued)

R51/53	Toxic to aquatic organisms, may cause long term adverse effects in the aquatic environment
R52/53	Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Note **Section 1.3 for further information on the Environmental Risk phrases**

Table 1.2.1.2

Safety precaution phrases used in the classification, packaging, labelling and provision of information on dangerous substances.

S1	Keep locked up
S2	Keep out of reach of children
S3	Keep in a cool place
S4	Keep away from living quarters
S5	Keep contents under . . . (appropriate liquid to be specified by the manufacturer)
S6	Keep under . . . (inert gas to be specified by the manufacturer)
S7	Keep container tightly closed
S8	Keep container dry
S9	Keep container in a well ventilated place
S12	Do not keep the container sealed
S13	Keep away from food, drink and animal feeding stuffs
S14	Keep away from . . . (incompatible materials to be indicated by the manufacturer)
S15	Keep away from heat
S16	Keep away from sources of ignition—No Smoking
S17	Keep away from combustible material

Table 1.2.1.2 (continued)

S18	Handle and open container with care
S20	When using do not eat or drink
S21	When using do not smoke
S22	Do not breathe dust
S23	Do not breathe gas/fumes/vapour/spray (appropriate wording to be specified by manufacturer)
S24	Avoid contact with skin
S25	Avoid contact with eyes
S26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
S27	Take off immediately all contaminated clothing
S28	After contact with skin, wash immediately with plenty of . . (to be specified by the manufacturer)
S29	Do not empty into drains
S30	Never add water to this product
S33	Take precautionary measures against static discharges
S34	Avoid shock and friction
S35	This material and its container must be disposed of in a safe way
S36	Wear suitable protective clothing
S37	Wear suitable gloves
S38	In case of insufficient ventilation, wear suitable respiratory equipment
S39	Wear eye/face protection
S40	To clean the floor and all objects contaminated by this material use . . . (to be specified by the manufacturer)

Table 1.2.1.2 (continued)

S41	In case of fire and/or explosion do not breath fumes
S42	During fumigation/spraying wear suitable respiratory equipment (appropriate wording to be specified by the manufacturer)
S43	In case of fire, use ... (indicate in the space the precise type of fire fighting equipment. If water increases the risk, add "never use water")
S44	If you feel unwell, seek medical advice (show the label where possible)
S45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
S46	If swallowed, seek medical advice immediately and show the container or label
S47	Keep at temperature not exceeding ... °C (to be specified by the manufacturer)
S48	Keep wetted with ... (appropriate material to be specified by the manufacturer)
S49	Keep only in the original container
S50	Do not mix with ... (to be specified by the manufacturer)
S51	Use only in well ventilated areas
S52	Not recommended for interior use on large surface areas
S53	Avoid exposure - obtain special instructions before use
S54	Obtain the consent of pollution control authorities before discharging to waste-water treatment plants
S55	Treat using the best available techniques before discharge into drains or the aquatic environment
S56	Do not discharge into drains or the environment, dispose to an authorised waste collection point
S57	Use appropriate containment to avoid environmental contamination
S58	To be disposed of as hazardous waste

Table 1.2.1.2 (continued)

S59	Refer to manufacturer/supplier for information on recovery/recycling
S60	This material and/or its container must be disposed of as hazardous waste
S61	Avoid release to the environment. Refer to special instructions / safety data sheet
S62	If swallowed, do not induce vomiting: seek medical advice immediately and show the container or label

Combined safety phrases

S1/2	Keep locked up and out of reach of children
S3/9	Keep in a cool, well ventilated place
S3/7/9	Keep container tightly closed in a cool, well ventilated place
S3/14	Keep in a cool place away from ... (incompatible materials to be indicated by the manufacturer)
S3/9/14	Keep in a cool, well ventilated place away from ... (incompatible materials to be indicated by the manufacturer)
S3/9/49	Keep only in the original container in a cool, well ventilated place
S3/9/14/49	Keep only in the original container in a cool, well ventilated place away from (incompatible materials to be indicated by the manufacturer)
S3/9/49	Keep only in the original container in a cool, well ventilated place
S3/14	Keep in a cool place away from...(incompatible materials to be indicated by the manufacturer)
S7/8	Keep container tightly closed and dry
S7/9	Keep container tightly closed and in a well ventilated place
S7/47	Keep container tightly closed and at a temperature not exceeding...°C (to be specified by manufacturer
S20/21	When using do not eat, drink or smoke

Table 1.2.1.2 (continued)

S24/25	Avoid contact with skin and eyes
S29/56	Do not empty into drains, dispose of this material and its container to hazardous or special waste collection point
S36/37	Wear suitable protective clothing and gloves
S36/37/39	Wear suitable protective clothing, gloves and eye/face protection
S36/39	Wear suitable protective clothing, and eye/face protection
S37/39	Wear suitable gloves and eye/face protection
S47/49	Keep only in the original container at temperature not exceeding...°C (to be specified by the manufacturer)

SUMMARY

Descriptive terms used on labels and in other sources of information have meanings which must be understood by the users of chemicals.

In particular, the health significance of the descriptive terms must be appreciated as correct precautions must be taken to prevent these effects.

SELF ASSESSMENT QUESTIONS

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Without reference to the preceding text, list the terms defined and attempt to make your own definitions.

Compare your definitions with those given.

Ask your tutor about any aspect of the given definitions that you do not understand or that you would like to know more about.

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1.2

HEALTH EFFECTS OF CHEMICALS

1.2.2 - TOXICOLOGY

OBJECTIVE

After reading this section you should have an understanding of the relationship between toxicity and the dose or exposure concentration of the substance causing the toxic response.

You should understand how the **dose or concentration / effect relationship** and **dose or concentration / response relationships** have formed the basis for classifying potentially toxic substances.

You should also understand how the dose or concentration / effect relationship and dose or concentration / response relationship may be used to establish **permissible exposure levels** with the application of **uncertainty (assessment or safety) factors**.

You should know what constitutes an **adverse effect** and some of the general considerations to be applied to the assessment of adverse effects.

You should understand the concepts of **hazard characterization and risk assessment** as applied to potentially toxic substances.

You should also understand how the human body responds to chemicals and how this knowledge is used in assessing potential toxicity.

1.2.2.1 - What is toxicology?

Toxicology is the fundamental science of **poisons**.

A poison is generally considered to be any substance which can cause severe injury or death as a result of a physicochemical interaction with living tissue.

However, **all substances are potential poisons** since all of them can cause injury or death following excessive exposure.

On the other hand, **all chemicals can be used safely** if exposure of people or susceptible organisms is kept below defined tolerable limits, that is if handled with appropriate precautions.

If no tolerable limit can be defined, zero exposure methods must be used.

Exposure is a function of the amount (or concentration) of the chemical involved and the time of its interaction with people or organisms at risk.

For very highly toxic chemicals, **tolerable exposure** may be close to zero.

In deciding on what constitutes a tolerable exposure, the chief problem is often in deciding what constitutes an injury or adverse effect.

An **adverse effect** is defined as an abnormal, undesirable, or harmful change following exposure to the potentially toxic substance.

The ultimate adverse effect is death but less severe adverse effects may include altered food consumption, altered body and organ weights, visible pathological changes, or simply altered enzyme levels.

A statistically significant change from the normal state of the person at risk is not necessarily an adverse effect. The extent of the difference from normal, the consistency of the altered property, and the relation of the altered property to the total wellbeing of the person affected have to be considered.

An effect may be considered harmful if it causes functional or anatomical damage, irreversible change in homeostasis, or increased susceptibility to other chemical or biological stress, including infectious disease. The degree of harm of the effect can be influenced by the state of health of the organism.

Reversible changes may also be harmful but they may often be essentially harmless. An effect which is not harmful is usually reversed when exposure to the potentially toxic chemical ceases.

Adaptation of the exposed organism may occur so that it can live normally in spite of an irreversible effect.

In immune reactions leading to hypersensitivity or allergic responses, the first exposure to the causative agent may produce no adverse response though it sensitizes the organism to respond adversely to future exposures.

The amount of exposure to a chemical required to produce injury varies over a very wide range depending on the chemical and the form in which it occurs.

The extent of possible variation in harmful exposure levels is indicated in Table 1,2.2.1.1 (1.2.2.2) which compares LD_{50} values for a number of potentially toxic chemicals. The LD_{50} value is more descriptively called the median lethal dose as defined below.

Median lethal dose (LD_{50}):-The statistically derived single dose of a chemical that can be expected to cause death in 50% of a given population of organisms under a defined set of experimental conditions. Where LD_{50} values are quoted for human beings, they are derived by extrapolation from studies with mammals or from observations following accidental or suicidal exposures.

TABLE 1.2.2.1.1

Approximate acute LD_{50} values for some potentially hazardous substances*.

Substance	LD_{50} male rat(mg/kg body weight Oral Administration
Ethanol	7 000
Sodium chloride	3 000
Cupric sulphate	1 500
DDT	100
Nicotine	60
Tetrodotoxin	0.02
Dioxin (TCDD)	0.02

* Values obtained from the Merck Index, The Sigma-Aldrich Material Safety Data Sheets (Sigma-Aldrich Library of Chemical Safety Data), and Casarett and Doull's Toxicology (See Annex 1 (1.4)).

The LD_{50} has often been used to classify and compare toxicity among chemicals but its value for this purpose is limited.

A commonly used classification of this kind is shown in Table 1.2.2.1.2.

Such a classification is entirely arbitrary and not entirely satisfactory. For example, it is difficult to see why a substance with an LD_{50} of 200mg/kg body weight should be regarded only as harmful while one with an LD_{50} of 199mg/kg body weight is said to be toxic when the difference in values cannot be statistically significant.

Table 1.2.2.1.2

An example of a classification of toxicity based on acute LD_{50} values (Used in European Union Directives on Classification, Packaging and Labelling of Chemicals)

Category	LD_{50} Orally to Rat (mg/kg body weight)
Very toxic	Less than 25
Toxic	From 25 to 200
Harmful	From 200 to 2000

In decisions relating to chemical safety, the toxicity of a substance is less important than the risk associated with its use.

Risk Predicted or actual frequency (probability) of a chemical causing unacceptable harm or effects as a result of exposure of susceptible organisms or ecosystems.

Assessment of risk is often assessment of the probability of exposure.

Conversely, **Safety** Practical certainty that injury will not result from exposure to a hazard under defined conditions: in other words, the high probability that injury will not result.

Practical certainty Numerically specified low risk or socially acceptable risk applied to decision making.

In assessing permissible exposure conditions for chemicals, uncertainty factors are applied.

Uncertainty factor Mathematical expression of uncertainty that is used to protect populations from hazards which cannot be assessed with high precision.

For example, the 1977 report of the U.S. National Academy of Sciences Safe Drinking Water Committee proposed the following guidelines for selecting **uncertainty (assessment or safety) factors** to be used in conjunction with no observed effect level (NOEL) data.

The NOEL should be divided by the following uncertainty factors:

1. An uncertainty factor of 10 should be used when valid human data based on chronic exposure are available.

2. An uncertainty factor of 100 should be used when human data are inconclusive, e.g. limited to acute exposure histories, or absent, but when reliable animal data are available for one or more species.

3. An uncertainty factor of 1000 should be used when no long-term, or acute human data are available and experimental animal data are scanty. This approach is subjective and is being continually updated. Safety control often involves the assessment of acceptable risk since total elimination of risk is often impossible.

"Acceptable" risk Probability of suffering disease or injury that will be tolerated by an individual, group, or society. Assessment of risk depends on scientific data but its "acceptability" is influenced by social, economic, and political factors, and on the perceived benefits arising from a chemical or process.

SUMMARY

You should now have some idea what toxicology is all about.

The damage caused by any chemical is directly proportional to the amount of the chemical to which anyone has been exposed (the dose) and the time of exposure. It also depends upon the age, sex, and general health status of the person at risk.

The severity of any harmful reaction is concentration dependent but it is often difficult to know the effective concentration at the site of action and so the dose is used as a substitute.

Preventing exposure is the best way to ensure safety but, if this is impossible, a safe permissible exposure may need to be established.

Some concepts related to this have been defined and discussed.

You should know and understand the definitions given as they are fundamental to toxicological thinking.

SELF ASSESSMENT QUESTIONS

****

What information would you require to determine the exposure to a potentially toxic chemical of people at risk?

What is an adverse effect? List some examples of adverse effects that may be used to detect toxicity.

What is the median lethal dose and how is it used?

What is risk?

What is safety? How are uncertainty factors used?

What is acceptable risk?

****

1.2.2.2 - Exposure to potentially toxic substances and their adverse effects

OBJECTIVE

You should know the routes of human exposure to potentially toxic chemicals and the ways in which resultant effects may depend upon these routes, exposure pattern and the properties of the chemicals.

You should know about allergy and its possible consequences.

You should know about idiosyncratic reactions, delayed effects and irreversible effects.

You should know about the complexities of possible interactions between chemicals and their effects.

Introduction

Injury can be caused by chemicals only if they reach sensitive parts of a person or other living organism at a sufficiently high concentration and for a sufficient length of time.

Thus, injury depends upon the physicochemical properties of the potentially toxic substances, the exact nature of the exposure circumstances, and the health and developmental state of the person or organism at risk.

Major routes of exposure are through the skin **(topical)**, through the lungs **(inhalation)**, or through the gastrointestinal tract **(ingestion)**.

In general, for exposure to any given concentration of a substance for a given time, inhalation is likely to cause more harm than ingestion which, in turn, will be more harmful than topical exposure.

Skin (dermal or percutaneous) absorption

Many people do not realise that chemicals can penetrate healthy intact skin and so this fact should be emphasized.

Amongst the chemicals that are absorbed through the skin are aniline, hydrogen cyanide, some steroid hormones, organic mercury compounds, nitrobenzene, organophosphate compounds and phenol.

Some chemicals, such as phenol, can be lethal if absorbed for a sufficient time from a fairly small area (a few square centimetres) of skin. If protective clothing is being worn, it must be remembered that absorption through the skin of any chemical which gets inside the clothing will be even faster.

Inhalation

Gases and vapours are easily inhaled but inhalation of particles depends upon their size and shape. The smaller the particle, the further into the respiratory tract it can go.

Dusts with an effective aerodynamic diameter of between 0.5 and 10 micrometres (the respirable fraction, the PM10 fraction) can persist in the alveoli and respiratory bronchioles after deposition there.

Peak retention depends upon aerodynamic shape but seems to be mainly of those particles with an effective aerodynamic diameter of between 1 and 2 micrometers. Particles of effective aerodynamic diameter less than 1 micrometre tend to be breathed out again and do not persist either in the alveoli or enter the gut (see below).

Remember: The effective aerodynamic diameter is defined as the diameter in micrometers of a spherical particle of unit density which falls at the same speed as the particle under consideration.

Dusts of larger diameter either do not penetrate the lungs or lodge further up in the bronchioles and bronchi where cilia (the mucociliary clearance mechanism) can return them to the pharynx and from there to the oesophagus.

From the oesophagus dusts are excreted through the gut in the normal way: it is possible that particles entering the gut in this way may cause poisoning as though they had been ingested in the food.

A large proportion of dust breathed in will enter the gut directly and may affect the gut directly by reacting with it chemically or indirectly from contamination with micro-organisms. As already mentioned, some constituents of dust may be absorbed from the gut and cause systemic effects.

Physical irritation by dust particles or fibres can cause very serious adverse health effects but most effects depend upon the solids being dissolved. Special consideration should be given to asbestos fibres which may lodge in the lung and cause fibrosis and cancer even though they are insoluble and therefore not classical toxicants: similar care should also be taken with manmade mineral fibres.

Insoluble particles may be taken in by the macrophage cells in the lung which normally remove invading bacteria (phagocytosis). If phagocytic cells are adversely affected by ingestion of insoluble particles, their ability to protect against infectious organisms may be reduced and infectious diseases may follow.

Note **Phagocytosis** is the process whereby certain body cells, notably macrophages and neutrophils engulf and destroy invading foreign particles. The cell membrane of the phagocytosing cell (phagocyte) invaginates to capture and engulf the particle. Hydrolytic and oxidative enzymes are released around the particle to cause its destruction: these enzymes may leak from the phagocyte and cause local tissue damage. Tissue damage may release biologically active substances which cause further adverse effects.

Some insoluble particles such as coal dust and silica dust will readily cause fibrosis of the lung. Others, such as asbestos, may or may not cause fibrosis depending on the exposure conditions.

Remember that tidal volume (the volume of air inspired and expired with each normal breath) increases with physical exertion; thus absorption of a chemical as a result of inhalation is directly related to the rate of physical work. This is why jogging and other active exercise has been discouraged in certain cities during periods of severe air pollution.

Ingestion

Airborne particles breathed through the mouth or cleared by the cilia of the lungs will be ingested. Otherwise, ingestion of potentially toxic substances in the work, domestic, or natural environment is likely to be accidental and commonsense precautions should minimize this.

The nature of the absorption processes following ingestion is discussed elsewhere.

The importance of **concentration and time of exposure** has already been pointed out.

It should be remembered that exposure may be continuous or repeated at intervals over a period of time; the consequences of different **patterns of exposure** to the same amount of a potentially toxic substance may vary considerably in their seriousness.

In most cases, the consequences of continuous exposure to a given concentration of a chemical will be worse than those of intermittent exposures to the same concentration of the chemical at intervals separated by sufficient time to permit a degree of recovery.

Repeated or continuous exposure to very small amounts of potentially toxic chemicals may be a matter for serious concern if either the chemical or its effects have a **tendency to accumulate** in the person or organism at risk.

A chemical may accumulate if absorption exceeds excretion; this may happen with substances that combine a fairly high degree of lipid solubility with stability.

Adverse Effects

Adverse effects may be local or systemic. **Local effects** occur at the site of exposure of the organism to the potentially toxic substance. Corrosives always act locally. Irritants frequently act locally.

Most substances which are not highly reactive are absorbed and distributed around the affected organism causing **systemic injury** at a **target organ** or tissue distinct from the absorption site.

The **target organ** is not necessarily the organ of greatest accumulation.

Adipose (fatty) tissue accumulates **organochlorine pesticides** to very high levels but does not appear to be harmed by them.

Some substances produce both local and systemic effects; for example, **tetraethyl lead** damages the **skin** on contact and is then absorbed and transported to the **central nervous system** where it causes further damage.

Effects of a chemical can accumulate even if the chemical itself does not. There is evidence that this is true of the effects of organophosphate pesticides on the nervous system.

A particularly harmful effect that may accumulate is death of nerve cells, since **nerve cells cannot be replaced** though damaged nerve fibres can be regenerated.

It will be clear that the balances between absorption and excretion of a potentially toxic substance and between injury produced and repair are the key factors in determining whether any injury follows exposure.

All of the possible adverse effects cannot be discussed here but some aspects should be mentioned specifically.

Production of mutations, tumours and cancer, and defects of embryonic and fetal development have been referred to in Section 1.2.1.

Adverse effects related to allergies are a cause of increasing concern.

Allergy (allergic hypersensitivity) is the name given to disease symptoms following exposure to a previously encountered substance **(allergen)** which would otherwise be classified as harmless.

Essentially, an allergy is an adverse reaction of the altered immune system.

The process which leads to the disease response on subsequent exposure to the allergen is called **sensitization**.

Allergic reactions may be very severe and even fatal.

To produce an allergic reaction, most chemicals must act as **haptens**, that is - combine with proteins to form **antigens**.

Antigens entering the human body or produced within it cause the production of antibodies; usually at least a week is needed before appreciable amounts of antibodies can be detected and further exposure to the allergen can produce disease symptoms.

Most common symptoms are **skin ailments** such as **dermatitis and urticaria**, or **eye problems** such as **conjunctivitis**; the worst possibility is death resulting from **anaphylactic shock**.

Of particular importance in considering the safety of individuals is the possibility of **idiosyncratic reactions**.

An idiosyncratic reaction is an excessive reactivity of an individual to a chemical, for example - an extreme sensitivity to low doses as compared with the average member of the population. There is also the possibility of an abnormally low reactivity to high doses.

An example of a group of people with an **idiosyncrasy** is the group which has a **deficiency in the enzyme required to convert methaemoglobin (which cannot carry oxygen) back to haemoglobin**; this group is exceptionally **sensitive to chemicals like nitrites** which produce methaemoglobin.

Another factor to be considered is whether the adverse effects produced by a potentially toxic chemical are likely to be immediate or delayed

Immediate effects appear rapidly after exposure to a chemical while **delayed effects** appear only after a considerable lapse of time.

Amongst the most serious delayed effects are **cancers**; carcinogenesis may take 20 or more years before tumours are seen in humans.

Perhaps the most difficult adverse effects to detect are those that follow years after exposure in the womb; a well established example of such an effect is the **vaginal cancer** produced in young women whose mothers have been exposed to **diethylstilbestrol** during pregnancy.

Another important aspect of adverse effects to be considered is whether they are **reversible or irreversible**.

For the **liver**, which has a great capacity for regeneration, many adverse effects are reversible and complete recovery can occur.

For the **central nervous system**, in which regeneration of tissue is severely limited, most adverse effects leading to morphological changes are irreversible and recovery is, at best, limited.

Carcinogenic and teratogenic effects are also irreversible, but suitable treatment may reduce the severity of effects.

A major problem in assessing the likely effect of exposure to a chemical is making allowance for possible **interactions**.

The simplest interaction is an **additive effect**; this is an effect which is the result of two or more chemicals acting together and which is the simple sum of their effects when acting independently. In mathematical terms: 1 + 1 = 2, 1 + 5 = 6 etc.

The effects of **organophosphate pesticides** are usually additive.

More complex is a **synergistic (multiplicative) effect**: this is an effect of two chemicals acting together which is greater than the simple sum of their effects when acting alone; it may be called **synergism**. In mathematical terms: 1 + 1 = 4, 1 + 5 = 10 etc.

Asbestos fibres and cigarette smoking act together to increase the risk of lung cancer by a factor of forty, taking it well beyond the risk associated with independent exposure to either of these agents.

Another possible form of interaction is **potentiation**.

In potentiation, a substance which on its own causes no harm makes the effects of another chemical much worse. This may be considered to be a form of synergism. In mathematical terms: 0 + 1 = 5, 0 + 5 = 20 etc.

For example - **isopropanol**, at concentrations which are not harmful to the liver, increases (potentiates) **liver damage** caused by a given concentration of carbon tetrachloride.

The opposite of synergism is **antagonism**: an antagonistic effect is the result of a chemical counteracting the adverse effect of another; in other words, the situation where exposure to 2 chemicals together has less effect than the simple sum of their independent effects; such chemicals are said to show antagonism. In mathematical terms: 1 + 1 = 0, 1 + 5 = 2 etc.

Tolerance is a decrease in sensitivity to a chemical following exposure to it or a structurally related substance.

For example - **cadmium** causes tolerance to itself in some tissues by inducing the synthesis of the metal-binding protein, **metallothionein**. However, it should be noted that cadmium-metallothionein sticks in the kidney causing nephrotoxicity.

Resistance is almost complete insensitivity to a chemical. It usually reflects metabolic capacity to inactivate and eliminate the chemical and its metabolites rapidly.

SUMMARY

You have now learnt about routes of human exposure to potentially toxic chemicals and how effects depend upon exposure pattern and the properties of the chemicals involved.

You have also learned about allergy (hypersensitivity) and possible allergic reactions.

You should know what an idiosyncratic reaction is, what a delayed toxic effect is and what may constitute an irreversible effect.

Local and systemic injuries have been discussed.

Definitions and examples have been given of possible interactions between potentially toxic chemicals.

SELF ASSESSMENT QUESTIONS

****

What are the routes of human exposure to potentially toxic chemicals?

Name 5 chemicals that are readily absorbed through the skin.

What diameter of particle can reach the alveoli?

What are phagocytosis and tidal volume and why are they important in human toxicology?

How are inhalation and ingestion related?

What combinations of exposure pattern and chemical properties are likely to be the most harmful?

What are the key factors in determining whether injury follows exposure to a potentially toxic chemical?

What is hypersensitivity (allergy)?

What are the most common symptoms of allergy?

Define "idiosyncratic reaction and give an example.

Give an example of a delayed toxic effect and name the potentially toxic chemical that causes it.

Name 3 adverse effects that are essentially irreversible.

What is systemic injury and what is a target organ?

What is the importance of body fat in relation to potentially toxic substances?

What are the possibilities for interactions between potentially toxic substances in causing injury? Give examples.

****

1.2.2.3 - Dose-response and concentration-response relationships

OBJECTIVE

You should understand the use of dose/response and concentration/response relationships to quantify toxicity (especially with regard to mortality) and the limitations of the LD_{50} or LC_{50} as a basis for comparison of toxicity.

You should know about fixed dose testing as a possible substitute for conventional determination of the LD_{50} and LC_{50}.

You should know the fundamental considerations relating to extrapolation from quantitative results with experimental animals to assess the corresponding relationships for human beings.

You should be familiar with typical test requirements currently applied to new chemicals.

Introduction

The classic dose-response or concentration-response relationship is shown in Figure 1 (1.2.2.3); this is a theoretical curve and in practice such a Gaussian curve is rarely found.

This relationship forms the basis of the determination of the LC_{50} or the LD_{50}.

The LC_{50} and LD_{50} are specific cases of the generalized values defined below:

LC_n:-The exposure concentration of a toxicant lethal to n% of a test population.

LD_n:-The dose of a toxicant lethal to n% of a test population.

Median lethal concentration (LC_{50}):-The statistically derived exposure concentration of a chemical that can be expected to cause death in 50% of a given population of organisms under a defined set of experimental conditions.

Median lethal dose (LD_{50}):-The statistically derived single dose of a chemical that can be expected to cause death in 50% of a given population of organisms under a defined set of experimental conditions.

Figure 1 (1.2.2.3) The Relationship of Dose or Concentration of a Toxicant to the Response Produced in Terms of Mortality

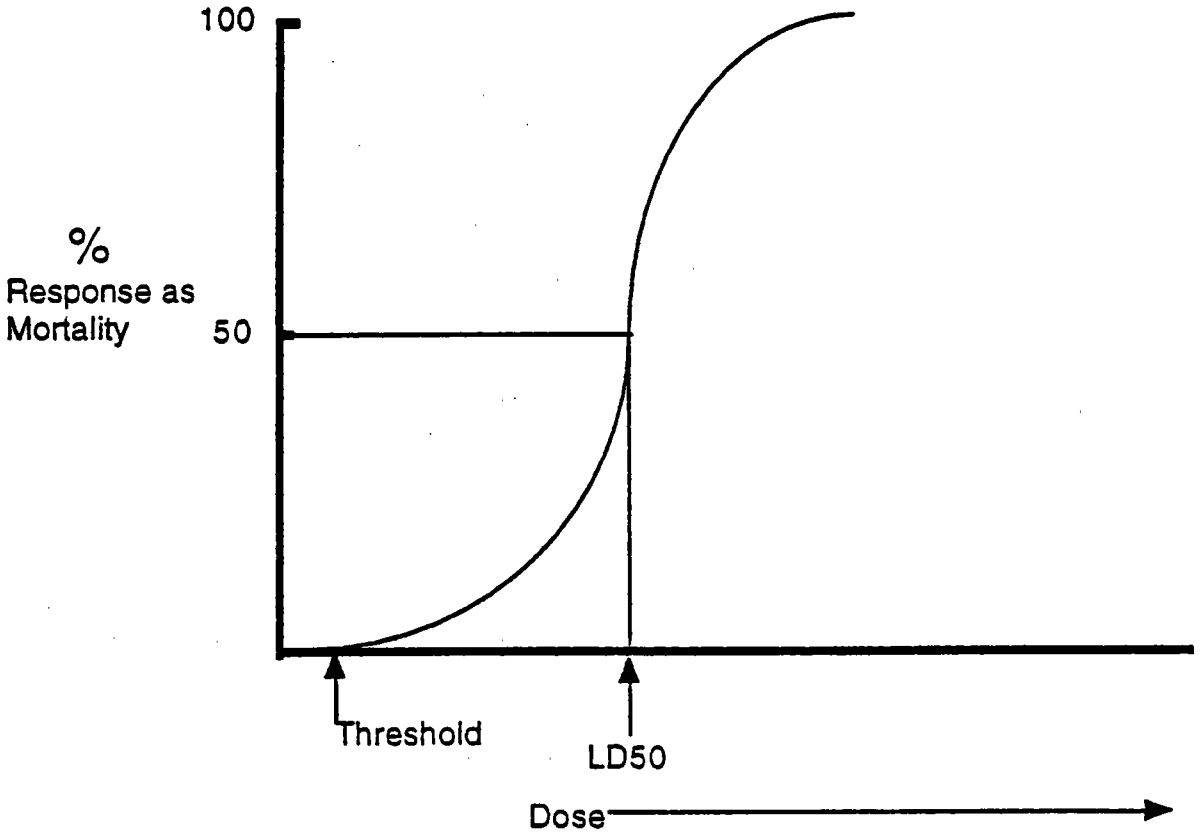
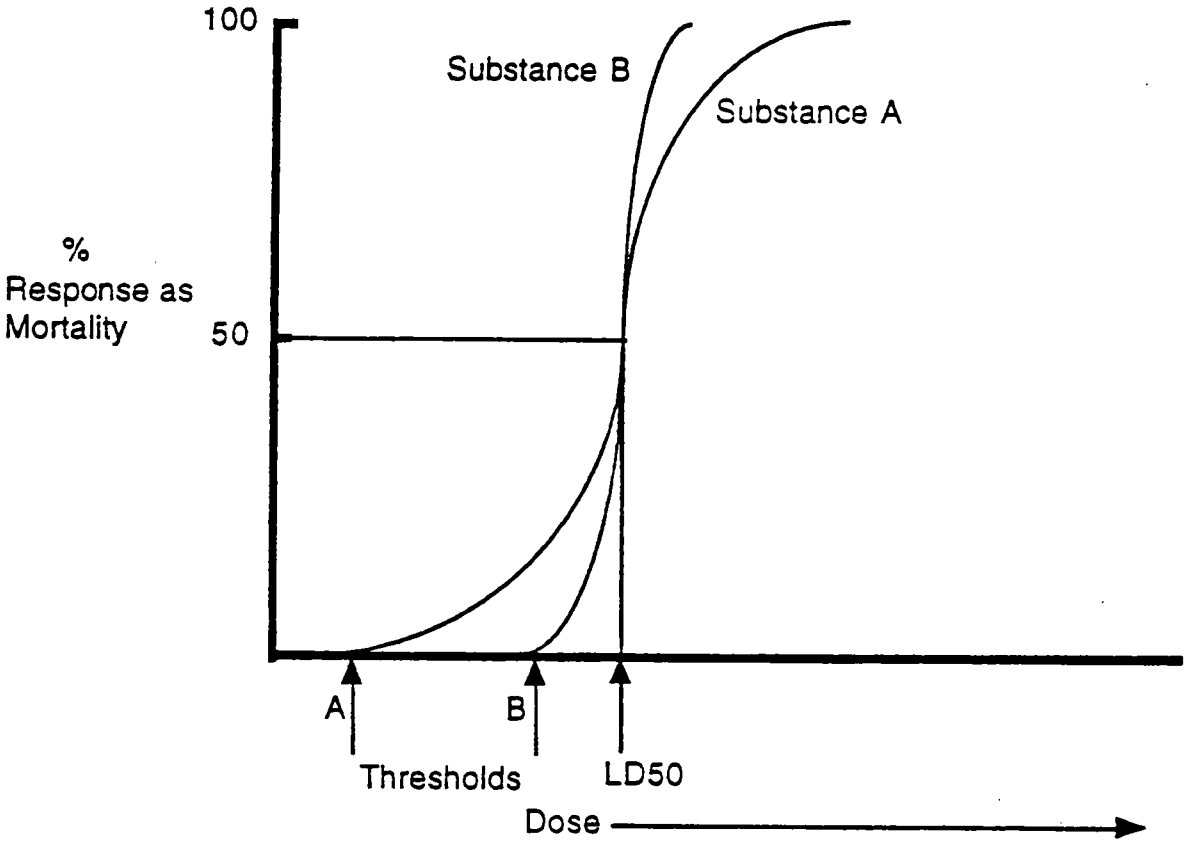


Figure 2 (1.2.2.3) A Comparison of the Dose-Response Relationships of Two Toxicants to Show the Potential for Error in Using LD50 Values for Comparison of Toxicities



Another important value that may be derived from the relationship shown is the **threshold dose or concentration**, the minimum dose or concentration required to produce a detectable response in the test population.

The threshold value can never be derived with absolute certainty and therefore the **lowest observed effect level (LOEL)** or **no observed effect level (NOEL)** is used instead in deriving regulatory standards.

The use of the LD_{50} in the classification of potentially toxic chemicals has been described; it must be emphasized that such a classification is only a very rough guide to relative toxicity.

The LD_{50} tells us nothing about sublethal toxicity.

Any classification based on the LD_{50} is strictly valid only for the test population on which it is based and on the route of exposure.

The LD_{50} tells us nothing about the shape of the dose-response curve on which it is based.

Thus, 2 chemicals may appear to be equally toxic since they have the same LD_{50} but one may have a much lower lethal threshold and kill members of an exposed population at concentrations where the other has no effect.

See Figure 2 (1.2.2.3). Remember, these are theoretical curves and in practice, Gaussian curves of this sort are rarely, if ever, found.

The determination and use of the LD_{50} is likely to decline in future as **fixed dose testing** becomes more widely used.

In fixed dose testing, the test substance is administered to rats or other test species at one dose level: the dose level is selected from preset levels which equate with regulatory classification or ranking systems.

Dosing is followed by an observation period of 14 days. The dose at which toxic signs are detected is used to rank or classify the test materials.

A retrospective study of LD_{50} values showed that between 80% and 90% of those compounds which produced signs of toxicity but no deaths at dose levels of 5, 50 or 500 mg/kg body weight oral administration had LD_{50} values from the same studies of more than 25, from 25 to 200, or from 200 to 2000 mg/kg body weight, the European Union classification banding for very toxic, toxic and harmful.

The initial test dose level should be selected with a view to identifying toxicity without mortality occurring.

Thus, if a group of 5 male and 5 female rats is tested with an oral dose of 500 mg/kg body weight and no clear signs of toxicity appear, the substance should not be classified in any of the categories of toxicity applied.

If toxicity is seen but no mortality, the substance can be classed as 'harmful'.

If mortality occurs, retesting with a dose of 50mg/kg body weight is required.

If no mortality occurs at the lower dose but signs of toxicity are detected, the substance would be classified as 'toxic'.

If mortality occurs at the lower dose, retesting at 5mg/kg body weight would be carried out and if signs of toxicity were detected and/or mortality occurred, the substance would be classified as very toxic.

For full risk assessment, testing at 2000mg/kg body weight is also required if no signs of toxicity are seen at 500 mg/kg body weight.

Fixed dose testing reduces the number of animals required and, because mortality need not occur, also greatly reduces any possible animal suffering.

Fixed dose testing can also identify substances which have high LD_{50} values but still cause acute toxic affects at relatively low doses or exposures.

In assessing the significance of LD_{50} or other toxicological values, pay attention to the units used in expressing dosage.

Normally dosage is expressed in mg/kg body weight but it may be expressed as mg/cm^2 body surface area as this has been shown in a number of cases to permit more accurate extrapolation between animals of different sizes and from test species to humans.

For biocides, selective toxicity is the key property so that they can be used to kill pests with minimal harm to other organisms.

Selective toxicity depends upon differences in biological characteristics which may be either quantitative or qualitative.

Hence, minimizing the amount of pesticide used and targeting its application is crucial to avoid harm to nontarget organisms.

Toxicity testing is primarily aimed at establishing by tests on laboratory animals what effects chemicals are likely to have on human beings who may be exposed to them.

On a body weight basis, it is assumed for toxicity data **extrapolation** that humans are usually about ten times more sensitive than rodents.

On a body surface area basis, humans usually show about the same sensitivity as test mammals, that is they respond to about the same dose per unit of body surface area.

Knowing the above relationships, it is possible to estimate the exposure to a chemical that humans should be able to tolerate.

In a number of countries there is now a defined set of tests which must be carried out on every new chemical which is to be used or produced in an appreciable quantity, usually above 1 tonne per year.

Table 1.2.2.3 gives an example of test requirements applicable in a number of countries.

Table 1.2.2.3

Example of information requirements in some countries for notification and hazard assessment of new chemicals

BASE SET INFORMATION

1. IDENTITY OF THE SUBSTANCE
1.1 Name
1.1.1 Names in the IUPAC nomenclature
1.1.2 Other names (usual name, trade name, abbreviation)
1.1.3. CAS number (if available)
1.2 Empirical and structural formula
1.3 Composition of the substance
1.3.1 Degree of purity (%)
1.3.2 Nature of impurities, including isomers and by-products
1.3.3 Percentage of (significant) main impurities
1.3.4 If the substance contains a stabilising agent or an inhibitor or other additives, specify:
nature, order of magnitude: . . . ppm; . . . %
1.3.5 Spectral data (UV, IR, NMR)
1.4 Methods of detection and determination
A full description of the methods used or the appropriate bibliographical references

2. INFORMATION ON THE SUBSTANCE
2.1 Proposed uses
2.1.1 Types of use
Describe: the function of the substance and the desired effects
2.1.2 Fields of application with approximate breakdown
(a) closed system
- industries.
- farmers and skilled trades
- use by the public at large

(b) open system
- industries
- farmers and skilled trades
- use by the public at large

2.2 Estimated production and/or imports for each of the anticipated uses or fields of application

2.2.1 Overall production and/or imports in order of tonnes per year
1, 10, 50 100, 500, 1 000 and 5 000
- first 12 months
- thereafter

2.2.2 Production and/or imports, broken down in accordance with 2.1.1 and 2.1.2, expressed as a percentage
- first 12 months
- thereafter

2.3 Recommended methods and precautions concerning:

2.3.1 Handling

2.3.2 Storage

2.3.3 Transport

2.3.4 Fire (nature of combustion gases or pyrolysis, where proposed uses justify

2.3.5 Other dangers, particularly chemical reaction with water

2.4 Emergency measures in the case of accidental spillage

2.5 Emergency measures in the case of injury to persons (e.g. poisoning)

3. PHYSICOCHEMICAL PROPERTIES OF THE SUBSTANCE

3.1 Melting point

3 2 Boiling point
...°C at ...Pa

3 3 Relative density
(D_4^{20})

3.4 Vapour pressure
Pa at ..°C
Pa at ..°C

3.5 Surface tension
N/m (..°C)

3.6 Water solubility
mg/litre (..°C)

3 7 Fat solubility
Solvent—oil (to be specified)
mg/100g solvent (..°C)

3.8 Partition coefficient
n-octanol/water

3.9 Flash point
..°C. open cup and closed cup

3.10 Flammability

3.11 Explosive properties

3.12 Auto-flammability
..°C

3.13 Oxidizing properties

4. TOXICOLOGICAL STUDIES

4.1 Acute toxicity

4.1.1 Administered orally

LD_{50} mg/kg

Effects observed, including in the organs

4.1.2 Administered by inhalation

LC_{50} (ppm). Duration of exposure in hours

Effects observed, including in the organs

4.1.3 Administered cutaneously (percutaneous absorption)

LD_{50} mg/kg

Effects observed, including in the organs

4.1.4 Substances other than gases shall be administered via two routes at least one of which should be the oral route. The other route will depend on the intended use and on the physical properties of the substance. Gases and volatile liquids should be administered by inhalation (a minimum period of administration of four hours). in all cases, observation of the animals should be carried out for at least 14 days. Unless there are contraindications, the rat is the preferred species for oral and inhalation experiments. The experiments in 4.1.1, 4.1.2 and 4.1.3 shall be carried out on both male and female subjects.

4.1.5 Skin irritation

The substance should be applied to the shaved skin of an animal, preferably an albino rabbit.

Duration of exposure in hours

4.1.6 Eye irritation The rabbit is the preferred animal.

Duration of exposure in hours

4.1.7 Skin sensitization To be determined by a recognized method using a guinea-pig.

4.2 Sub-acute toxicity

4.2.1 Sub-acute toxicity (28 days)

Effects observed on the animal and organs according to the concentrations used, including clinical and laboratory investigations

Dose for which no toxic effect is observed

4.2.2 A period of daily administration (five to seven days per week) for at least four weeks should be chosen.

The route of administration should be the most appropriate having regard to the intended use, the acute toxicity and the physical and chemical properties of the substance.

Unless there are contra-indications, the rat is the preferred species for oral and inhalation experiments.

4.3 Other effects

4.3.1 Mutagenicity (including carcinogenic pre-screening test)

4.3.2 The substance should be examined during a series of two tests one of which should be bacteriological, with and without metabolic activation, and one non-bacteriological.

5 ECOTOXICOLOGICAL STUDIES

5.1 Effects on organisms

5.1.1 Acute toxicity for fish

LC_{50} (ppm)
Duration of exposure
Species selected (one or more)

5.1.2 Acute toxicity for Daphnia

LC_{50} (ppm)
Duration of exposure

5.2 Degradation - biotic and abiotic

The BOD and the BOD/COD ratio should be determined as a minimum

6 POSSIBILITY OF RENDERING THE SUBSTANCE HARMLESS

6.1 For industry/skilled trades

6.1.1 Possibility of recovery
6.1.2 Possibility of neutralization
6.1.3 Possibility of destruction:
- controlled discharge
- incineration
- water purification station
- others.

6.2 For the public at large

6.2.1 Possibility of recovery
6.2.2 Possibility of neutralization
6.2.3 Possibility of destruction:
- controlled discharge
- incineration.
- water purification station
- others

SUMMARY

You should now be aware of the classic dose/response or concentration/response relationship and its use as a basis for toxicity classification for regulatory purposes.

You should also understand the main limitations of such data.

The importance of the units used to express dosage has been emphasized.

A typical base set of data has been listed as an example of the kind of information now required by regulatory authorities for the assessment of potential chemical hazards.

SELF ASSESSMENT QUESTIONS

****

What is the classic dose/response or concentration/response relationship and what are the derived values that may be used for regulatory purposes?

What are the limits on the use of the LD_{50} to classify the toxicity of chemicals?

What units should be used to express dosage to permit extrapolation from test animals to other animals or human beings at risk?

What are the main components of a typical set of information requirements for registration of a new chemical?

****

1.2.2.4 - Human biotransformation of chemicals and mechanisms of action

OBJECTIVE

You should know what happens to potentially toxic substances following absorption and the differences in body distribution and effects that may result from different routes of absorption.

You should know about the main biotransformation reactions that occur normally as a part of essential life processes and can affect absorbed chemicals: you should understand how they can contribute to either detoxification or formation of derivatives with increased toxicity (biotoxification).

You should know why fat soluble substances may cause special problems and the role of biliary excretion and enterohepatic circulation.

You should know about immune reactions, immunotoxicity, and their possible consequences.

You should be able to distinguish between toxicokinetics and toxicodynamics. Mutagenesis and carcinogenesis should be understood as examples of toxicodynamics.

Absorption of chemicals

If we ignore the medical administration of drugs, there are several routes by which people can take in foreign chemicals (**xenobiotics**).

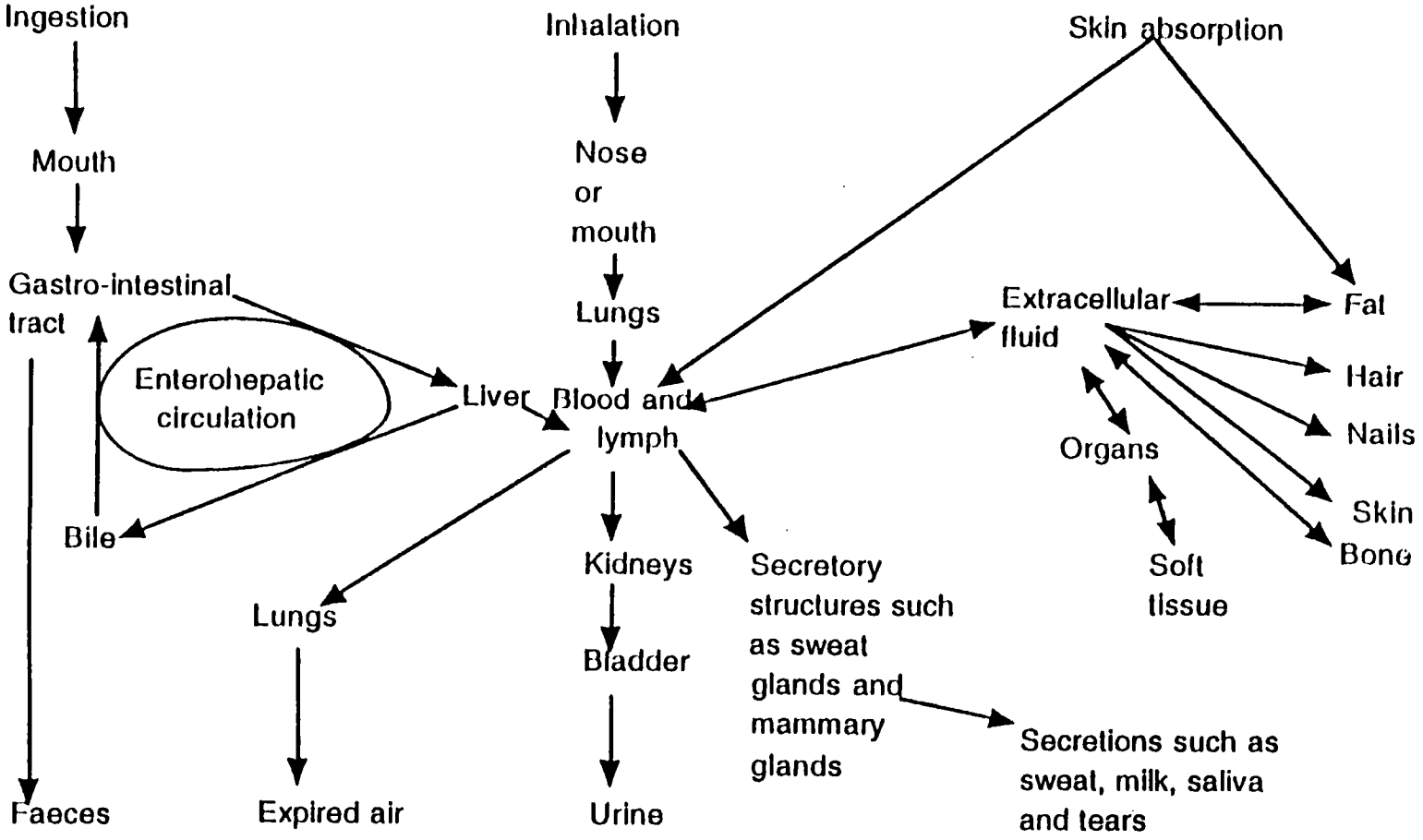
The main routes are (1) through the skin or mucous membranes such as the conjunctiva, (2) through the lungs (inhalation), and (3) through the gastro-intestinal tract (ingestion).

Figure 1 (1.2.2.4) shows what happens to xenobiotics absorbed by these routes.

The severity of the effects produced by any given dose, amount or concentration of a chemical or chemical formulation is related to the route of absorption amongst other things (*Note to the student: can you list other relevant factors?*).

Usually absorption is most rapid from the lungs, less rapid from the gastro-intestinal tract and least rapid through the skin.

Figure 1 (1.2.2.4) Routes of Absorption, Distribution and Excretion of Potentially Toxic Substances



The lungs evolved for efficient exchange of gases and present little resistance to the uptake of chemicals in the vapour state.

Respirable particulates may lodge in the lungs if they are small enough (less than 7 micrometres in diameter) and/or of a shape or chemistry that prevents their removal by the normal bronchial ciliary action.

Diseases which can result from inhalation of particulates include silicosis, asbestosis, berylliosis etc.

Some respirable particulates may dissolve easily in the fluids of the respiratory tract: such particulates may affect the upper respiratory tract more than the bronchioles and alveoli.

The gastro-intestinal tract evolved to absorb nutrients in a selective manner; potentially toxic chemicals that are chemically similar to normal nutrients may be absorbed preferentially.

The skin evolved as a protective covering against a hostile environment and is relatively impermeable to many chemicals.

However, many chemicals are absorbed readily through the skin, for example phenols and organophosphate pesticides, and these can be lethal.

Distribution and metabolism of chemicals

Once absorbed, chemicals from the lungs, skin and mouth may enter the general blood circulation directly and be rapidly spread round the body in an unmodified form.

Chemicals absorbed from the stomach or intestine enter the hepatic portal system and are taken to the liver where they may be modified by a series of reactions often referred to as **biotransformation** - see Figures 1 (1.2.2.4), 2 (1.2.2.4) and 3 (1.2.2.4).

Biotransformation reactions in the liver have been referred to as "detoxification" but this term is misleading because they can also increase the toxicity of a number of chemicals - "biotoxification" as in Figures 4 (1.2.2.4) and 5 (1.2.2.4).

Figure 2 (1.2.2.4) and Figure 3 (1.2.2.4) show the possible fates of chemicals following absorption and indicates how the fate of a chemical may depend upon its physicochemical properties.

Biotransformation reactions are subdivided into **phase I and phase II reactions**.

The phase I reactions are catalyzed by the cytochrome P450 family of enzymes and other enzymes of the smooth endoplasmic reticulum.

Phase I reactions include oxidation, reduction, hydrolysis, dealkylation, deamination, dehalogenation, ring formation, and ring breakage.

Phase II reactions are conjugation reactions - covalent linkage of the absorbed chemicals, or of the products of the phase I reactions, with compounds such as glutathione, glucuronic acid, or amino-acids.

The conjugates produced are generally more water soluble than the chemicals from which they are derived and so are more easily excreted.

Chemicals which undergo phase I and phase II reactions are normally those which are fat soluble (lipophilic).

Fat soluble substances tend to accumulate in body tissue and milk if not converted to an excretable form.

Excretion of conjugates mostly occurs in the bile.

Some conjugates may be broken down to components by bacteria in the gut; the components may again be absorbed and go through phase II reactions; this process is called **enterohepatic circulation**.

Enterohepatic circulation slows excretion of the substances involved and must be allowed for in evaluating the likely effects of any potentially toxic substances.

As Figure 2 (1.2.2.4) shows, water soluble (hydrophilic) substances and dissociated polar substances go directly to the blood circulation, from which they may be lost in expired air from the lungs (if they vapor
ise readily), through the kidney in the urine following ultrafiltration and/or active secretion or in other secreted fluids such as tears, saliva, milk, sweat etc.

Highly lipophilic and metabolically stable substances tend to accumulate in body fat - see Figure 3 (1.2.2.4); if this fat is mobilized under stress conditions, the substances may return to the blood and cause acute intoxication before undergoing phase I and phase II reactions in the liver and other organs.

In the blood, fat soluble substances associate reversibly with blood cells, albumin, and lipoproteins.

Immunological reactions

Free molecules can react with other body components, altering their properties and hence their biological functions; chemical alteration of body components may result in the immune system treating these components as foreign with harmful results.

Antibodies may be produced which bind to abnormally altered body components and trigger inflammation, tissue breakdown and other harmful effects.

Biotoxification

Figure 5 (1.2.2.4) shows some examples of the way in which biotransformation can lead to increased toxicity.

Polycyclic aromatic hydrocarbons are converted to arylating derivatives which can react with DNA and proteins to cause mutations, cancers, embryonic abnormalities (teratogenesis), immunological sensitization and cell death.

Aryl amines are converted to aryl hydroxylamines which can carry out arylation reactions and also convert haemoglobin to methaemoglobin, a derivative which can no longer carry oxygen.

Nitrate in the diet can be converted to nitrite by bacteria in the intestine and, in the presence of substances containing amino groups, converted further by the same bacteria to nitrosamines.

Nitrite can convert haemoglobin to methaemoglobin thus lowering the ability of the blood to carry oxygen.

This reaction has led to the death of babies given milk prepared from proprietary milk powder dissolved in water containing too much nitrate; death is caused by the tissues being deprived of oxygen ("blue baby" syndrome).

Nitrate contamination of drinking water may arise from excessive use of nitrate as fertilizer by farmers.

A special case of biotoxification is the process known as "lethal synthesis" - see Figure 6 (1.2.2.4); the classic example of this is the conversion of the rat poison fluoro-acetic acid to fluorocitric acid which inhibits aconitase, a key enzyme in the citric acid cycle, the central reaction system in biological oxidation and energy release.

Toxicodynamics

We have now looked at 2 of the phases in the production of toxicity, namely the chemical phase (exposure phase) and the toxicokinetic phase - see Figure 7 (1.2.2.4).

The final phase is the toxicodynamic phase which covers the reactions which are the immediate cause of toxicity.

The alkylation and arylation of DNA to cause mutations (already referred to) is part of the toxicodynamic phase; one possible consequence of these reactions is tumour development and cancer as described below: some aspects of this are summarized in Figure 8 (1.2.2.4).

Any molecules which can act as alkylating or arylating agents in their original state or following biotransformation may attack DNA causing changes in the molecular structure and thus causing mutations (**mutagenesis**).

If such mutations occur in gametes (eggs or sperm), they are heritable and may affect future generations.

If mutations occur in other body cells, they are called **somatic mutations** and may cause benign or malignant tumour development.

A mutated cell does not necessarily form a tumour; if DNA repair mechanisms operate, as they often do, the damaged DNA may be removed and replaced and the cell will return to normal.

If DNA repair does not occur, the initiated cell may become the focus of a benign or malignant tumour.

Alternatively, the cell with damaged DNA may be 'initiated' and may function normally until exposed to another chemical called a 'promoter'. A chemical causing such **initiation** is said to be an 'initiator'.

Initiation may be defined as a stochastic process that involves one or more heritable alterations in DNA induced by diverse factors including mutagenic chemicals, ionizing radiation and viruses.

A promoter is a substance which does not itself cause tumour development but which, by its action, permits a potentially carcinogenic mutation caused by an initiator to be expressed in local cell proliferation (**promotion and progression**) leading to tumour formation. One or more of these may become malignant and lead to cancer.

The distinction between promoters and initiators is becoming blurred as they all seem now to be fundamentally genotoxic.

Cancer may also result from exposure to substances which poison the immune system preventing it from removing potentially cancerous cells before tumours develop.

Once tumours develop, some may prove to be cancerous (malignant) and spread throughout the body but many will be localized (benign) and may be safely left or removed by surgery.

Malignant tumours are characterized by their ability to invade adjacent tissues and to metastasize (cells break off from the original tumour and move in the lymphatics or blood stream to another part of the body which they invade and where secondary growths are formed).

Immunotoxicity

Many toxic effects are mediated through the immune system, a complex system with many components.

Depression of the system will lower resistance to infectious disease and facilitate development of cancer.

Enhancement of the system can also lead to disease processes of which the most common are listed below in the final paragraph of this section.

However, it should be noted that immunomodulatory agents can stimulate some components of the immune system and, at the same time, depress others.

If a chemical or derivative (such as a modified body component) functions as an antigen, hypersensitivity to the chemical will result and, in the case of a body component, the ability of the immune system to distinguish between self and nonself molecules may be compromised and result in immunological damage to essential cells and tissues..

Consequences may include asthma, rhinitis, conjunctivitis, haemolytic anaemia, myasthenia gravis, glomerulonephritis, systemic lupus erythematosus, contact dermatitis, and even infertility.

Figure 2 (1.2.2.4) Distribution and Excretion of Potentially Toxic Substances which are Hydrophilic or Polar

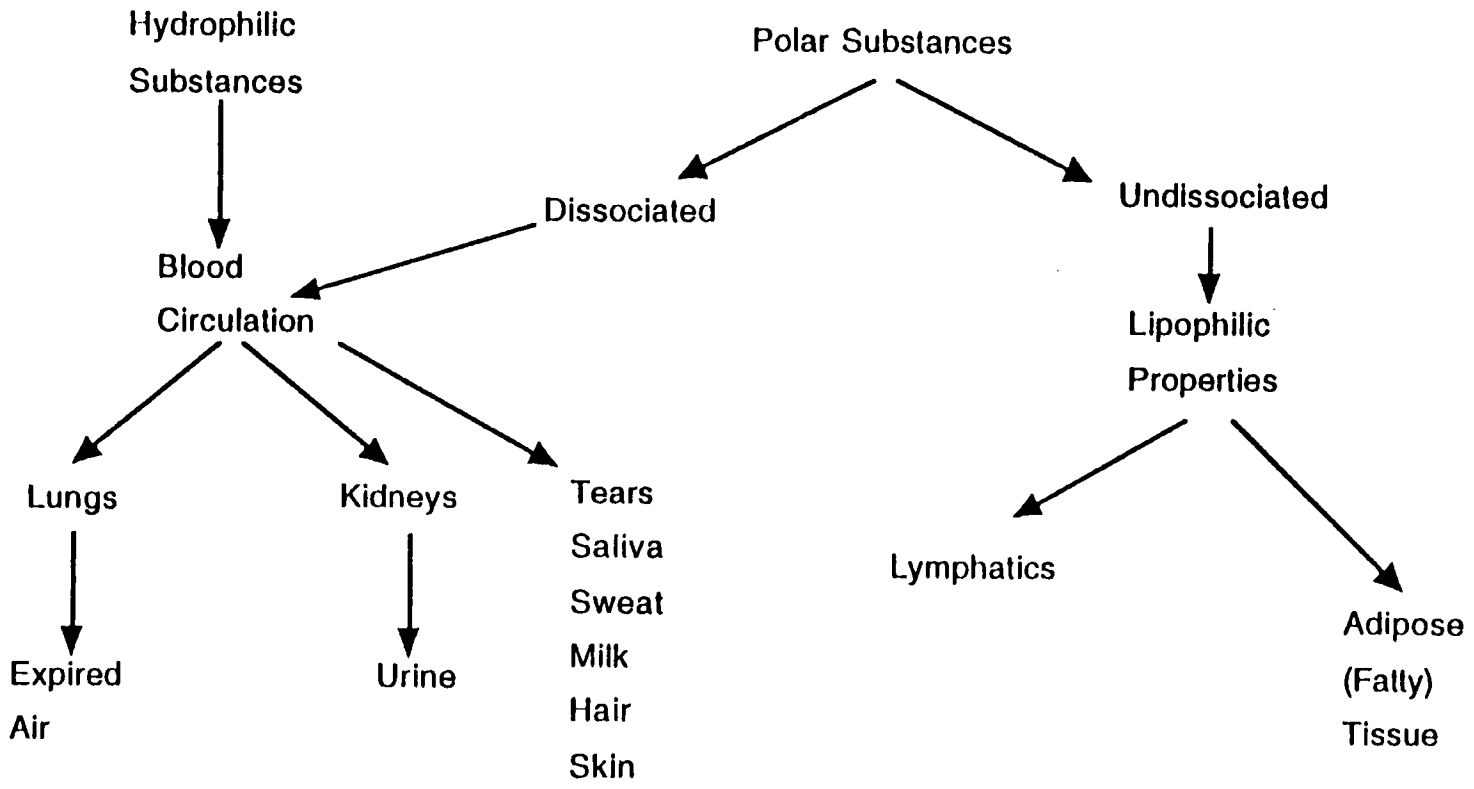


Figure 3 (1.2.2.4) Distribution and excretion of Potentially Toxic Substances which are Lipophilic

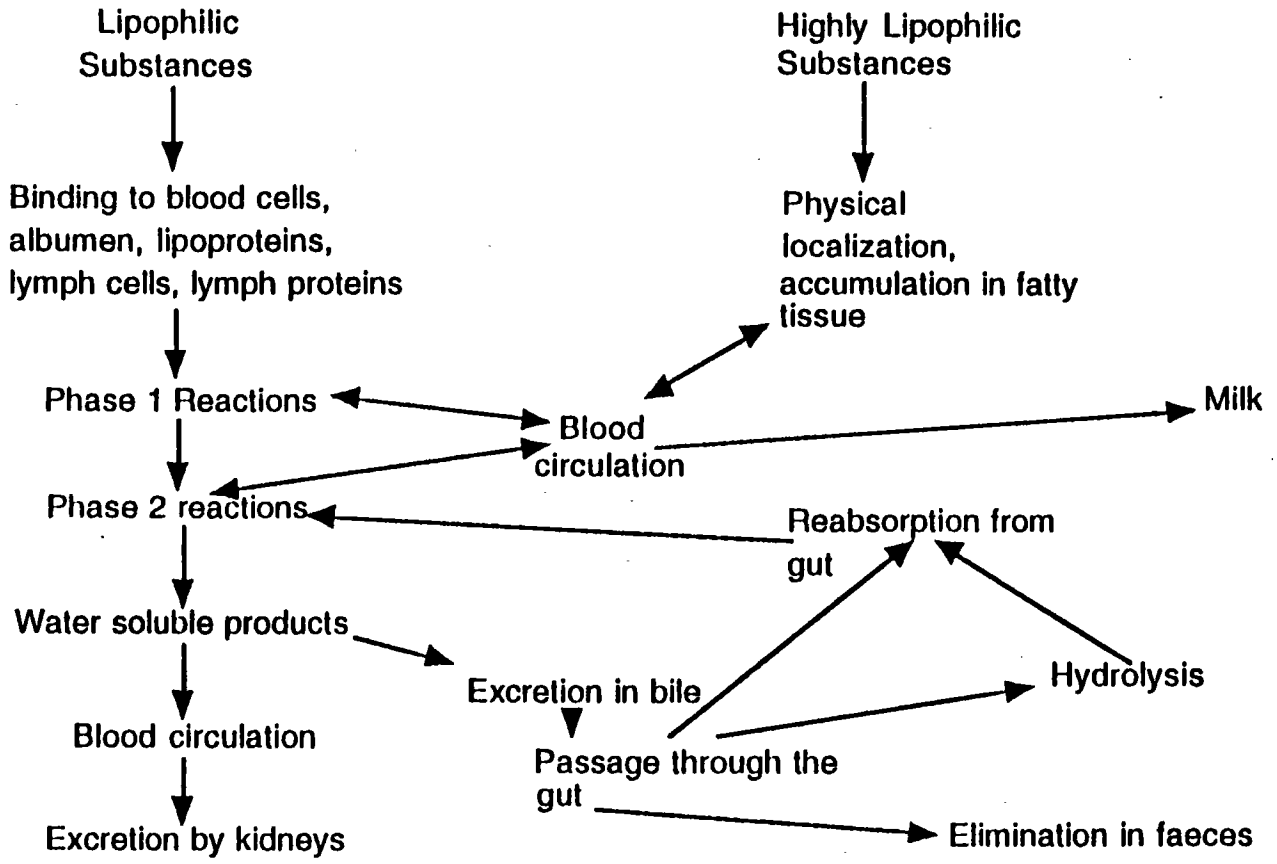


Figure 4 (1.2.2.4) Main steps in Biotransformation of of Potentially Toxic Substances which are Arylating or Alkylating Agents or Metals

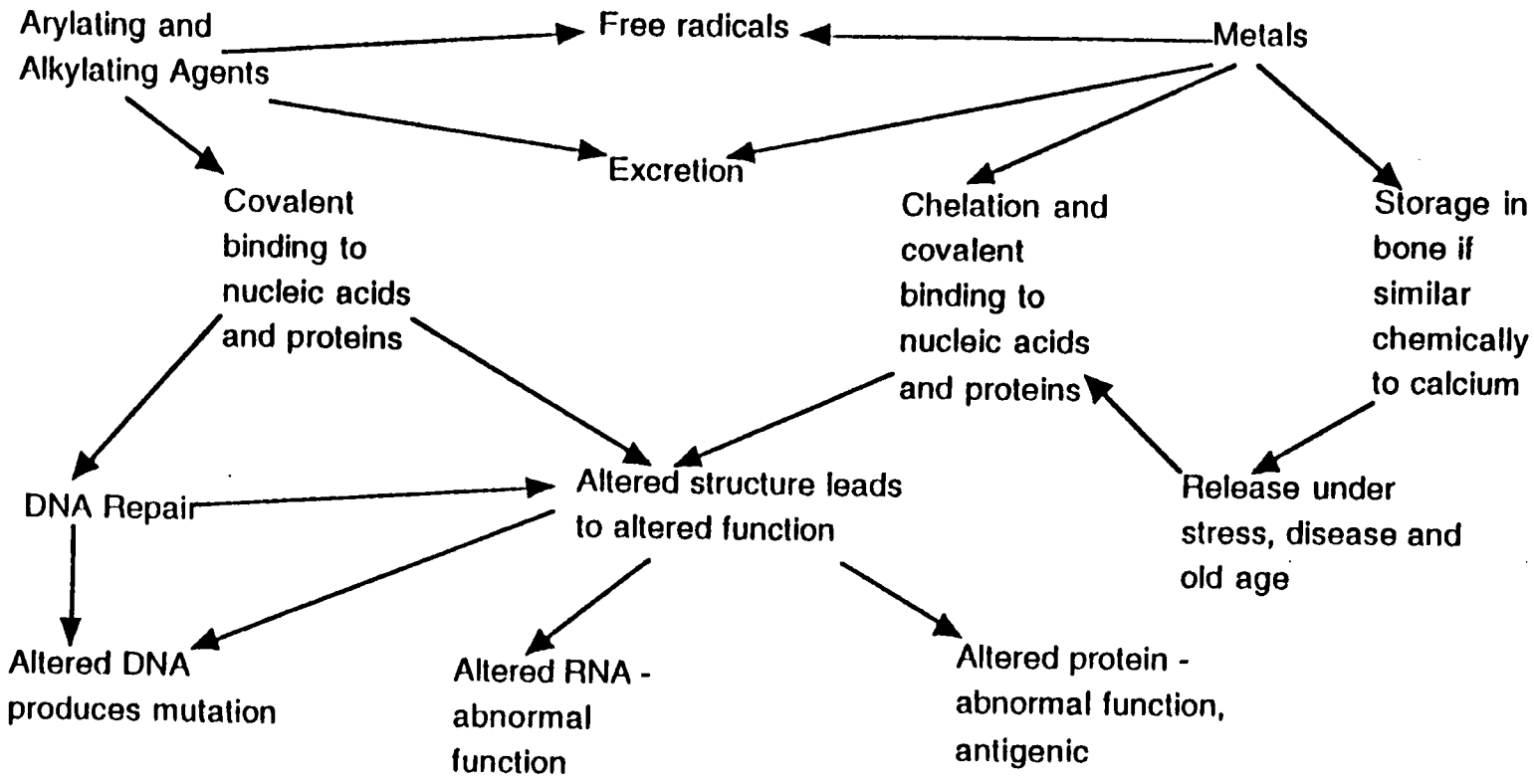


Figure 5 (1.2.2.4) Examples of biotoxification

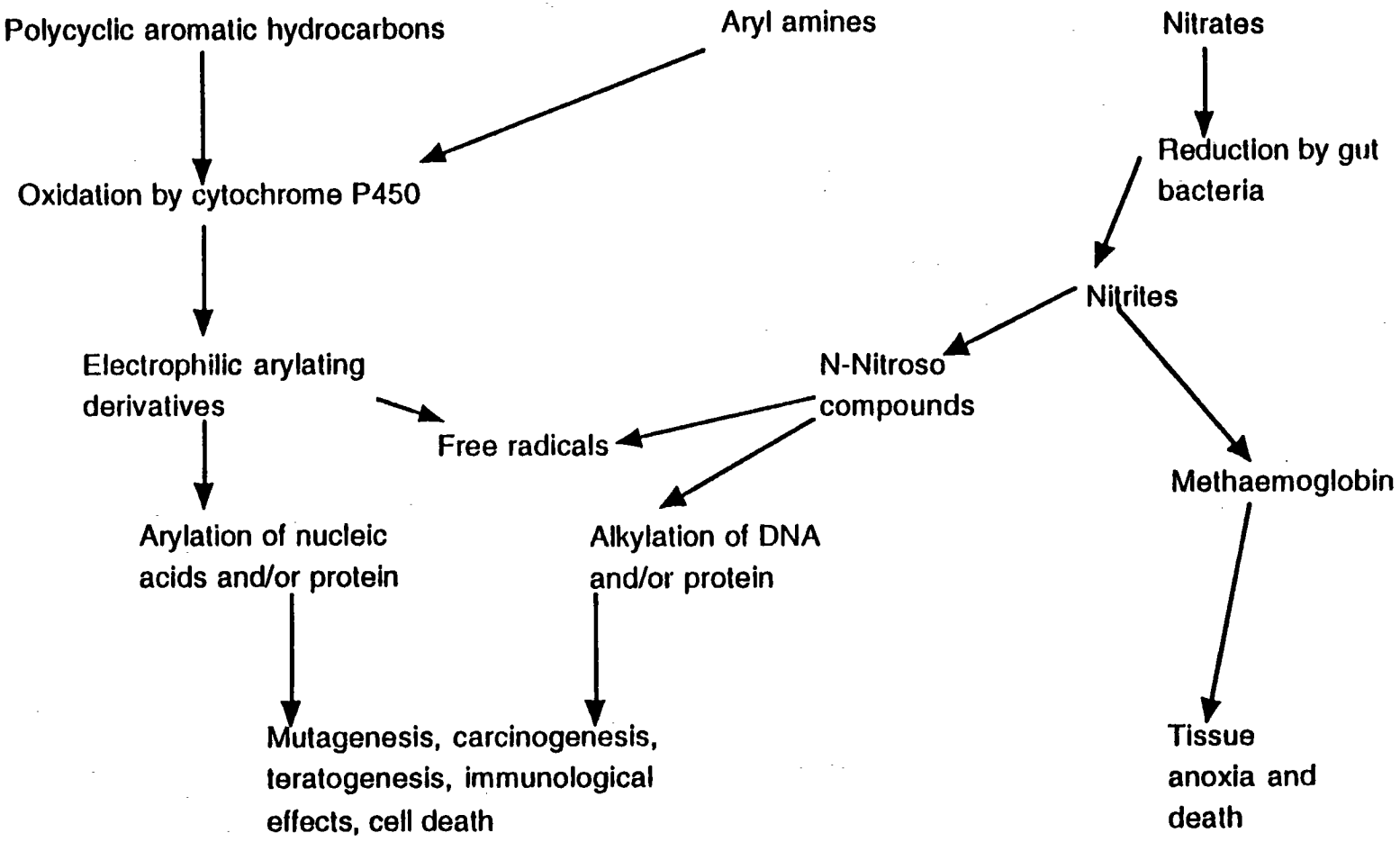


Figure 6 (1.2.2.4) "Lethal Synthesis"

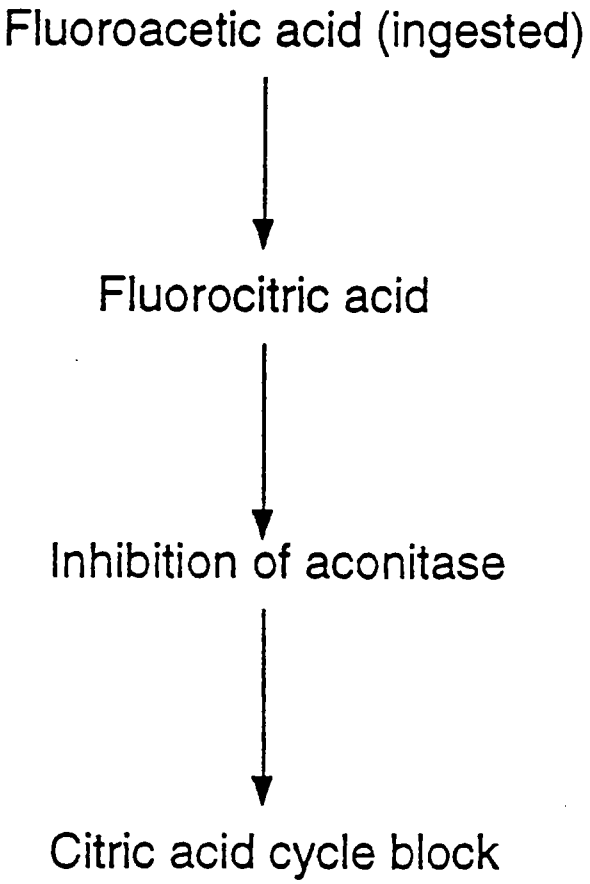


Figure 7 (1.2.2.4) Phases in the Production of Toxicity

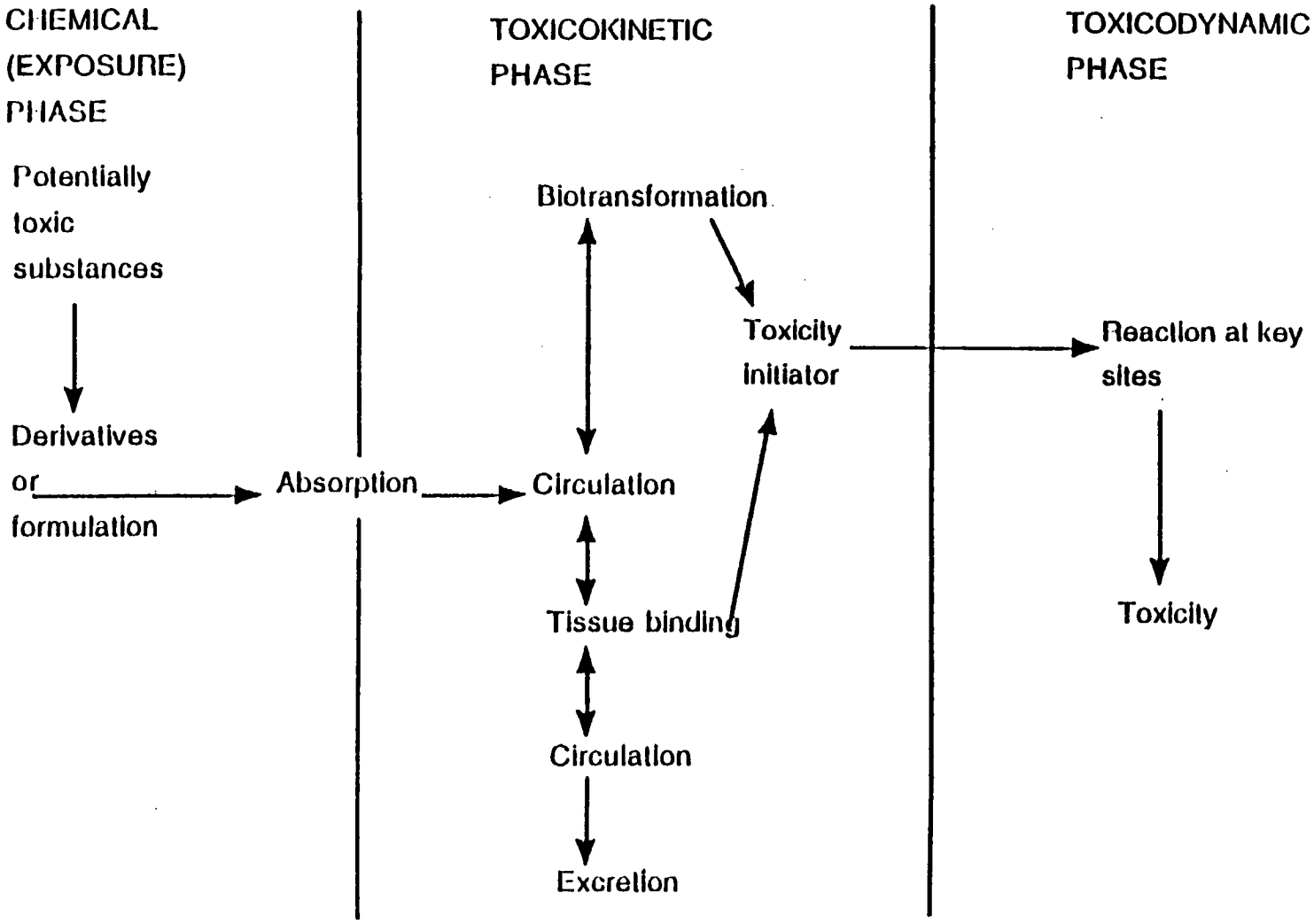
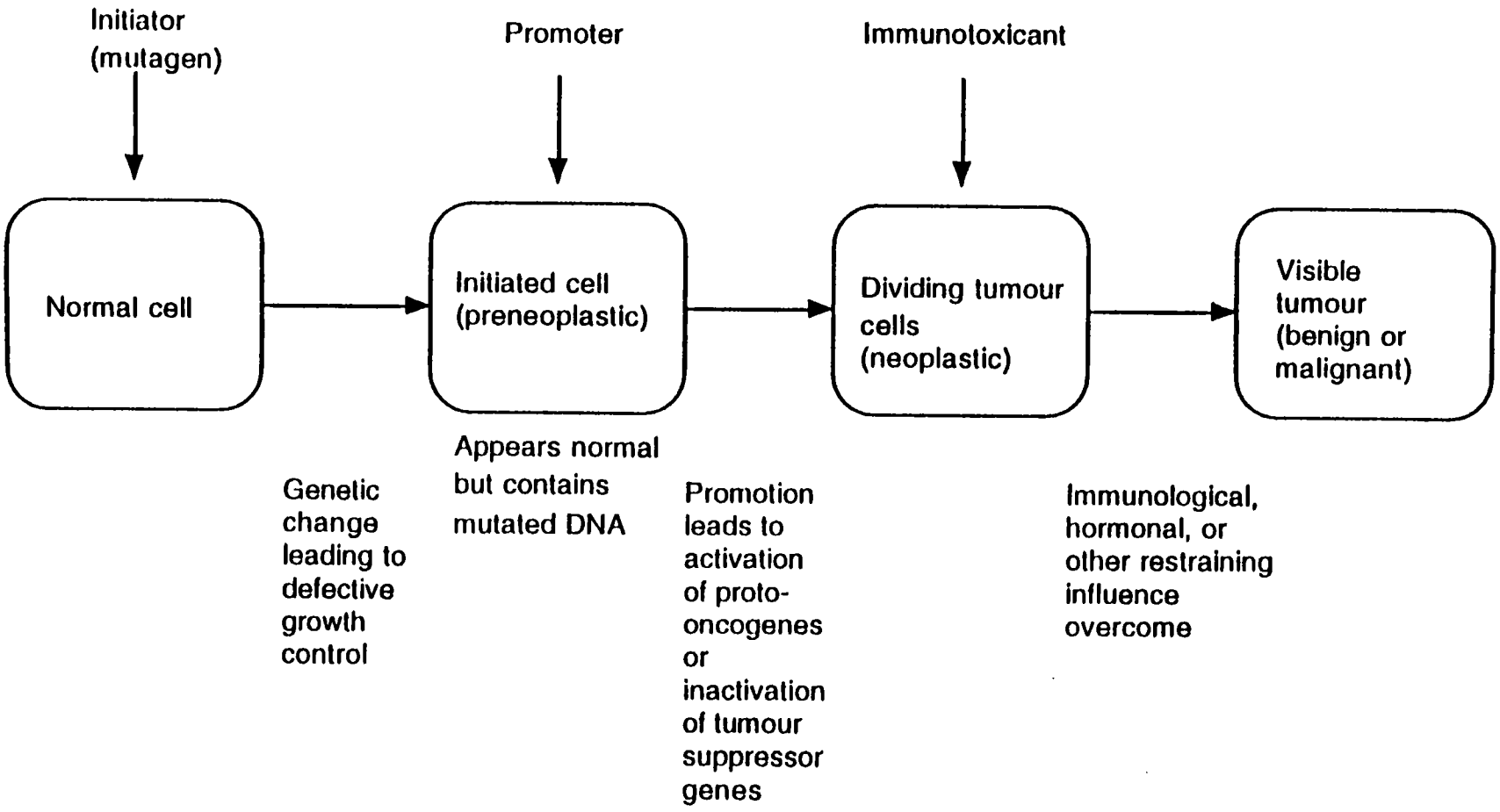


Figure 8 (1.2.2.4) Steps in the Development of Tumours



SUMMARY

You should now be familiar with the main routes of distribution of potentially toxic substances in the body and the related possibilities of biotransformation.

You should know the routes of excretion and the reasons why fat - soluble substances may not be excreted effectively and may remain in the body with long-term consequences.

You should now realize the possible role of the immune system in producing harmful effects.

The distinction between toxicokinetics and toxicodynamics has been explained and you should know the current ideas on some aspects of the toxicodynamics of mutagenesis and carcinogenesis.

SELF ASSESSMENT QUESTIONS

****

Draw a diagram to illustrate the main routes (including biotransformations) that may be followed in the body by xenobiotics between absorption and excretion.

Give four examples of the possibilities of biotoxification.

How may biotoxification contribute to mutagenesis and carcinogenesis?

How can chemical reactions with body components lead to adverse immunological reactions? Give 10 examples of adverse health effects which can have an immunological basis.

****

1.2.2.5 - Standard setting

OBJECTIVE

You should learn from this part of the module the principles underlying the establishment of permissible exposure levels.

This involves the application of various models to the available information and you should have a knowledge of the general approach involved in each.

You should learn the definitions of the main types of regulatory value currently in use.

Introduction

Toxicity testing provides the basis for hazard characterization and risk assessment in relation to human populations at risk.

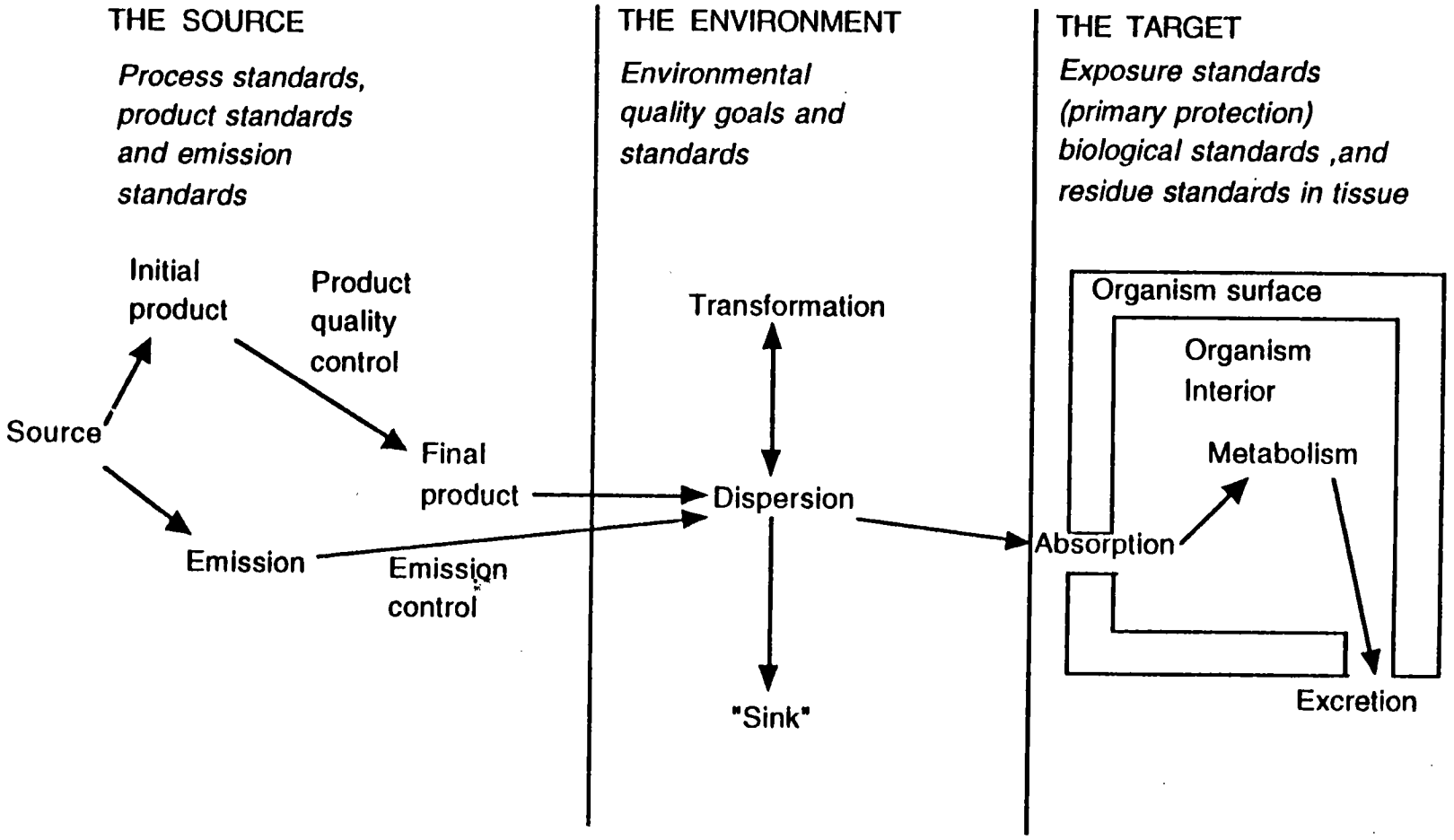
From chronic toxicity tests, a **lowest observed effect level (LOEL)** or **no observed effect level (NOEL)** can be obtained for the species studied. For a NOEL the effects looked for and not observed need to be defined, described and clearly identified.

Estimation of a safe exposure level for humans requires the application of an **uncertainty (safety) factor** to the NOEL.

The purpose of the uncertainty factor is to protect the most susceptible people and therefore it must be very large, usually 1,000 when little reliable chronic toxicity information is available. In deciding this, the reliability of the originators of the data under consideration must be established and the data must have been obtained following the application of good laboratory practice or an equivalent system of quality assurance.

Planning for chemical safety requires scientific assessment of risk followed by pragmatic evaluation of the risk associated with various possibilities of exposure to potentially toxic substances in order to determine risk management options. See Figure 1 (1.2.2.5).

Figure1 (1.2.2.5) Points where Standards may be Set on a Pollutant Pathway



The evaluation of risk often includes consideration of what is believed to be an **acceptable level of risk** to decide what exposure can be tolerated for risk management purposes. This is a societal decision. One fatality in a million people at risk (1 in 10^6) is considered in some countries to be an acceptable level of risk for many risky situations but there may be circumstances where a greater risk, for example - one in a hundred thousand (1 in 10^5), may be considered tolerable if the risk is balanced by a very considerable benefit.

It should be emphasized that an increase in mortality in the general population due to a specific cause at such a small rate would be virtually impossible to detect with current epidemiological techniques.

Acceptability of risk is influenced by many factors and some of those which may be considered are listed below:

1. Potential benefits of manufacture and use of the chemical

   Economic advancement in industrial and agricultural processes

   Provision of employment

   Increased government revenue

   Improved health

   Improved standard of living

2. Potential harm from manufacture and use of the chemical

   Economic cost of environmental and health damage

   Loss of employment

   Increased government expenditure on control of chemical manufacture and use and on health care

   Damage to health and quality of life

One of the biggest problems in **risk extrapolation** is in deciding what approach to use to extend the dose-response curve from high dose, high frequency responses to low dose, low frequency responses.

The aim of extrapolation to low dose, low frequency responses is to ensure that risk is not underestimated.

The following are the main types of mathematical modelling approaches that have been applied to extrapolation:

1. Distribution models - assume that every member of a population has a critical dose or exposure below which no adverse effect will be observed and that the critical dose varies among individuals according to a chosen probability distribution, usually Gaussian.

2. Mechanistic models - assume that the detailed processes for the production of adverse effects under consideration are known.

Note The mechanistic approach is favoured for mutagenic carcinogens since the existence of a critical dosage for such carcinogens is not generally accepted; unfortunately, the correct mechanistic model for carcinogenesis is also uncertain.

3. Pharmacokinetic models - assume that the key events in producing adverse effects are those of biotransformation and that the effective dose or concentration is that of the reactive metabolites produced.

4. Time to tumour models - based on the time to observance of tumours and the proportion of animals developing tumours in a test population following exposure to the potential carcinogen.

Note If the estimated time to tumour appearance following a given exposure is much greater than the normal lifetime of any individual in the population at risk, that exposure is probably safe in practical terms.

The following are some of the regulatory or guideline values that are based on risk assessments using the models described: they have a strict legal meaning and may be specific to a country.

Acceptable daily intake (ADI) Estimate of the amount of a substance in food or drinking water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard human = 60kg).

Air quality standard See **Environmental quality standard**.

Ambient standard See **Environmental quality standard**.

Ceiling value (CV) Maximum permissible airborne concentration of a potentially toxic substance, a concentration which should never be exceeded in the breathing zone.

Ceiling recommended exposure limit (CREL) See **Recommended exposure limit**.

Control limit (used in the United Kingdom) Airborne concentration of a potentially toxic substance which is judged to be "reasonably practicable" for the whole spectrum of work activities and which must not normally be exceeded.

Emission standard Quantitative limit on the emission or discharge of a potentially toxic substance from a source. The simplest form for regulatory purposes is a uniform emission standard (UES) where the same limit is placed on all emissions of a particular contaminant. See **Limit values**.

Environmental quality objective (EQO) Quality to be aimed for in a particular aspect of the environment, for example "the quality of water in a river such that coarse fish can maintain healthy populations". Unlike an environmental quality standard, an EQO is not usually expressed in quantitative terms and it is not legally enforceable.

Environmental quality standard (EQS) Maximum concentration of a potentially toxic substance which can be allowed in an environmental compartment, usually air (**air quality standard - AQS**) or water, over a defined period. Synonym: ambient standard. See **Limit values**.

Immediately dangerous to life or health concentration (IDLH) According to the U.S. National Institute for Occupational Safety and Health (NIOSH), the maximum exposure concentration from which one could escape within 30 minutes without any escape-impairing symptoms or any irreversible health effects. This value should be referred to in respirator selection.

Limit values (LV) Limits at or below which Member States of the European Community must set their environmental quality standards and emission standards; these limits are set by Community Directives.

Maximum allowable concentration (MAC) Exposure concentration not to be exceeded under any circumstances.

Recommended exposure limit (REL) According to the U.S. Occupational Safety and Health Administration (OSHA), unless noted otherwise, time weighted average concentrations for up to a 10 hour workday during a 40 hour working week. A ceiling REL is designated by "C" preceding the value and, unless noted otherwise, should not be exceeded at any time.

Recommended limit Maximum concentration of a potentially toxic substance which is suggested to be safe. Such limits often have no legal backing in which case a control or statutory guide level which should not be exceeded under any circumstances may be set. See **Control limit**.

Safety factor See **Uncertainty factor**.

Short term exposure limit (STEL) According to the U.S. Occupational Safety and Health Administration (OSHA), the time weighted average (see below) airborne concentration to which workers may be exposed for periods up to 15 minutes, with no more than 4 such excursions per day and at least 60 minutes between them. See **Time weighted average**.

Suggested no adverse response level (SNARL) Maximum dose or concentration which, on the basis of current knowledge, is likely to be tolerated by an organism without producing any adverse effect.

Temporary safe reference action level (TSRAL) Inhalational exposure level which is safe for a short time but which should be reduced as soon as possible or appropriate respiratory protection employed.

Threshold limit value (TLV) Guidelines defined by the American Conference of Governmental Hygienists to establish the airborne concentration of a potentially toxic substance to which it is believed that healthy working adults may be exposed safely through a 40 hour working week and a full working life. This concentration is measured as a time weighted average concentration (see below). They are developed only as guidelines to assist in the control of health hazards and are not specifically for use as legal standards although they may be used as such by some countries.

Time weighted average concentration (TWA) Concentration of a substance to which a person is exposed in ambient air, averaged over a period, usually 8 hours. For example, if a person is exposed to 0.1mg m^{-3} for 6 hours and 0.2mg m^{-3} for 2 hours, the 8 hour TWA is (0.1x6 + 0.2x2) / 8 = 0.125 mg m^{-3}.

Uncertainty factor (UF) Mathematical expression of uncertainty that is used to protect populations from hazards which cannot be assessed with high precision.

SUMMARY

You should now have some understanding of the different types of regulatory values used in legislation relating to chemical safety and how these regulatory values are set in relation to "safety" and the legal concept of "acceptable risk".

You should know the kinds of assumption and model that are applied in deriving regulatory values and why regulatory values must generally allow a large margin for error (uncertainty factor).

SELF ASSESSMENT QUESTIONS

****

What is a LOEL and what is a NOEL? How may a permissible exposure level be derived from a NOEL?

What are the essentials of -

1. A distribution model
2. A mechanistic model
3. A pharmacokinetic model
4. A time to tumour model?

Define the following terms:

Acceptable daily intake
Ambient standard
Ceiling value
Control limit
Emission standard
Environmental quality objective
Environmental quality standard
Immediately dangerous to life or health concentration
Limit value
Maximum allowable concentration
Permissible exposure limit
Recommended exposure limit
Recommended limit
Uncertainty factor
Short term exposure limit
Suggested no adverse response level
Temporary safe reference action level
Threshold limit value
Time weighted average concentration.

****

1.2.3 - IDENTIFICATION OF CHEMICAL HAZARDS

OBJECTIVE

You should be able to provide a list of all potentially hazardous chemicals in your place of work or home along with related **Material Safety Data Sheets** such as the **IPCS International Chemical Safety Cards.**

You should be able to use Material Safety Data Sheets in surveys for the assessment of potential chemical hazards and in planning preventive and emergency measures.

Preparation of an inventory and material safety data sheets

A list should be prepared listing all potential chemical hazards requiring consideration.

Information should be obtained on all chemicals in the list and a Material Safety Data Sheet prepared for each one following the model provided or one which is similar. Chemical suppliers should often be able to provide you with the information that you need for your Data Sheet.

Many chemical products are mixtures and you may have difficulty finding out what all the components are; however it is essential that you insist on this information as minor components of a mixture in quantitative terms may have severe toxic effects.

When the components of a mixture are known, assessing the likely toxicity is still difficult, even if they have already been evaluated individually. This is because little is known of the way most chemicals interact in causing harm.

The simplest assumption to make in the absence of other evidence is that the effects of the chemicals in a mixture will be additive.

Remember that minor components of a mixture may be extremely toxic, for example - benzene in xylene or dioxin in the herbicide, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).

Remember also that a major component of any product is the 'vehicle' or carrier, such as a solvent, in which the chemical is made available. Thus, solvents such as trichloroethane may be more of a problem than the substances they have been used to dissolve.

A list of information sources is provided separately and these should be referred to where data are not available from chemical suppliers and to check the validity of essential data from whatever source since errors can occur.

Study of (Material) Safety Data Sheets should allow assessment to be made of the probable nature and effects of exposure to potentially dangerous substances.

Assessment should concentrate on the toxicity of the substance and its dose/effect relationship, likely routes of exposure, for example through the skin or lungs, the amount and concentration of the substance involved in the exposure, and the probable time of exposure. From this information, likely effects (or absence of effects) may be deduced.

Following assessment, emphasis should be placed on the techniques required for safe handling.

Consideration should be given to the possibility of accidents and to methods of accident prevention.

Emergency measures to deal with accidents should be planned and put in place ready to be operated at the shortest possible notice.

Consideration should also be given to the safe disposal or other fate of any waste materials produced. Appropriate plans and procedures should be established.

You should make your own survey of places where potentially toxic substances are to be manufactured, used or stored, and sites for the disposal of potentially toxic waste

Survey of places associated with potentially toxic substances

Prepare a checklist, a series of questions to which the correct answer is "yes". Any "no" answers will need explanation and probably action to ensure safety.

Examples of checklist questions are given on the next page.

Survey of places associated with potentially toxic substances 1

Below is a checklist, a series of questions to which the correct answer is "yes". **Any "no" answers will need explanation and probably action to ensure safety.**

General checklist questions	**Answer**
Do those responsible have a chemical safety policy?	
Do those responsible have adequate knowledge of chemical hazards?	
Do those working with potentially toxic substances have adequate knowledge of chemical hazards?	
Do processes involving chemicals appear to be under control?	
Is ventilation and temperature control adequate in buildings where potentially toxic chemicals are produced, used, or stored?	
Do noise levels and lighting permit safe use of chemicals?	
Is there a regular check on potential chemical hazards and revision of control measures if necessary?	
Are all chemical containers labelled correctly?	
Are chemicals stored properly and potentially reactive mixtures prevented by separate storage?	
Is a plan of storage arrangements immediately available for emergency services in event of an accidents?	

NOTES

Survey of places associated with potentially toxic substances 2

Examples of specific questions	**Answer**
Do the people using chemicals know what chemicals they are using and the precautions that they should take?	
Are the correct precautions being taken in practice?	
Is complete documentation available on all the chemicals in use, on potentially hazardous intermediates, and on waste products, their treatment and disposal?	
Are there effective emergency plans including first aid provision, necessary equipment, and emergency procedures which are practised and kept up to date?	
Have processes involving potentially toxic substances been fully characterized, preferably in the form of a flow sheet?	
Is there regular monitoring to check for leaks from equipment to prevent emission of chemicals and to stop it if it occurs?	
Are there hazard warning notices and labels on equipment where required?	
Are local medical personnel and hospitals aware of possible causes of poisoning and prepared to cope, for example by having available appropriate antidotes or other treatment?	

NOTES

SUMMARY

Identification of chemical hazards is a sequential process.

A list is prepared of all potentially toxic substances.

(Material) Safety Data Sheets are completed for all substances in the list.

A survey is carried out of the places associated with the potentially toxic substances and the safety of the existing situation assessed.

SELF ASSESSMENT QUESTIONS

****

Without reference to the text, draw a model Material Safety Data Sheet and write a short description of how your Material Safety Data Sheet enables you to assess potential hazards, especially those resulting from toxicity.

Without reference to the text, prepare a checklist for a survey of places where potentially toxic substances are to be found.

****