CHAPTER 6

Industrial toxicology

Chapter outline

In this chapter you will learn about the hazards of exposure to industrial chemicals using some examples:

- Means of exposure
- Toxic effects
- Vinyl chloride
- Cadmium
- Aromatic amines
- Asbestos
- Legislation

Industrial chemicals

Industrial diseases have existed ever since man began manufacturing on a large scale, and during the industrial revolution occupational diseases became common. Some were well known to the general public and are still known by their original, colloquial names. These diseases were, and some still are of great importance socially, economically and medically. Many occupations carry with them the risk of a particular disease or group of diseases. Thus, mining has always been a hazardous occupation and **miners** suffer **silicosis**, while **asbestos workers** suffer **asbestosis** and **mesothelioma**, and **paper** and **printing workers** are prone to **diseases of the skin**. A man spends on average one-third of his life at work and, therefore, the environment in that workplace can be a major factor in determining his health. Although the working environment has improved immeasurably over the last century, some occupations are still hazardous despite legislation and efforts to improve conditions.

There are now many thousands of chemical substances used in industry ranging from metals and inorganic compounds to complex organic chemicals. The people who work in the industries which use them are therefore at risk of exposure. Fortunately, exposure is often minimized by using chemicals in closed systems so

that operators do not come into contact with them, but this is not always the case. In Third World countries, however, some of which are rapidly industrializing, exposure levels are higher and industrial diseases are more common than in the fully developed countries. Consequently exposure to toxic substances in the workplace is still a very real hazard. Furthermore even in the best regulated industrial environment, accidents may happen and can lead to excessive exposure to chemicals.

Means of exposure

Just as with environmental exposure, exposure in the workplace may occur via any or all of the three major routes: by **oral ingestion**, by **inhalation**, and by absorption following **skin contact**. The most common routes of exposure are, however, via inhalation and skin contact. These routes of exposure apply to **gases**, **vapours**, **aerosols**, **volatile solvents** and other liquids as well as to **dusts** and **fibres**. The skin and lungs may come into contact with substances in all of these states and the substances can either be absorbed or cause *local* toxic effects.

Toxic effects

The toxic effects of industrial chemicals may be either **chronic** or **acute**. The acute inhalation of solvents in large quantities can cause **asphyxiation**, **unconsciousness** or **death**, for example. Inhalation of large quantities of very irritant substances, such as **methyl isocyanate** for instance, may cause immediate **bronchoconstriction** and **pulmonary oedema** leading to death. Both of these pulmonary effects are locally mediated rather than systemic effects. However, such acute effects are usually accidental and so are probably less common than the chronic industrial diseases. They may cause subsequent chronic toxicity, however.

Inhalation of some chemicals, such as industrial gases, metal fumes or organic solvents, leads to irritation or damage to the respiratory tract which may be acute or chronic. In the long term **cancer** or debilitating **respiratory diseases** may result. In the acute phase **irritation** and **allergic responses** may occur. Absorption of substances via the lungs is efficient and rapid and may lead to systemic effects such as **narcosis** from solvents or **kidney damage** from metal salts such as **uranium dioxide**.

Exposure of the skin to some substances in the workplace may cause local irritation, whilst others can lead to **contact dermatitis** or other types of chronic skin disease. Some compounds may be absorbed through the skin and cause toxic effects elsewhere in the body. For example, the insecticide **parathion** has been known to cause fatal poisoning following skin absorption.

As might be expected the respiratory system and skin are the organs most commonly affected by industrial chemicals. Indeed, the most prevalent occupational disease is dermatitis and this accounts for more working days lost in the UK than all other prescribed (see Glossary) industrial diseases together. Dermatitis may have many causes including exposure to organic and inorganic chemicals. Furthermore, chemical agents may act simply as **irritants** or they may be **sensitizers**. In some cases the symptoms may be similar such as the induction of inflammation for example. The number of primary irritants is large and includes many different types of chemical substance such as acids, alkalis, metals and solvents and solid organic and inorganic chemicals. Many of these substances will affect the skin in different ways: solvents will degrease skin, whereas acids and alkalis will denature skin proteins.

Skin sensitizers act via an **immunological** mechanism to cause contact dermatitis. The chemical may pass through the epidermis and react with proteins such as keratin, to produce an antigen. This 'foreign', antigenic protein then initiates the production of antibodies. Re-exposure to the substance will then initiate an allergic reaction. There are a large number of sensitizers of many different chemical types as shown in Table 6.1. **Nickel** and its salts are a well-known cause of contact dermatitis (nickel itch). This may result from occupational exposure and also from exposure to nickel in jewellery.

Sensitization may also be a problem following inhalation exposure where it may lead to a systemic effect such as asthma. **Toluene-diisocyanate** is a **pulmonary sensitizer** which is widely used in industry.

Some compounds such as the **chlorinated hydrocarbons** cause occupational **acne**, which results from plugging of the pores and increased production of keratin.

Vinyl chloride

Vinyl chloride or vinyl chloride monomer (VCM) as it is commonly known is the starting point in the manufacture of the ubiquitous plastic polyvinyl chloride **(pvc)**. This plastic was introduced a number of years ago and there have been many workers exposed or potentially exposed to vinyl chloride during the course of their working lives. However, safety standards in factories and working practices have not always been as rigorous as they are today and were perhaps not always observed. In some cases workers were required to enter reaction vessels periodically to clean them, despite the fact that they still contained substantial traces of vinyl chloride. As vinyl chloride is a gas it can be inhaled but is also readily absorbed through the skin. This was sufficient for some of the workers to be overcome by solvent **narcosis**. The chronic toxic effect of this was not immediately apparent but the most severe lesion, a liver tumour known as **haemangiosarcoma**, was very rare and was observed only in epidemiological studies of workers in this industry. This tumour was generally confined to workers exposed to extremely high concentrations of vinyl chloride. This type of liver tumour has now also been produced in experimental animals. The hygiene and safety standards applied to working with vinyl chloride are now stricter. However, this occurred with the benefit of hindsight and with more foresight the tragedy might have been avoided.

TABLE 6.1 *Types of skin sensitizers*

Type	Chemical class/example
Dye intermediaries	Aniline compounds
Dyes	*p*-Phenylenediamine
Photographic developers	Hydroquinone
Anti-oxidants	o- and *p*-toluidine
Insecticides	Organophosphorus compounds
Resins	Urethane
Coal tar derivatives	Anthracene
Explosives	Picric acid
Metals	Nickel, Chromium

Chronic exposure to vinyl chloride results in 'vinyl chloride disease' which comprises **Raynauds phenomenon** (see Glossary), **skin** changes, changes to the **bones** of the hands, **liver** damage and in some cases haemangiosarcoma. The bone changes are due to **ischaemic damage** following degeneration and occlusion of small blood vessels and capillaries. The liver may become fibrotic. It has been suggested that the vinyl chloride syndrome has an immunological basis, as **immune complexes** are deposited in vascular epithelium and **complement activation** is a feature.

The toxic effects of vinyl chloride may result in part from *metabolic activation*, as it is metabolized by cytochrome P450 to the reactive intermediates, **chloroethylene oxide** or **chloroacetaldehyde**, which *alkylate* **DNA** and this may thereby lead to cancer (Figure 3.5). The metabolism is *saturable* and the incidence of liver tumours produced in animals reaches a maximum. The tumour incidence therefore correlates with the amount of vinyl chloride metabolized rather than the dose. The reactive intermediate may also react with other macromolecules and cause the tissue damage seen either directly or via an immunological reaction.

The lessons from this example are that safety standards need to be stringent in factories and that animal studies are important in assessing potential toxicity and highlighting the type of toxic effect that might be expected. This should be known before human exposure occurs. As a consequence of this type of industrial problem legislation is now in force in most major Western countries which deals specifically with industrial chemicals. For example, in the UK all chemicals produced in quantities of greater than 1 tonne have to undergo toxicity testing (see Chapter 12), whilst strict occupational hygiene limits, known variously as **Maximum Exposure Limits** (MEL; UK) or **Threshold Limit Values** (TLV; USA) for industrial chemicals are enforced.

Cadmium

Cadmium is a metal which is widely used in industry in alloys, in plating, in batteries and in the pigments used in inks, paints, plastic, rubber and enamel. It is also found **naturally** and may be present in food although it is poorly absorbed from the gut (5–8 per cent). However, up to 40 per cent of an inhaled dose is absorbed and therefore the presence of cadmium in **cigarette smoke** is more significant. It is an extremely toxic substance and the major hazard is from inhalation of cadmium metal or cadmium oxide. Cadmium has many toxic effects, primarily causing **kidney damage**, as a result of chronic exposure, and **testicular damage** after acute exposure, although this does not seem to be a common feature in humans after occupational exposure to the metal. It is also a **carcinogen** in animals causing tumours in the testes as well as at the site of exposure.

Kidney damage may be a delayed effect even after single doses, being due to the accumulation of cadmium in the kidney, as a complex with the protein metallothionein. **Metallothionein** is a low molecular weight protein involved with the transport of metals within the body. Due to its chemical similarity to zinc, cadmium exposure induces the production of this protein and 80–90 per cent of cadmium is bound to it *in vivo*. The cadmium–metallothionein complex is transported to the kidney, filtered through the glomerulus and is reabsorbed by the proximal tubular cells. Within these cells the complex is degraded by proteases to release cadmium which may damage the cells or recombine with more metallothionein.

The testicular damage occurs within a few hours of a single exposure to cadmium and results in necrosis, degeneration and complete loss of spermatozoa. The mechanism involves an effect on the vasculature of the testis. Cadmium reduces blood flow through the testis

and **ischaemic necrosis** results from the lack of oxygen and nutrients reaching the tissue. In this case cadmium is probably acting mainly indirectly by affecting a physiological parameter.

The half-life of cadmium in the body is between 7 and 30 years and it is excreted through the kidneys, particularly after they become damaged.

After acute inhalation exposure lung irritation and damage may occur along with other symptoms such as diarrhoea and malaise while chronic inhalation exposure can result in emphysema occurring before kidney damage is observed. Cadmium can also cause disorders of calcium metabolism and the subsequent loss of calcium from the body leads to **osteomalacia** and brittle bones. In Japan this became known as **Itai-Itai ('Ouch-Ouch!') disease** when it occurred in women eating rice contaminated with cadmium.

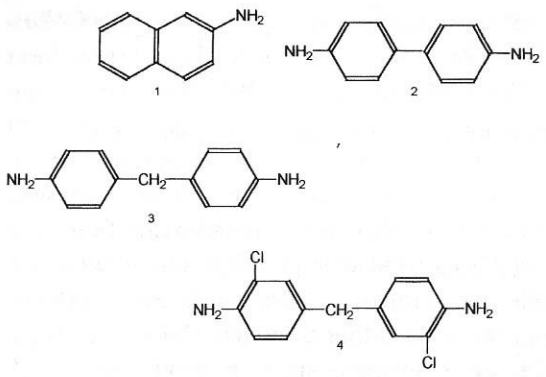

FIGURE 6.1 *The structures of some carcinogenic aromatic amines. 1: 2-naphthylamine; 2: benzidine; 3: 4,4'-diamino-diphenylmethane (DADPM); 4: 3,3'-dichloro-4,4'-diamino-diphenylmethane, (4,4'-methylene-bis-(2-chloroaniline, MBOCA)).*

Aromatic amines

Aromatic amines are widely used in the rubber and dye industry and cause various toxic effects. **2-Naphthylamine**, which was formerly used in the rubber industry is one of the few compounds known to be a **human carcinogen** causing **bladder cancer**. It was withdrawn from industrial use in 1949. The earliest cases of bladder cancer due to aromatic amines were reported in Germany in 1895 amongst aniline dye workers.

There are a number of different aromatic amines used in industry (Figure 6.1) and some of them are known to be carcinogenic at least in animals. However, 2-naphthylamine has been extensively studied and serves as an example. The mechanism of the bladder cancer is believed to involve metabolism. 2-Naphthylamine undergoes hydroxylation at the nitrogen atom followed by conjugation of the resulting hydroxyl group with glucuronic acid (Figure 3.15). When the conjugate is excreted into the urine, however, it breaks down under the acidic urinary conditions to yield a **reactive metabolite** which can then react with cellular macromolecules such as DNA.

It has recently been proposed that the **acetylator phenotype** may be a factor in bladder cancer induced by aromatic amines. Acetylation is one route of detoxication for these compounds (Figure 6.2) and consequently slow acetylators would be exposed to more of the aromatic amine than rapid acetylators.

Other aromatic amines used in industry which are carcinogenic in animals are **methylene-*bis*-*o*-chloroaniline (MBOCA)**, **benzidine**, ***o*-tolidine**, **4-aminobiphenyl** and **diaminodiphenylmethane (DADPM)** (Figure 6.1). This latter compound was responsible for an outbreak of jaundice in the UK, which became known as **Epping Jaundice**. A solution of the chemical was spilt onto the floor of a lorry which subsequently carried sacks of flour. These became contaminated with the substance

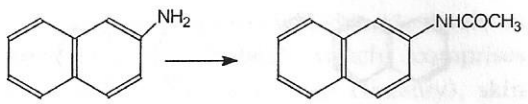

FIGURE 6.2 *The acetylation of 2-naphthylamine.*

and people who ate the bread made from this flour became ill with jaundice. DADPM causes bile duct damage and liver tumours in rodents rather than bladder tumours. The target organ for the aromatic amines, however, seems to depend on the species as in rodents liver tumours generally result whereas in the dog bladder tumours occur more often.

Workers who are occupationally exposed to aromatic amines should undergo cytological examination of urine as well as other screening procedures. **Aniline**, the simplest aromatic amine, causes **methaemoglobinaemia** and consequently cyanosis after acute exposure. After chronic exposure anaemia with mild cyanosis may occur.

Asbestos

The industrial diseases associated with exposure to asbestos illustrate that even chemically inert substances can be very toxic. The term asbestos covers a group of fibrous mineral silicates which have differing chemical compositions. It is widely used in industry because of its ability to withstand heat and to provide insulation. **Chrysotile** (white asbestos) is the form most commonly used and is relatively inert biologically but **crocidolite** (blue asbestos) and a common contaminant of white asbestos is especially hazardous as it may cause **mesothelioma**, a rare form of cancer, and also **bronchial carcinoma** (cancer of the lung).

It has been estimated that deaths due to asbestos will peak at between 2–3000 per year in the UK and 10 000 per year in the US over the 30-year period from 1983. There have been more than 400 known deaths from mesothelioma alone in the UK and this cancer is solely associated with exposure to asbestos. Extensive exposure is normally via inhalation in factories manufacturing asbestos products or during its use as an insulating material, such as in power stations and in warships during the Second World War. More recently, workers have been exposed potentially to asbestos during the demolition of buildings in which it has been used. It is widely used in brake linings. The general population is also exposed to asbestos in food and water. It has been used as a material for filters and, hence, may appear in drinks, and it occurs in drinking water in some areas where mining takes place. However, the toxicological importance of this route of exposure is currently uncertain, but gastrointestinal tumours have been ascribed to asbestos after inhalation exposure.

Exposure to asbestos via inhalation can lead to the following conditions:

1 **Asbestosis** or interstitial **fibrosis of the lung**;

2 Benign **pleural disease**;

3 **Bronchial carcinoma**;

4 **Malignant mesothelioma**.

Asbestosis is a dose-related disease and requires heavy exposure for a prolonged period. Particles of asbestos can be detected in the fibrotic areas of the lung and sputum and the air spaces become obliterated with collagen. The asbestos fibres become coated with an iron-containing protein. The disease develops over a variable period of time with breathlessness becoming more severe. Monitoring the lung function of exposed workers in some way, such as by measuring vital capacity, should be carried out as a consistent reduction could indicate the effects of asbestos exposure.

Although asbestos is chemically inert, the fibres are cytotoxic and will haemolyze red blood cells. The length of the fibre seems to be an important factor in the toxicity – **fibres** which are *longer* than **10–20 μm** will cause fibrosis but shorter ones do not. This is due to the *inability* of **macrophages** to *phagocytose* the long fibres fully and so the macrophage cell membrane is damaged and enzymes leak out. These enzymes and other cellular constituents may be involved in the development of **fibrosis**. The lung normally can remove hazardous particles but the long asbestos fibres are not adequately removed and as already indicated they are also not effectively removed by macrophages. An immunological mechanism is also involved and asbestos fibres cause a change in the cell surface of the macrophage after ingestion. This is a change in the receptors for C_3 complement and IgG antibodies. The complement pathway is also activated.

In the UK there is legislation to control the use of asbestos and workers must have a medical examination before and at regular intervals during their exposure. Crocidolite is no longer used in the UK, the use of amosite (brown asbestos) is not encouraged, and the general use of asbestos for insulation will probably be banned. The control limit for crocidolite and amosite in the environment is 0.2 fibres per ml and 0.5 fibres per ml for other forms of asbestos.

Bronchial carcinoma may result from prolonged exposure to asbestos and occurs in approximately 50 per cent of those workers who develop asbestosis. As well as the dose and duration of exposure, the type of exposure is also important. The use of asbestos products, such as in textiles, where asbestos of a particular particle size is generated, is probably important in the development of the disease.

Mesothelioma is a rare form of cancer which affects the chest lining and is associated only with exposure to asbestos, especially but not exclusively, crocidolite. **Crocidolite** from the north-west Cape Province in South Africa is more *potent* than that from the Transvaal. Prolonged exposure to high levels of asbestos is not necessary for the development of mesothelioma and it has developed in people not occupationally exposed to asbestos. Although the latent period is usually long, typically 30 years after exposure, once diagnosed the disease is usually fatal within months rather than years. The tumour may eventually spread to the lung and may eventually encase it.

The mechanisms underlying asbestos-induced cancer are currently unknown but do not seem to involve genotoxic mechanisms. Animal studies as well as human data have shown that asbestos fibres alone will cause cancer of the mesothelium. Unlike other types of chemical carcinogen, asbestos is not metabolized or activated *in vivo* but once present in the tissues it remains there permanently although the fibres do migrate from the airways to the pleural cavity. Consequently, even exposure to high levels for short periods of time may be sufficient to eventually cause mesothelioma.

The **size of the fibres** appears to be a critical factor, with those 0.3 μm in diameter and 5 μm in length being the *most active*. The extent of exposure in terms of the concentration of fibres in inhaled air is also important. Other factors have also been identified. There may be a synergistic effect between smoking and asbestos in the induction of pulmonary carcinogenesis.

Legislation

In the UK, the USA and in most other major Western industrialized nations there is legislation which sets limits on the levels of toxic substances in the workplace. This involves setting

exposure levels based on the results of human epidemiological data and on the results of animal toxicity studies. It requires monitoring of the occupational environment for compliance. The experimental evidence of toxic effects usually includes, the determination of a dose–response relationship and no-effect levels in experimental animals. Limited studies, such as exposure to solvents for irritant effects, for skin sensitization may, however, be conducted in human volunteers under carefully controlled conditions after ethical considerations have been made.

The maximum level of exposure for a compound is known as the Maximum Exposure Limit **(MEL)** in the UK or the threshold limit value **(TLV)** in the USA. These are calculated on the basis of exposure over a normal working day usually from a knowledge of the toxicity of the compound in experimental animals **(NOAEL)** with a margin of safety included in the estimate (see Chapters 1 and 12). Such occupational exposure limits are set by the regulatory body, in the case of the UK this is the Health and Safety Executive, and these should not be exceeded. The fact that industrial diseases still occur suggests that some factories do not adhere to these limits or that safety precautions such as the wearing of masks are not taken. Unfortunately with some diseases, such as cancer, the development time is long and therefore diseases may occur many years after the initial, critical exposure when safety standards were not as strict as those today.

This long latency period also means that the detection of industrial diseases is often difficult, as there has to be a sufficient rarity and sufficiently increased frequency of the disease within a particular population for **epidemiologists** to detect it. In the UK however, new legislation requires all new chemical substances not already covered by existing legislation (drugs and pesticides) to undergo **toxicological testing** and consequently exposed people can be screened for the likely toxic effects. In addition, it allows hazards to be identified so that control measures, such as suitable labelling, can be effected. Despite this, however, new occupational diseases will undoubtedly continue to appear resulting from exposure many years ago. Also, new and unexpected toxic effects may also occur.

Summary and learning objectives

Many of the chemicals used in industry are chemically reactive molecules and are likely to interact with biological systems and cause damage in some cases at the site of exposure.

Exposure is most commonly via skin and lungs. ***Toxic effects*** on the skin such as irritation, sensitization and contact dermatitis as caused by nickel are the most common occupational diseases and in some cases may have an immune basis. Similarly, allergic lung disease such as asthma may result from exposure to industrial chemicals and some extremely reactive irritant chemicals (e.g. toluene diisocyanate) cause pulmonary sensitization, oedema, bronchoconstriction, and maybe death. Certain industrial chemicals cause cancer which may develop many years after exposure.

High levels of exposure to ***vinyl chloride*** have occurred in manufacturing plants and resulted in rare liver cancer developing some years later. Apart from this vinyl chloride also caused liver damage and effects on skin and bones. The liver damage and cancer are caused by a reactive metabolite produced by cytochrome P450 which reacts with protein and DNA.

Cadmium is an element widely used in industry in various forms. Its toxic effects include kidney damage following oral or inha-

lation exposure, brittle bones (Itai-Itai disease) and, after chronic inhalation of cadmium fumes, lung irritation and emphysema. In rodents testicular damage and tumours may occur. Cadmium is bound to metallothionein but release of free cadmium from this complex in the kidney underlies the nephrotoxicity.

A variety of ***aromatic amines*** are used in industry such as the production of rubber. A number of these are suspect or known carcinogens such as ***2-naphthylamine***. Metabolic activation by cytochrome P450, conjugation of the hydroxylated product and release of the reactive metabolite in the urine allows interaction of the metabolite with bladder cell DNA. This is responsible for the carcinogenicity. 2-Naphthylamine can be detoxified by acetylation, therefore the slow acetylator status is a factor and slow acetylators are more at risk from bladder cancer.

Other aromatic amines used in industry are also carcinogenic or toxic in other ways (jaundice, methaemoglobinaemia).

In contrast, ***asbestos*** is a relatively inert substance but causes lung cancer (mesothelioma, bronchial carcinoma) and asbestosis, a chronic lung disease. The fibres lodge in the lungs, are taken up by phagocytic cells which leak cell contents and damage the surrounding tissue. Fibre size is a crucial factor. Exposure to such chemicals and minerals is now tightly controlled by ***legislation*** and exposure levels (TLV, MEL) are set.

Questions

Q1. Indicate which is true and which is false. Skin sensitization is an important occupational disease and can be caused by:

a vinyl chloride
b cadmium
c nickel
d asbestos.

Q2. Which of the following industrial chemicals are known human carcinogens?

a cadmium
b vinyl chloride
c 2-naphthylamine
d asbestos.

Q3. In order to calculate the TLV for an industrial chemical which of the following are needed?

a latency period
b half-life
c NOAEL
d daily exposure level.

Q4. The toxicity of asbestos is affected by which of the following?

a fibre size
b form of asbestos
c route of exposure
d dose
e exposure period.

Q5. Which of the following is caused by both cadmium and vinyl chloride?

a testicular damage
b kidney damage
c bone damage
d ischaemia.

SHORT ANSWER QUESTION

Q6. Explain how the acetylation and glucuronic acid conjugation are important in 2-naphthylamine carcinogenicity.