GENERAL TOXICOLOGY

1 INTRODUCTION TO GENERAL TOXICOLOGY

> ***'What is it that is a poison? All things are poison and none without poison. Only the dose determines that a thing is poison.'***
>
> Paracelsus 1538

The question, 'Is it toxic or is it safe?' about a substance is false in that it infers that some things, no matter how large the dose, will not impair health. 'Safe' and extremely toxic are the opposite ends of a continuous spectrum, with real substances lying along it in various positions. Toxicology is the study principally of dose/effect relationships, but the nature of the effect and its mechanism are also of particular importance.

Toxicology falls into several areas:-

CLINICAL - concerned with treatment

FORENSIC - concerned with identification

PREDICTIVE - concerned with qualitative and quantitative assessment.

Modern industrial toxicology is largely predictive, with epidemiology also playing a part where substances not initially subjected to predictive tests are involved. It exists to establish 'safe working conditions'. However, it is impossible to measure a safe level of a poison i.e.. it is not possible to measure a non-effect! Therefore, industrial toxicology concerns itself with:-

- ☐ The measurement of unsafe exposure levels, extrapolated to lower levels.
- ☐ An examination frequency/dose relationships.
- ☐ The severity and nature of effects.

2 HAZARD AND RISK

The form of a material is important in determining the risk to health from that material. No matter how toxic a substance is, if it cannot gain entry into (or onto) the body it cannot exert it's toxic effect and the risk to health is zero. So that the easier it is

absorbed the greater the potential risk to health of a toxic material. For instance, a solid lump of Cadmium metal is hardly likely to present any risk to health. However the same material under the influence of a gas welding torch will produce fresh fume of Cadmium oxide which if inhaled has serious effects on the lung - the result often being fatal.

Some Definitions

Toxicants	substances that produce adverse biological effects of any nature
Toxins	specific toxic proteins produced by living organisms (mushroom toxin or tetanus toxin)
Poisons	toxicants that cause immediate death or illness when experienced in very small amounts
Systemic Toxin	toxin that affects the entire body or many organs rather than a specific site
Xenobiotic	a foreign substance taken into the body. It is derived from the Greek term xeno which means "foreigner." Xenobiotics may produce beneficial effects (such as a pharmaceuticals) or they may be toxic (such as lead).

Hazard is an intrinsic property of a material, determined by it's chemical characteristics and it's biological activity. Whereas, RISK takes into account the hazard and the amount of the material entering the body, i.e. EXPOSURE .

RISK = HAZARD x EXPOSURE

An individual's exposure to a hazardous agent is related to the ***concentration*** of a substance (or the level of a physical agent) and the ***duration*** of exposure. So it is necessary in judging whether a work situation presents a real risk to health to take into account the form of the hazardous material(s) (solid, dust, fume, liquid, mist, gas), the scale of use and handling methods. If the material is a dust, the particle size will be important, and if a liquid, it's vapour pressure.

Following exposure, a substance may exert a harmful effect at the site of contact, or may be ***absorbed*** into the body. Some substances are rapidly ***eliminated*** and ***excreted*** fairly rapidly. In other cases the substances may be ***distributed*** in the body, and possibly ***stored*** in fat, the bones, or one or more organ.

AIRBORNE CONTAMINANTS

Contaminants are either **gaseous** (gases and vapours) or **aerosols (**a suspension of solid or liquid particles in a gas**)**

Gas A formless fluid that fully occupies a space or enclosure and can only be changed to a liquid or a solid state by the continued effect of increased pressure and/or decreased temperature. Note: Above a certain temperature, known as the *Critical Temperature*, a gas cannot be liquefied by pressure alone. Gases do not usually exist as liquids or solids at normal room temperatures and pressures. e.g.. Diborane, Arsine. Sizes - molecular.

Vapour Gaseous forms of substances that also exist in the solid or liquid state at normal temperatures and pressures. They can be condensed to these states by either increasing the pressure or decreasing the temperature. e.g.. Mercury, Lead Alkyls, Water etc. Sizes - molecular.

The 'readiness' of a material to form a vapour is indicated by it's vapour pressure. The vapour pressure increases with temperature - sometimes quite rapidly e.g. Mercury. Solids as well as liquids may form a vapour e.g.. Iodine This is known as sublimation.

Where a gas or vapour is formed at a particular temperature from two or more constituents, the total pressure is the sum of the constituent partial pressures, which depend in turn on the intrinsic vapour pressure of the constituent materials.

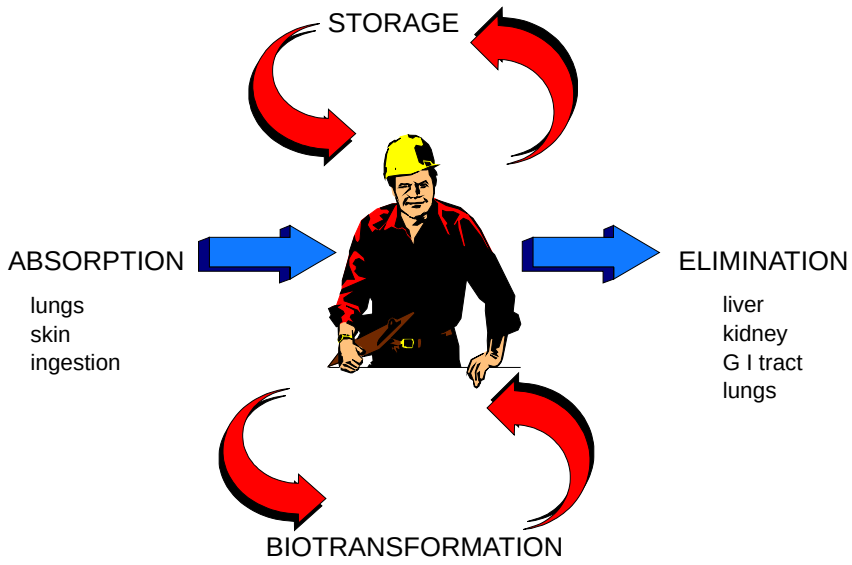
Dust Solid particles of wide size range and shape generated by mechanical processes such as abrasion and crushing, or released by handling or other disturbances. e.g.. Coal dust from coal cutting. Chromium containing dust from furnace demolition.

Sizes - Wide ranging. Sizes of importance in occupational hygiene 0.01 - 150 µm. Particles greater than about 75 µm will not remain airborne for long after their generation and it is particle sizes < about 25 µm that present a risk through inhalation

Mist An airborne suspension of liquid droplets generated from a liquid by, for instance, splashing, bubble formation, nebulising or by condensation from the vapour or gaseous state (or phase) to the liquid state. e.g.. Oil mist from coolants used in metal cutting. Acid/Chromate mists from electroplating.

Sizes - Wide ranging. Sizes of importance in occupational hygiene 0.01 - 150 µm (Particles change in size once formed to greater or lesser degree depending upon liquid compositions).

Fume Sub - micron particles often generated by condensation of materials from the gaseous state usually after volatilisation from molten or liquid state. Fume particles may be solid or liquid or both depending upon the properties of the parent material. The formation of fumes is often accompanied by chemical reactions, for instance oxidation in the case of metal fumes. e.g.. Lead oxide fume. Iron oxide fume. Sizes - 0.001 - 1.0 µm. Agglomeration of particles may occur to produce larger aggregates.



Where the substance causes harm at the point of contact, it is said to exert a **LOCAL** effect. Examples of this include skin and respiratory irritation.

Where the substances is absorbed and distributed around the body, causing harm at a site remote from the site of absorption, it is said to exert a **SYSTEMIC** effect.

ACUTE effects occur very soon (less than one day) after contact or absorption.

CHRONIC effects occur some time (at least one month) after exposure. The onset may take a long time and/or the effect may last a long time, so that it is possible to speak of a chronic effect or chronic exposure.

3 ABSORPTION

3.1 Transport Across Membranes

In order to pass into the body, toxicants have to cross cellular membranes. The mechanisms by which this occurs are important in determining the characteristics of substances which are favourable to absorption.

Passive diffusion

This is probably the most important mechanism for the absorption of toxicants into the body. For it to occur there must be a *concentration gradient* (i.e. a difference in

concentration of the compound on either side of the membrane). There are two other major factors which influence the diffusion process:

- the *lipid solubility* of the substance;
- the *degree of ionisation*. In most cases only non-ionised molecules can diffuse across membranes. This is because ionised molecules too large because they are hydrated .

Filtration

This occurs where a molecule is small enough to pass through the pores in a membrane. The degree to which this occurs will depend on the size of the pores, which varies between different tissues.

Active Transport

Here, transport occurs *against* a concentration gradient, and involves the expenditure of metabolic energy. A carrier molecule transports the substance across the membrane. It is particularly important for the elimination of substances from the body.

Facilitated Diffusion

This is similar to active transport, in that a carrier molecule is involved. However the process does not involve moving against a concentration gradient or the expenditure of energy.

3.2 Inhalation

In many situations, the main route of entry and absorption of toxic materials into the body is through the respiratory system. The lungs are a particularly efficient route of entry for gases and small particulates.

The amount of air inhaled depends varies from person to person, but is highly dependent on work rate. Typically, a person at rest inhales about 6 litres per minute, which is 360 litres per hour. Someone carrying out moderate work would have a higher breathing rate of around 1000 litres (i.e. 1 cubic metre) of air every hour.

Highly water soluble gases and particles may be absorbed into the bloodstream in the upper respiratory tract, but absorption normally occurs in the alveoli. Here, the gas molecules diffuse across the alveolar membranes and dissolve in the blood. Hence, the main factor determining the rate of uptake of a gas into the body is its solubility in blood. There are some exceptions to this, where the gas molecule interacts in some way with the blood itself; for example, carbon monoxide binds to haemoglobin molecules in the red blood cells. The ratio of the concentration of the gas in the alveoli and the blood is referred to as the *partition coefficient*. The higher this coefficient, the greater the solubility of the gas in the blood.

With particulate matter, the size of the particles is very important, determining both how long particles remain airborne to be inhaled, and whether they reach the deep regions of the lung where they can be absorbed. Only particles smaller than about 10 microns (one thousandth of a millimetre) will reach the alveoli. Larger particles are removed on the ***mucocilliary escalator***, but may then be swallowed and ingested through the gastro-intestinal tract.

Particle Settlement

Particle Diameter (microns)	Time to fall 2 metres
0.01	343 days
0.1	27 days
1.0	16 hours
10.0	11 minutes
100.0	8 seconds

Particles reaching the deep lung may be removed by phagocytes, which are special scavenger cells within the deep lung. The most important type are the macrophages, which transfer the particles to the mucoscilliary escalator. Clearance can also occur via the lymphatic system.

Very small particles, less than 1 micron in diameter, can be transferred across the alveolar membranes into the blood. Soluble particles (solids and liquids) can be dissolved and transferred into the blood.

3.3 Skin absorption

Skin contact with hazardous substances can damage the skin. Skin absorption may also occur, particularly with lipid (fat) soluble materials. The rate of absorption then depends on the surface area covered and whether the skin has been damaged or not. Skin damage increases absorption. Many solvents may be absorbed though he skin as well as some more toxic materials e.g.. organophosphate based pesticides. Some materials may 'carry' other substances with them through the skin, enhancing absorption e.g. dimethyl sulphoxide. Metals and metal compounds may also be absorbed this way e.g.. Mercury and some selenium compounds.

3.4 Ingestion

Ingestion of environmental pollutants can occur when foodstuffs or the water supply are contaminated. There are a number of ways in which this can occur, including

- ☐ pollution of foodstuffs with pesticide residues
- ☐ pollution of water supplies by industrial emissions or run off of agro-chemicals applied to crops
- ☐ settlement of airborne pollutants on plants
- ☐ uptake of pollutants by animals or fish which are then eaten by humans.

Ingestion is not a common route of exposure in industry. However, it can be a problem with toxic materials such as lead, which may be ingested accidentally, for example, due to transfer of the materials from dirty hands during eating, drinking or smoking.

Larger particles which are inhaled, which are too large to reach the deep lung are eliminated from the respiratory system via the mucocilliary escalator. They can then be swallowed, and may then be absorbed through the gut.

The site, rate and degree of absorption depends on a number of factors, including degree of ionisation, lipid solubility and molecular size. The more a substance is ionised, the less likely it to be lipid soluble. As the stomach is acidic, weak organic acids are largely unionised, so absorption can take place. In contrast, the intestine is alkaline, and so organic bases are absorbed here.

3.5 Injection

In some occupations, particularly medicine, there is an additional route of exposure - accidental injection, often referred to as “needle stick” injuries. This leads to very rapid and efficient absorption of the material into the body. This can present a very high risk particularly as the substances used for therapeutic treatments are often highly toxic.

4 DISTRIBUTION AND STORAGE

Following absorption, substances are distributed throughout the body via the blood and lymphatic systems. This is a dynamic process which depends on uptake and elimination rates, as well as the blood flow to the different tissues and their affinities for the substance. In the blood, the substances may be

- suspended in the plasma
- dissolved in the plasma

- bound to plasma proteins
- bound to blood cells.

Some toxic materials are removed from circulation in the body by storage in tissues, and then lost by elimination at a slow rate. e.g.. lead may be stored for very long periods in the bones. Cadmium is stored for very long periods in body tissues.

The main sites of storage are :

- ☐ plasma proteins in the blood
- ☐ the liver
- ☐ the kidney
- ☐ fatty tissues (e.g. DDT, dioxins, PCBs)
- ☐ bone (e.g. lead, fluorine, strontium)

The liver and kidney are particularly important, as they are involved in the elimination of harmful substances from the body.

5 ELIMINATION

5.1 Excretion

Substances are eliminated from the body by excretion via various routes, particularly the lungs, kidney (via the urine) and liver. In some cases excretion may occur through other routes (e.g., hair, nails, skin, sweat and milk).

Gaseous or vapour forms of toxic materials e.g.. solvents may be eliminated in part by transport to the lungs and loss in the breath. Alveolar exchange is governed by the partial pressure differences of the material in the blood and the alveolar air. Many organic solvents can be excreted in this way, as are gases and vapours which have a low solubility in blood. The route is not of such great importance for metals.

Compounds with molecular weights below 250, are mainly excreted via the kidneys. Excretion via the liver in the bile and faeces can also occur, mainly with substances which have a molecular weight greater than 500.

Some substances, including a number of metals (e.g. lead, mercury, copper) and some organic compounds (e.g. ethanol) can be excreted in the saliva. In such cases there is a high risk of reabsorption as the saliva is swallowed. Organic liquids can also be excreted in the sweat.

Substances which concentrate in fatty tissues, including heavy metals, organochloride pesticides and dioxins can accumulate in milk. They can then be passed on to a breast fed child.

5.2 Biotransformation

Materials entering the body may be involved in metabolic chemical processes which change their chemical form in order to make them more water soluble and, therefore, more readily eliminated via the urine. This process mainly occurs in the liver. Unfortunately it is sometimes the ***metabolites*** that cause damage.

A common detoxification reaction is the removal of ethyl alcohol:

$$C_2H_5OH > \text{oxidation} > CH_3CHO > \text{oxidation} > CH_3COOH$$

Metals will often be conjugated with organic species in the body to form water soluble polar compounds which are able to be excreted.

Phase I type reactions include oxidation, reduction and hydrolysis. Phase II type reactions include conjugation and synthesis. Other processes may go on to generate toxic forms of activated oxygen.

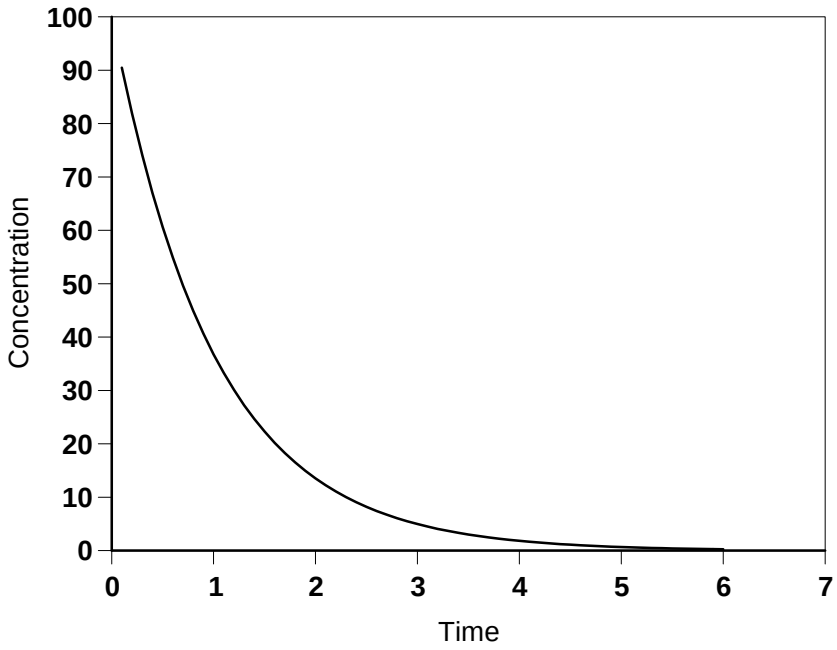
5.3 Biological half life

In all cases, the reduction in body burden follows an exponential pattern and a common way of characterising the rate of elimination is the biological half-life $t_{0.5}$ which is the time taken for the original concentration (body burden) to drop to half the initial level.

The absolute rate of elimination is determined by reaction kinetics, which can be multistage and complex.

Biological half-lives vary considerably:

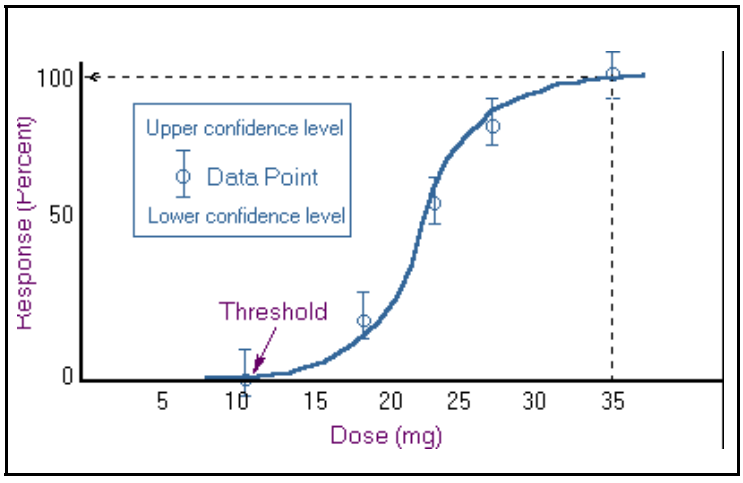
Toluene	~ 10 hours
Selenium	~ 10 days
Mercury	~ 6 weeks
Cadmium	~ 25 years or more



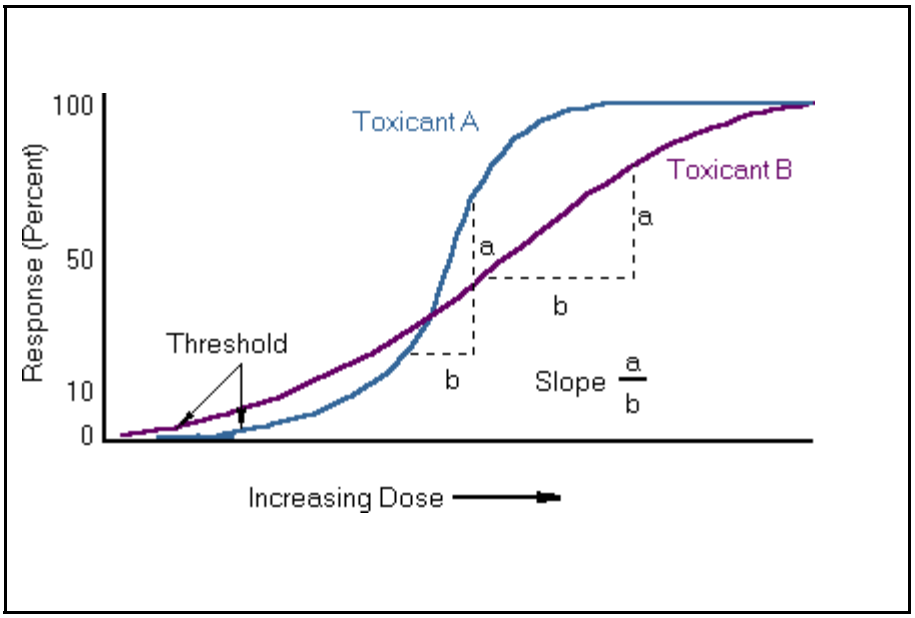
6 DOSE - RESPONSE RELATIONSHIPS

The dose-response relationship is a fundamental and essential concept in toxicology. It correlates exposures and the spectrum of induced effects. Generally, the higher the dose, the more severe the response. The dose-response relationship is based on observed data from experimental animal, human clinical, or cell studies.

If a graph is constructed of the dose against the effect, it will normally take the form of a sigmoid curve (see below). For most substances, small doses do not produce a toxic effect. However as the dose is increased a point is reached where the body can no longer tolerate the substance - this is known as the threshold dose level. From that point, the curve increases with higher dose levels.



Although threshold dose defines the lowest dose which will cause a toxic effect, it is not the only aspect of the dose-response relationship which determines how a substance will affect an individual. The slope and shape of the curve are also important



In the above diagram, for example, toxicant A has a higher threshold dose than B. However, as A has a steeper slope than B, once the threshold has been passed, serious effects occur much more rapidly with toxicant A.

7 TYPES OF EFFECT

7.1 Asphyxiants

Asphyxiants fall into two groups: simple asphyxiants and chemical asphyxiants. ***Simple asphyxiants*** cause problems simply by excluding oxygen**.** The normal level of oxygen in air is 21% but levels down to about 18% or 19% can be tolerated without too much discomfort, for a while. Of course this effect occurs also at high altitudes due to the low partial pressure of oxygen - 'Mountain Sickness'. Levels reduced down to 16% are dangerous to life and may occur when the level of an inert gas such as nitrogen builds up to exclude oxygen. The ubiquitous use of liquid nitrogen makes this an ever present risk to life if used in enclosed spaces. Death occurs simply by exclusion of oxygen.

Generally nitrogen and the other inert gases are quite inactive physiologically but the removal of oxygen by oxidising metals may result in a depletion of oxygen, and an increase in the concentration of nitrogen. Old disused wells with rusting ironwork in them are a source of danger, as the oxidising iron uses up the oxygen, effectively raising the concentration of nitrogen.

Chemical asphyxiants on the other hand interfere with respiration by preventing the transport of oxygen to the tissues. The most common of these is Carbon monoxide, which forms very stable carboxyhaemoglobin with haemoglobin. Unlike normal haemoglobin, carboxyhaemoglobin does not break down at the normal partial pressures of oxygen and hence the oxygen transport mechanism is 'locked out'. The administration of higher partial pressures of oxygen by breathing pure oxygen for a while, will reverse the reaction to some extent.

7.2 Irritants

Irritants are substances which produce an inflammatory response in tissues on direct contact. They can effect the skin, eyes, and different parts of the respiratory system.

7.3 Corrosives

There is really not a lot to say about this class of materials except that they destroy tissue on contact. Such substances as the concentrated acids, selenium dioxide etc. These will cause severe damage to skin on contact and will continue to cause damage as long as they remain. Some of these corrosive materials may also be inhaled e.g. diborane, bromine vapour, chromic acid mist.

7.4 Narcotics.

These have a generalised effect on the central nervous system (CNS) known as narcosis. It includes disturbed vision, dizziness, tremors, salivation, CNS depression, confusion and possibly anaesthesia. There is also a possibility of coma. Continued exposure to high concentrations can lead to death due to respiratory or heart failure.

The majority of volatile organic compounds have this effect such as the hydrocarbon solvents like toluene and xylene, and the chlorinated hydrocarbons like trichloroethylene.

7.5 Sensitizers

These are substances which can lead to the development of an allergic reaction in susceptible individuals. This can affect the respiratory system (the most common confdition being asthma) or the skin (leading to allergic contact dermatitis). Asthma in particular is a growing problem in the general population and may be associated with exposure to environmental pollutants.

Sensitization is a major and growing problem in industry causing a loss in working time and much personal misery. Nickel is a very common cause of skin sensitization resulting in dermatitis. Platinum salts, epoxy resins and isocyanates are examples of respiratory sensitizers.

Respiratory sensitizers have a number of characteristics:-

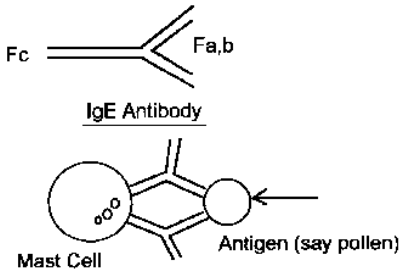
- ☐ Sensitization is agent specific.
- ☐ The risk of sensitization is thought to be related to the concentration of sensitizer inhaled.
- ☐ It is thought that the onset of sensitization may be particularly associated with short-term exposures to unusually high concentrations of the sensitizer.
- ☐ Only some of the individuals at risk will become sensitized - in those that do, their sensitization is thought to be irreversible.
- ☐ Symptoms do not occur on the first exposure to the agent, so it may be difficult to identify when sensitization occurred. (& identify the causal agent)
- ☐ Further exposure of a sensitized person may lead to respiratory symptoms at concentrations which do not produce symptoms in an unsensitized population and which may not have other toxic effects. Sensitized employees may thus suffer acute health effects when exposed to concentrations of a sensitizer that have no evident effect on others doing identical jobs.

There are two groups of allergic lung disease:

- of the airways - e.g. rhinitis and bronchial asthma

- of the alveoli - Alveolitis (usually allergic although not always).

Action of IgE



Once 'educated' to make an antibody, the body produces them readily. e.g. isocyanates - when sensitized individuals react to extremely low levels.

7.6 Carcinogens

In normal cells, growth stimulus is intermittent e.g. If skin is damaged, a mechanism is activated which causes the cells to be stimulated to grow sideways. When the wound is healed the stimulus stops. In cancerous cells the stimulus is constant - but, the cell multiplication outgrows the blood supply, so such a situation on the skin would result in a necrotic centre with a raised cancerous rim. The extra growth may of course invade other tissues and organs causing disease and death.

The development of cancer occurs in stages. Initially a chemical etc. may cause a change in a cell (Not chemically detectable, but possibly immunologically detectable). That is, the cell becomes primed and later another chemical etc. attack may cause the primed cell to become frankly neoplastic. There is a DNA repair mechanism and some affected cells will be repaired in immunologically normal subjects.

The only way to protect a worker is to avoid the absorbance of known carcinogens. There does not appear to be a threshold level of exposure, although the probability of developing cancer increases with exposure duration and level. IARC, the International Agency for Cancer Research on Cancer publish monographs on studies carried out on the available literature for specific topics and families of chemical compounds. This work is done with a view to assessing the carcinogenic nature of materials and work processes. The monographs classify each subject of investigation according to its proven carcinogenic activity in humans or animals or its possible activity, or to state that there is insufficient evidence etc.

7.7 Mutagens

Mutagens are substances which cause changes in the DNA which can be transmitted during cell division. Such changes can occur either at the level of individual genes or at the chromosomal level. Changes in individual genes can result in the transmission of altered genetic messages while changes at the chromosomal level can result in the transmission of abnormalities in chromosomal number or structure.

7.8 Teratogens

Teratogens are substances which can have an adverse effect on the unborn child; disrupting fetal growth and producing malformation. Maternal exposure may result in perinatal death, low birth weight, birth defects, developmental or behavioural disabilities, and cancer. Damage to the fetus is most likely to occur in early pregnancy, particularly during the first 10 weeks., when many women may not be aware that they are pregnant.

Perhaps the most well known example of a teratogenic effect is the physical deformity produced by the drug thalidomide, which was administered to pregnant women. Occupational teratogens include *lead*, which can cause infertility in women,

miscarriage, low birth weight, and developmental disorders, and some *glycol ethers*, which can cause miscarriages, and reduce the sperm count in men.

IARC Carcinogen Classifications

IARC Designation	Definition
Group 1 Known human carcinogen	This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.
Group 2A Probable human carcinogen	This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans.
Group 2B Possible human carcinogen	This category is used for agents, mixtures and exposure circumstances for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is inadequate evidence of carcinogenicity in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.
Group 3 Not classifiable for human carcinogenicity	This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category
Group 4 Probably not carcinogenic to humans	This category is used for agents or mixtures for which there is evidence suggesting lack of carcinogenicity in humans and in experimental animals. In some instances, agents or mixtures for which there is inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

.

8 INTERACTIONS

It is very rare that anyone in the workplace is only exposed to one substance at any one time. In such circumstances, it is necessary to consider whether the substances can interact to increase (or, sometimes, decrease) the degree of toxicity.

If there is no interaction, so that each substances continues to produce the same effect as if nothing else was present, they are said to act **independently**. However, there are many situations where an interaction can occur.

Additive effects occur where the combined effect of the substances is equal to the sum of the effect which occurs when each agent acts alone. This usually occurs where substances exert the same effect on the same target organ, particularly when the same mechanism is involved. This type of interaction occurs for narcotic volatile organic compounds.

In other situations more complex interactions can occur. **Synergistic** reactions are said to occur when the combined effect is considerably greater than the sum of each agent acting alone. An example of this type of effect is the interaction between ethanol and carbon tetrachloride. Both can cause liver damage, but together they produce a much greater effect than would be expected from their individual effects.

Potentiation occurs where a non-hazardous substance increases the effect of another, toxic, substance. Isopropanol, for example, does not cause liver damage, but an individual exposed to both this alcohol and carbon tetrachloride, the ensuing liver damage is much greater than that which would result from exposure to carbon tetrachloride alone.

In some cases one substance can reduce the effect of another. This is referred to as an **antagonistic** interaction. For example, exposure to both zinc and cadmium results in less kidney damage than situations where only the latter is present.

9 TOXICITY TESTING

9.1 Introduction

Currently, testing done on animals is used to predict responses in man. The main animals used are laboratory mice and rats, rabbits, guinea pigs and dogs since their biochemistry is well known and therefore the effects can better be extrapolated to man. Where possible non animal tests are used because not only is it morally more acceptable, it is also cheaper, simpler and more accurate, but even so they must be validated against animal tests.

Toxicity testing is not particularly accurate since it necessarily involves extrapolation from high exposures used in testing to the low exposures found in practice. Higher

levels of exposure are necessary in testing to obtain sufficient numbers of positive results for proper statistical treatment. At low levels of exposure, large numbers of animals would need to be used to get a statistically significant result. e.g.. If the exposure to a substance causes an incidence of 0.1%, it would be necessary to use a population of 30,000 animals to obtain a statistically significant result. At an incidence of 0.1%, 100 people in 1 million would be affected. In practice, a range of doses are used with the highest one adjusted to cause some deaths, and therefore the mid and low doses would show some incidence of effect.

Tests may also be carried out for effects on fertility, fecundity and teratological problems.

9.2 Homeostasis

Living organisms react to maintain the status quo (homeostasis). Under normal conditions the challenge offered by alien substances is insufficient to cause noticeable effect, although changes will take place to maintain balance. As the level of challenge (exposure to a toxic substance) increases, normal function will be maintained, albeit at some cost to the organism. At more extreme exposures, breakdown of homeostasis occurs with resulting damage to the organism. The ultimate result being death.

9.3 Nomenclature

Results of toxicity tests are available in the literature in a number of standard forms, the most common of which is the LD50. The terms used indicate whether the dose causes death (LD) or other toxic effect (TD) and if it was administered as a lethal concentration in air (LC) or a toxic concentration in air (TC).

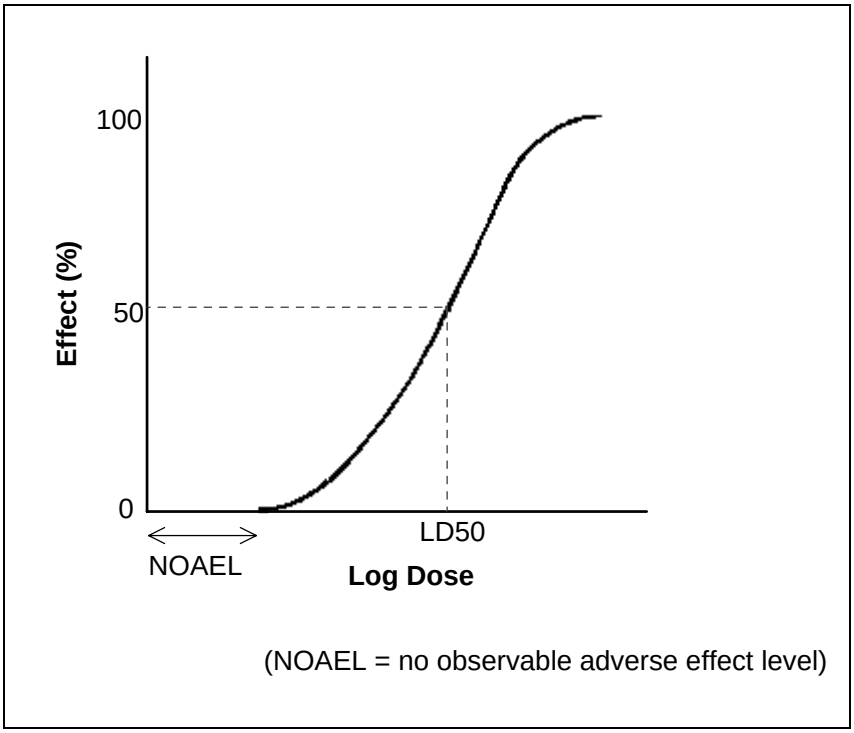
LD50 *Median Lethal Dose* - a calculated dose of a substance which is expected to cause the death of 50% of an entire defined experimental animal population. It is determined from the exposure to the substance by any route other than inhalation of a significant number from that population.

LC50 *Median Lethal Concentration* - the concentration of a substance which is expected to cause the death of 50% of an entire defined experimental animal population.

LDLo *Lowest Lethal Dose* - the lowest dose (other than LD50) of a substance introduced by any route, other than inhalation, over any given period of time in one or more divided portions and reported to have caused death in humans or animals. Note that this is NOT equivalent to the NOAEL.

TD50 *Median Toxic Dose* - the dose of a substance, introduced by any route, other than inhalation, which is expected to cause the 50% of an entire defined experimental animal population experiencing a given toxic effect.

***TDLo** Lowest Toxic Dose* - the lowest dose of a substance introduced by any route, other than inhalation, over any given period of time and reported to produce any toxic effect in humans or to produce carcinogenic, neoplastigenic or teratogenic effects in animals or humans.



9.4 Units of Dose

The units of dose are more usually quoted as the quantity administered per unit body weight e.g.. milligram per kilogram (mg/kg) or sometimes gram per kilogram (gm/kg). For absorption via the skin, the units are quantity per unit area and for inhalation experiments, parts per million (ppm) or milligrams per cubic metre (mg/m^3). A useful table giving perspective to the toxicity of a material is one due to Hodge-Sterner which is given below:-

LD50 Dose per Kg of Body Weight.	**Degree of Toxicity**	**Probable Lethal Dose**
<1.0 mg	Dangerously toxic	A taste
1 - 50 mg	Seriously toxic	A teaspoonful
50 - 500 mg	Highly toxic	An ounce
0.5 - 5 gm	Moderately toxic	A pint
5 - 15 gm	Slightly toxic	A quart
>15 gm	Extremely low toxicity	More than a quart