Health Effects of Hazardous Chemicals

Core Body of Knowledge for the Generalist OHS Professional

Second Edition, 2023

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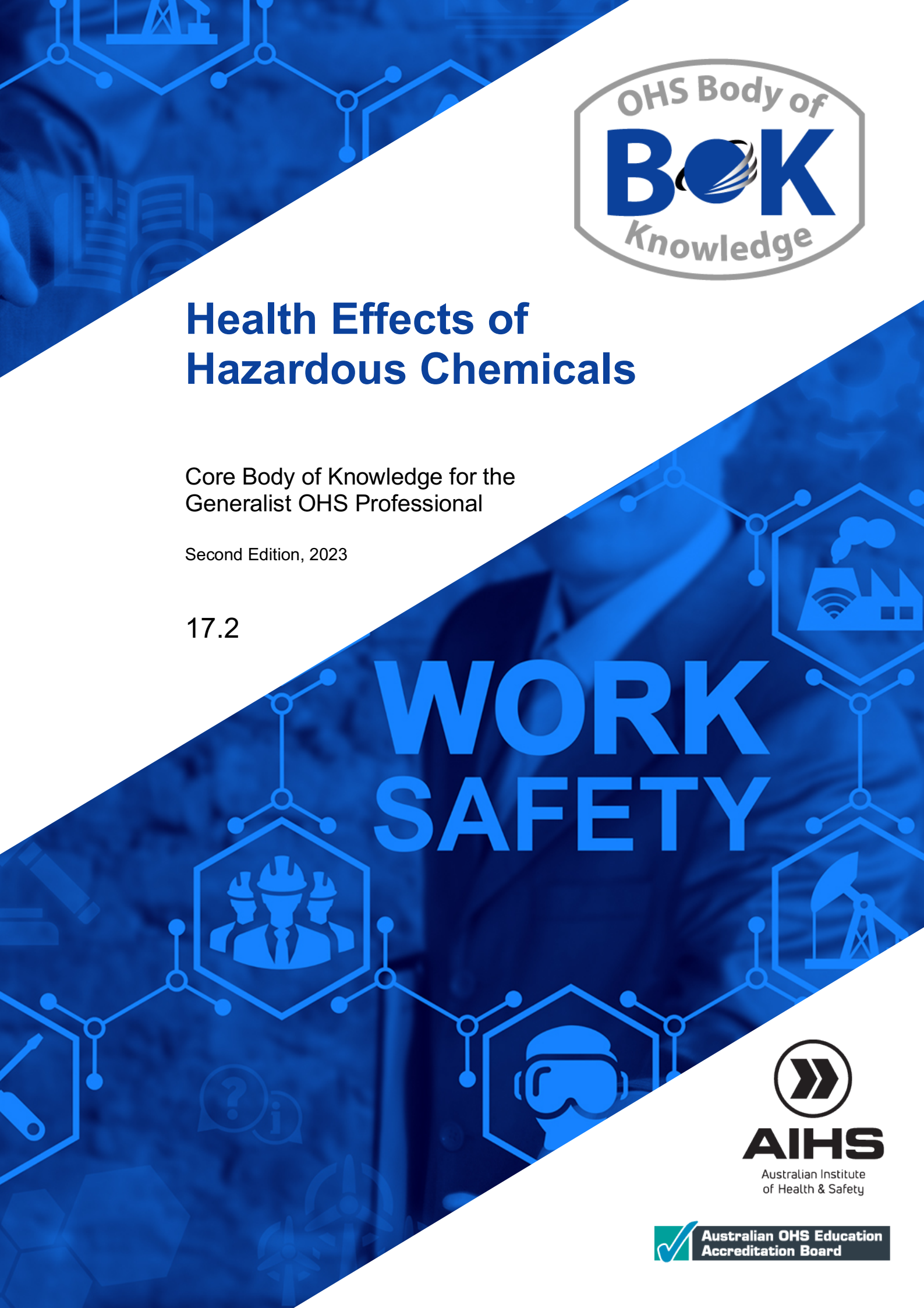

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Bibliography

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Health Effects of Hazardous Chemicals

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Health Effects of Hazardous Chemicals

Abstract

Toxicology has been referred to as 'the science of safety.' To understand the potential impact of toxins on the human body and to effectively contribute to mitigating the health impacts of hazardous chemicals on workers and others, generalist OHS professionals require knowledge about some fundamental aspects of toxicology. This chapter (one of four in a series of *OHS Body of Knowledge* chapters focused on hazardous chemicals), reviews some general principles of toxicology, including the dose-response relationship, LD_{50} values, acute and chronic toxicity, absorption, distribution, excretion and biotransformation. It addresses the classification of toxins and provides information on three specific groups of toxins with workplace relevance – carcinogens, reproductive and developmental toxins, and teratogens. It considers measures to protect workers, including future directions for worker health surveillance, and implications for OHS practice.

Keywords

chemical, health, toxicology, hazardous substances, OHS, chemical health effects

Contextual reading

For context, readers should refer to *OHS Body of Knowledge* 1 Preliminaries, 2 Introduction and 3 The Generalist OHS Professional: International and Australian Perspectives.

Terminology

Depending on the jurisdiction and the organisation, Australian terminology refers to 'Occupational Health and Safety' (OHS), 'Occupational Safety and Health' (OSH) or 'Work Health and Safety' (WHS). In line with international practice, this publication uses OHS with the exception of specific reference to the Work Health and Safety (WHS) Act and related legislation.

Jurisdictional application

This chapter includes reference to the Australian model work health and safety legislation. This is in line with the Australian national application of the *OHS Body of Knowledge*. Readers working in other legal jurisdictions should consider these references as examples and refer to the relevant legislation in their jurisdiction of operation.

Table of Contents

List of Figures

List of Tables

1 Introduction

In 2021, the World Health Organization advised that more than 160 million chemicals of natural and artificial origin have been identified (WHO, 2021). Indeed, our environment (work and non-work) is composed of chemicals. Even our bodies are complex systems of elements, molecules, chemical compounds and intricate biochemical systems. This chapter discusses the impact that exposure to certain chemicals can have on our wellbeing and quality of life now and into the future. It is one of four chapters in the *Occupational Health and Safety Body of Knowledge* (*OHS BoK*) that address chemical hazards.[1] Focusing on work-related exposures to toxins that may come from nature (of microbial, plant or animal origin) or are synthesised in industrial processes, this chapter reviews some key aspects of the science of toxicology.[2]

> Toxicology is a field of science that helps us understand the harmful effects that chemicals, substances, or situations, can have on people, animals, and the environment. Some refer to toxicology as the "Science of Safety" because as a field it has evolved from a science focused on studying poisons and adverse effects of chemical exposures, to a science devoted to studying safety. (NIEHS, 2022)

The Swiss physician known as Paracelsus[3] (1493–1541), widely considered the founder of toxicology, is the source of the dictum *All substances are poisons; there is none which is not a poison. The right dose differentiates poison from a remedy* (Gallo, 2008).[4] The dose-dependency of toxic effects means that seemingly harmless, and indeed essential, chemicals can become lethal in certain circumstances and that chemicals can become toxic in large amounts (e.g. NaCl – table salt) or small amounts (e.g. botulinum toxin – Botox).

Toxicology draws on information from other disciplines, including chemistry, physiology, biochemistry, biology, pharmacology, genetics and law. Furthermore, there are different branches of toxicology such as environmental toxicology, forensic toxicology, clinical toxicology and genetic toxicology. In terms of chemicals in the workplace, the focus is on **occupational toxicology**, but other branches of toxicology are often involved in the assessment and response to workplace exposures. It is sometimes the case that chemical exposure in both the non-work and work environments increases the cumulative dose and/or response to a toxic chemical (e.g. smoking- and asbestos-related disease; exposure to lead

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[1] *OHS BoK* 17.1 Managing Chemical Hazards provides a general overview of chemical hazards and how to control the associated risks; *OHS BoK* 17.3 Dusts, Fumes and Fibres examines the specific hazards associated with exposure to dusts, fumes and fibres; and *OHS BoK* Process Hazards (Chemical) focuses on control of chemical reactivity that may cause immediate damage to people, property and the environment.

[2] "The word *toxicology* is derived from the Latinised form of the Greek word *toxicon*, meaning 'arrow poison' (Wexler & Hayes, 2021).

[3] Born Philippus Aureolus Theophrastus Bombastus von Hohenheim.

[4] See *OHS Bok 17.3* Dusts, Fumes and Fibres for a historical perspective on the effects of hazardous chemicals on the health of workers.

associated with metal smelter work and incidental environmental lead contamination) (e.g. Fox et al., 2021). Exposure to toxic substances can be lethal. For example, a disastrous 1984 leak of methyl isocyanate gas at a fertiliser factory in Bhopal, India, resulted in the immediate death of thousands of people, with many thousands more suffering prolonged adverse health effects (Broughton, 2005).

Understanding the potential health effects of the multitude of chemicals used in industry, complicated by the constant appearance of new chemical compounds, presents a great challenge for generalist OHS professionals. Organisations that review the health effects of chemicals and provide updated information on the use of chemicals include Australian federal, state and territory regulators and international organisations such as the International Labour Organization (ILO), the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC). Generalist OHS professionals need to know how to use available information to assess the risk of workplace exposure to a particular chemical or a mixture of chemicals.[5] In complex situations, OHS professionals may need to work in collaboration with an occupational hygienist and/or an occupational physician to accurately assess exposure and potential harm. Environmental monitoring and/or health monitoring[6] may be necessary to inform a risk assessment.[7]

Recognising the complexity of the science of toxicology, the approach of this chapter is to help OHS professionals understand the potential impact of hazardous chemicals on the health and wellbeing of workers and others. After an explanation of some basic toxicological concepts with OHS-relevant examples (section 2), classification of toxins is considered (section 3). Information on three specific groups of toxins (carcinogens, reproductive and developmental toxins, and teratogens) (section 4) is followed by measures to protect workers, including future directions for worker health surveillance (section 5), and implications for OHS practice (section 6).

2 General principles of toxicology

To paraphrase Paracelsus (section 1), 'too much of anything is not good for you and even limited exposure to highly toxic substances can be bad.' Identifying the inherent toxicity of substances to humans and how much is too much is fundamental to toxicology. To illustrate, consider the two most critical substances in the maintenance of life – oxygen and water.

[5] See *OHS BoK* 17.1 Managing Chemical Hazards for information about the Global Harmonized System of Classification and Labelling of Chemicals (GHS), chemical labels and safety data sheets.

[6] See *OHS BoK* 17.3 Dusts, Fumes and Fibres.

[7] See *OHS BoK* 17.1 Managing Chemical Hazards and *OHS BoK* 17.3 Dusts, Fumes and Fibres for information on risk assessment.

Humans deprived of the 'right' amounts of oxygen and water will die within a few minutes to a couple of days due to hypoxia or dehydration, respectively. Despite this essential nature, consistent exposure to high concentrations of inspired molecular oxygen (O_2) can result in 'oxygen poisoning,' with both short-term reversible and permanent (potentially lethal) damage to cells of the lung, liver, blood, heart, retina, thyroid and cells of the body in general. Too much water intake – hyperhydration – can lead to rapid disruption of electrolyte and osmotic balance resulting in central nervous system effects, cardiac dysrhythmias, coma and death.

In 2007, a US radio station sponsored an on-air water-drinking contest – 'Hold your wee for a Wii' – that resulted in the death of a contestant. After drinking nearly 2 gallons (7.6 litres) of water in an attempt to win a Nintendo Wii, the contestant (who placed second) was found dead hours later due to water intoxication. The DJs were made aware of the dangers but did not inform the contestants. Ten radio station employees were fired and the parent company, Entercom Sacramento LLC, was ordered to pay USD$16.5 million to the deceased's family. (Clark & McHugh, 2009)

The route and site of exposure, as well as the duration and frequency of exposure to harmful/toxic/poisonous substances in the workplace are discussed in *OHS BoK* 7 The Human as a Biological System. Differences in the toxicity of substances relate to their chemical nature, particular physiologic mechanisms of action in humans, the types of cells/tissues/system(s) of the body they affect, and differences in individual susceptibility (i.e. human variability relating to genetic, personal, behavioural and external environmental factors). Variation in individual responses to toxin exposure are discussed in *OHS BoK* 17.3 with reference to workers exposed to respirable dusts, fumes and fibres.

2.1 Dose-response relationship

The dose-response relationship – "the association between the amount of a toxicant administered and the extent to which changes are observed in a biological system" (Aleksunes & Eaton, 2021, p. 16) – is a fundamental concept in toxicology that allows for a reasonable approximation of toxicity associated with substances known to have negative impacts on the body. Thus, signs, symptoms and/or effects of intoxication associated with exposure to a toxic substance observed in a population of exposed workers are proportional to the degree or extent of the exposure. "In occupational environments, *exposure* is often used as a proxy for *dose*" (Thorne, 2021, p. 582).

As explained by Aleksunes and Eaton (2021), the variation of individual responses to toxin exposure in a population typically presents as a normal (i.e. 'bell-shaped') frequency

distribution in which the majority of exposed individuals exhibit signs and symptoms of intoxication at an intermediate dose (Figure 1). This dose corresponds with the maxima (highest point) of the 'normal' distribution. Susceptible individuals exhibit signs and/or symptoms of intoxication at lower doses, while less-susceptible individuals begin to demonstrate effects of intoxication at higher doses.

> [Those responding to the lowest dose] at the left end of the curve are referred to as *hypersusceptible*, and those at the right end of the curve are termed *resistant*. If the number of individuals responding at each consecutive dose are added together, a cumulative, quantile dose-response relationship is obtained. (Aleksunes & Eaton, 2021, p. 18)

When sufficient doses are used with a large number of individuals per dose, a sigmoid (s-shaped) dose-response curve is observed, depicting the full spectrum of effects (Figure 1). Such dose-response models can be used to determine safe and hazardous levels of chemicals and to inform decision making for different regulatory purposes.

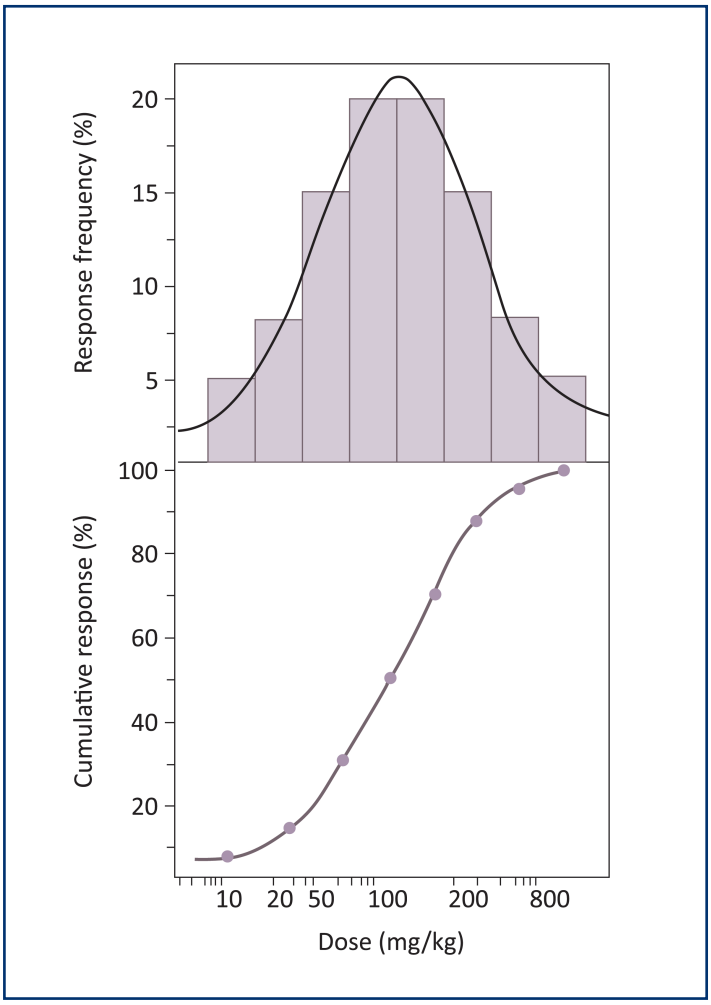

Figure 1: Dose-response relationship (modified from Aleksunes & Eaton, 2021, p. 18)

Animal and human case and population studies as well as human epidemiological data allow us to gauge the degree of toxicity and characterise the toxic effects of a wide variety of chemicals. However, this information is not always easy to obtain retrospectively with large enough numbers and in great enough detail to clearly demarcate safe exposure standards without extrapolating from experimental evidence derived from in vivo and in vitro[8] toxicological methods. In vivo toxicology uses experimental animals such as rats, mice, guinea pigs and rabbits to establish a dose-response relationship between exposure to a chemical and the extent of response (e.g. death) in exposed populations.

2.2 LD_{50} values

Lethal dose 50 (LD_{50}) is commonly used to estimate acute toxicity. By definition, the LD_{50} is the amount of a substance administered to individual test animals needed to kill 50% of the animals tested within a defined period of time, typically within a few hours of exposure (e.g. CCOHS, 2018). Use of LD_{50} values enables comparison of acute toxicity for different chemicals, or xenobiotics.[9]

Establishing useful LD_{50} values is problematic in terms of ethical justification of lethality trials in animal models and the difficulty in extrapolating experimental findings to humans (e.g. Rowan, 1983). Other issues include variability in the route of administration (oral, intraperitoneal, intravenous, etc.) and differences in susceptibility in the test populations as well as dietary, age and gender differences of the test species. Although LD_{50} values still appear in many safety data sheets, these 'lethal dose' estimates offer limited value in assessing consequences of occupational exposures except when an LD_{50} indicates extreme toxicity. Test guidelines (TGs) for acute and chronic toxicity testing are established by the Organisation for Economic Cooperation and Development (OECD).[10]

[8] An in vivo (Latin for 'within the living') study is performed on a living organism; an in vitro (Latin for 'in glass') study is performed in a controlled environment such as a test tube.

[9] The term *xenobiotic*, often used in toxicology, refers to any chemical that does not normally occur in a biological system (e.g. a microbial toxin or synthesised chemical that is not normally found in humans).

[10] See *OECD Guidelines for the Testing of Chemicals, Section 4* at https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

100% natural and not necessarily good for you

Ciguatoxin can affect humans who consume certain marine fish (e.g. narrow-barred Spanish mackerel). Ciguatoxin is a naturally occurring polycyclic ether originating from certain tropical marine dinoflagellate species and one of the most toxic substances known with an LD_{50} estimated to be 0.45 mcg/kg in mammalian animal models. There is no antidote or effective treatment for ciguatera poisoning.

Based on the probable lethal dose in a 70 kg person, a 5 g quantity of this toxin (the mass of a sugar sachet for a single coffee) would be expected to result in, for example, the immediate death of a little more than half of the population of Cairns Shire, Queensland (79,365 of 157,245 residents in the 2022 census), and a miserable protracted death for a significant proportion of those who survived the initial acute intoxication. The remainder of the surviving population would feel rather 'ordinary' for many months to years. Fortunately for the residents of Cairns, ciguatoxin is a rare molecule that is difficult to distribute widely among a disparate population.

To illustrate the meaning of LD_{50} by comparison, a 70 kg adult consuming a single 5 g acute dose of the heavy metal toxin cadmium oxide (LD_{50} 72 mg/kg) would stand an even chance of surviving the anticipated immediate toxic effects with available medical intervention (Bernhoft, 2013). A survivor would be expected to recover relatively quickly from this better-known toxic substance with little to no ongoing morbidity.[11]

The LD_{50} associated with direct exposure to many compounds can be estimated using in vitro cell culture techniques employing animal- and human-based cells. (This largely avoids the ethical issues associated with whole animal and animal population lethality studies.) In these types of toxicity studies, observable characteristics of living cells altered by exposure to a toxic substance (e.g. cell viability – growth, division rates and cell survival/death) and changes in cell metabolism and membrane integrity/leakage can be equated to an LD_{50} value (Bakand & Hayes, 2010). However, the reliability of consequent LD_{50} estimates is at best indicative of anticipated toxicity in exposed humans. While these methods are used for direct toxicity screening of chemicals, inhalation studies using whole animal models are still necessary to define the toxicity of inhaled substances (i.e. the median lethal concentration – LC_{50} – of airborne toxic chemicals resulting in the death of 50% of exposed subject animals). Also, methods have been developed to assess airborne contaminant exposure of cultured human cells in vitro (Aufderheide & Mohr, 2000; Bakand et al., 2006). These assessments of LD_{50} and LC_{50} guide the implementation of the hierarchy of control measures to mitigate risk of exposure to known chemical hazards.

2.3 Acute vs chronic toxicity

'Acute' and 'chronic' toxicity are important descriptors, particularly in the context of workplace exposure, as they distinguish between circumstances where individuals are exposed to a large dose in a single event (or multiple relatively large exposure doses in a

[11] See the LD_{50} comparison table for various substances in the Wikipedia entry, Median Lethal Dose, at https://en.wikipedia.org/wiki/Median_lethal_dose

short period of time) and intoxication resulting from multiple low-level exposures over a long period of time.

At a fertiliser manufacturing plant, **acute toxicity** associated with a large accidental release of highly concentrated anhydrous ammonia gas may be expected to immediately result in severe injury and death to unprotected workers while **chronic toxicity** associated with daily exposure to background levels of ammonia slightly above the recommended exposure limit may result in irritant effects causing relatively mild eye and respiratory mucosa complaints.

Highly sensitive systems of detection make it possible to demonstrate the presence of many contaminants typically at very low levels in fluids and tissues sampled from the body. The accumulation of these substances is proportional to the degree and timeframe of an individual's exposure together with their rate of metabolism and excretion. Some of these compounds have well-characterised toxic effects (e.g. cadmium-related kidney, bone and lung disease); others, including a variety of synthetic environmental contaminants (e.g. plasticisers and polyfluoroalkyl substances) are detectable in environmental and biological screens but have yet-to-be determined toxicological effects. Although there is no such thing as an uncontaminated natural environment or chemically pure and untainted individual, it remains prudent and a statutory requirement to minimise incidental environmental exposure to toxic contaminants, and to limit or entirely avoid exposure in a planned and practical way to known toxic substances at workplaces where these compounds are used intentionally.[12]

2.4 Absorption

Absorption – "the process by which toxicants cross body membranes to enter the bloodstream" – occurs for toxicants as it does for biologically essential substances such as oxygen, water and nutrients (Slitt, 2021, p. 87). Importantly, toxic chemicals are only toxic once they enter the body and exert a biological effect (i.e. pass through a route of exposure and act on their target/s). Three body systems represent the main routes of worker exposure – the respiratory system (inhalation), the integumentary system (dermal) and the digestive system (ingestion).[13] Figure 2 summarises the pathways of absorption (represented by black lines), distribution (blue lines) and excretion (green lines) (with enterohepatic circulation in red).

[12] See *OHS Bok* 17.1 Managing Hazardous Chemicals and *OHS Bok* 17.3 Dusts, Fumes and Fibres for information about relevant legislation and methods of controlling hazardous chemicals.

[13] See also *OHS BoK* 7 The Human as a Biological System.

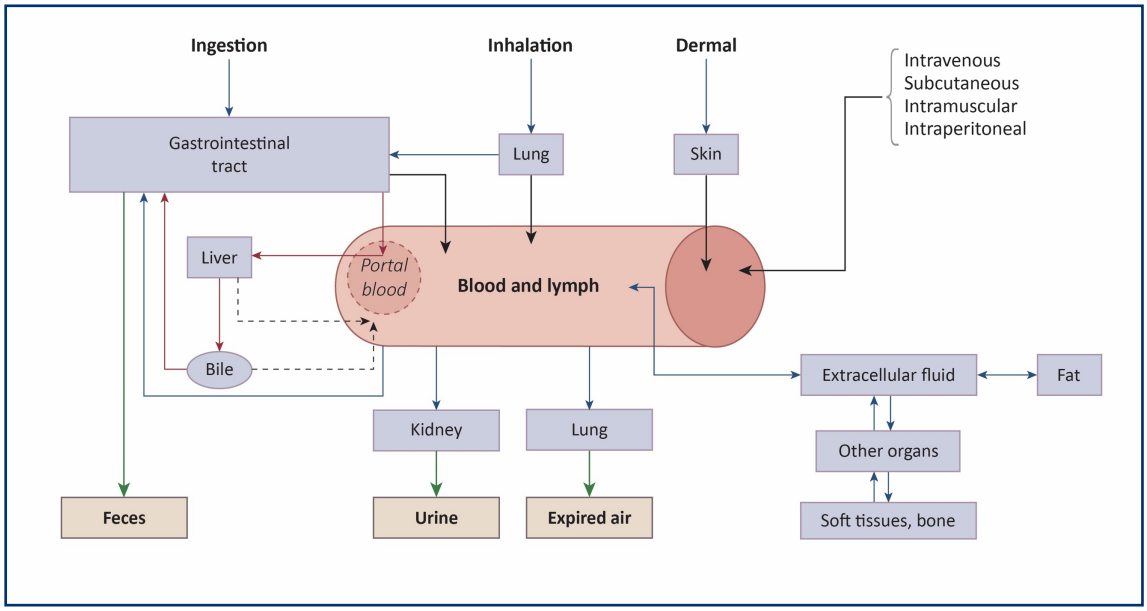

Figure 2: Summary of the disposition of toxicants as determined by absorption, distribution and excretion in the body (Slitt, 2021, 84)

The physical properties of substances (i.e. solid, liquid, gas) and workplace processes in which they are employed (e.g. mixing, heating, handling, spraying, etc.) establish the nature of the associated workplace hazard, while physicochemical properties defining a compound's propensity to be water-soluble (hydrophilic) or fat-soluble (hydrophobic) as well as the degree of chemical reactivity, pH, ionisation state and molecular weight of the molecule(s) dictate its absorption characteristics and mechanism of distribution in the body.

Consider a row of sealed bottles sitting impotently on a shelf but containing toxic substances required for some essential work process. From the point of view of exposure, this is not (yet) a problem for workers (or toxicologists). Apart from complicating OHS management processes relating to their acquisition, storage, use and disposal, compounds such as these only represent potential toxicological hazards to workers if control measures fail and a certain amount of exposure and absorption occur. Once they are 'out of the bottle,' toxicological considerations are in play.

Passive diffusion and a range of facilitated and active membrane transport processes allow gaseous, liquid and some ultrafine particulate toxicants to infiltrate and move through the epithelial cells of the lungs, gut and skin. Although most enter by simple diffusion, lipid-soluble substances are absorbed more quickly and extensively than water-soluble substances at these epithelial barriers. Membrane transporters, specific ion pores and the

cellular process of endopinocytosis[14] also play a role in absorption of toxicants. Some small ionic species (<200 daltons) can passively cross mucosal barriers directly into interstitial fluid by paracellular transfer through aqueous pores at the tight junctions between cells (Mitchell, 2020). Gases move passively into cells and interstitial fluids across the partial pressure gradient between the body's fluid compartments and the atmosphere (Mitchell, 2020).

Carbon monoxide implicated in seaplane crash

In December 2017, the crash of a seaplane into the Hawkesbury River, New South Wales, resulted in the deaths of the pilot and five passengers. An investigation by the Australian Transport Safety Bureau (ATSB, 2021) found that elevated levels of carbon monoxide were likely to have played a role in the tragic accident.

Carbon monoxide is rapidly absorbed through the lungs, aggressively binds haemoglobin in red blood cells and precipitously reduces red blood cell oxygen-carrying capacity, depriving the brain and other vital organs of oxygen (e.g. NIOSH, 2018). Without colour or smell, it is known as "the silent killer" (Blumenthal, 2001, p. 270). Carbon monoxide poisoning, which is a form of anaemic hypoxia that can progress from subtle onset symptoms to sudden incapacitation, is diagnosed by measuring carboxyhaemoglobin (COHb) in a blood sample (Blumenthal, 2001, p. 271).

The ATSB ordered toxicological testing of the seaplane occupants' retained blood samples for carbon monoxide exposure and the results revealed higher than normal levels of COHb (including 11% COHb for the pilot):

> This was almost certainly due to elevated levels of carbon monoxide (CO) in the aircraft cabin. The ATSB's wreckage examination established that several pre-existing cracks in the exhaust collector ring, very likely released exhaust gas into the engine/accessory bay, which then very likely entered the cabin through holes in the main firewall where three bolts were missing from the magneto access panels. … A 27 minute taxi, with the pilot's door ajar, before the passengers boarded likely exacerbated the pilot's elevated carboxyhaemoglobin level. As a result, the pilot would have almost certainly experienced effects such as confusion, visual disturbance and disorientation. Consequently, it was likely that this significantly degraded the pilot's ability to safely operate the aircraft. (ATSB, 2021, p. i).

2.5 Distribution

For a toxic substance to be absorbed it must mix with the aqueous milieu of the body's extracellular fluids and/or lipid membranes. Similar to the distribution of pharmaceutical drugs in the body, toxic molecules move across cell barriers, often bind to plasma proteins and ultimately partition into body fat and other tissues (Ritter et al., 2020).

[14] Endopinocytosis is a process in which external substances are engulfed by part of the cell membrane to form a small vesicle that is transported into the cell.

The biological 'target(s)' in the body upon which toxins exert their effect(s) are many and varied. A discussion of toxicodynamics addressing the various mechanisms by which toxic substances cause harm is beyond the scope of this chapter. However, toxicokinetics, which is a branch of toxicology dedicated to determining the fate of toxic substances in living organisms, includes the distribution/transportation of molecules after their absorption through routes of entry.

Aleksunes and Eaton (2021) summarise chemical toxicity as the following steps:

- *Delivery* of the chemical to the site of action, which includes absorption, distribution, metabolism and excretion of toxic substances
- *Interaction with target*, c*ellular dysfunction* and *disrepair,* which collectively determine the extent of toxicity.

There are three physiological water 'compartments' in the body where toxin solubility is considered (i.e. plasma water, interstitial water between cells outside the vascular system, and intracellular water). Typically, hydrophilic substances readily distribute to all three water compartments. Hydrophobic substances may undergo binding to plasma protein, dissolution into lipid-rich tissue (low water content) and sequestration in bone; these are important considerations in determining the impacts of toxic chemical distribution (e.g. Slitt, 2021).

Lead absorption, distribution and redistribution

Consider the toxicity of liberated lead stores associated with redistribution of lead from bone:

> In adults, approximately 80-90% of absorbed lead is stored in the bones due to its chemical similarity to calcium. These bone lead deposits are released into the blood during periods of enhanced bone resorption like menopause, forming a potential endogenous source of lead exposure. Postmenopausal women are at a higher risk for bone lead release because of hormonal and age-related changes in bone metabolism. Hence, high blood lead level coupled with concomitant environmental exposure exposes women in this age group to lead-related adverse outcomes like hypertension, reduced kidney and neurocognitive functions as well as increased risk of atherosclerosis and cardiovascular mortality. (Manocha et al., 2017, p. 261)

2.6 Excretion

Understanding the process of excretion effecting the removal of toxic substances from the body is an important aspect of toxicology. The equilibrium maintained between the toxin(s) being absorbed and the toxin/toxin analogue(s) simultaneously being removed from the body plays a large part in determining the degree of toxicity associated with various toxicants.

At the outset of intoxication, the quantity of a given toxin an individual is exposed to may not be completely absorbed; a certain proportion of toxin will pass by the body by exhalation in the breath, evaporation/sublimation from the skin, and/or passage through the gastrointestinal tract combined with faeces and/or vomitus bound to gut contents without being absorbed.

Absorbed toxins, on the other hand, may be excreted by the kidney in urine, by the hepatobiliary and digestive tracts in bile and faeces, and via eccrine glands that produce sweat, tears, saliva and milk, all of which have the ability to eliminate toxicants with varying degrees of efficiency (Slitt, 2021). The efficiency of elimination of individual toxicants depends greatly on the physicochemical properties of the toxicant (e.g. hydrophilicity/ hydrophobicity) and in many cases involves enzymatic alterations to the initial toxin molecule to render it more readily excreted in water. In general, "when the rate of absorption exceeds the rate of elimination, toxic compounds may accumulate, reach a critical concentration at a certain target site, and cause toxicity" (Slitt, 2021, p. 99). The more rapidly excreted a toxin, the shorter the period of acute toxicity.

2.7 Biotransformation

Biotransformation refers to the body's process of enzyme-catalysed chemical change to toxicant molecules that render them more excretable and, in most cases, less toxic on the way out.

Parkinson et al.'s (2021) summary of biotransformation knowledge includes the following key points:

- *Biotransformation* is the metabolic conversion of endogenous and xenobiotic chemicals to more water-soluble compounds.
- Xenobiotic biotransformation is accomplished by a limited number of enzymes with broad substrate specificities.
- Phase I reactions involve hydrolysis, reduction, and oxidation. These reactions expose or introduce a functional group (–OH, –NH2, –SH, or –COOH), and usually result in only a small increase in hydrophilicity.
- Phase II biotransformation reactions include glucuronidation, sulfonation (more commonly called sulfation), acetylation, methylation, and conjugation with glutathione (mercapturic acid synthesis), which usually result in [decreased toxicity and] increased hydrophilicity and elimination [via the kidneys and hepatobiliary system]. (p. 101).

3 Classification of toxins

OHS professionals have to contend with many known and potential occupational and environmental toxins and should be aware that there is no single method of classifying toxins. Rather, there are various approaches and toxin classification often relies on a combination of classification systems (Gupta, 2018). For example, toxins may be classified by their:

- *Effects*, e.g. carcinogens (cancer), mutagens (genetic mutation), teratogens (embryo malformation)
- *Target organ*, e.g. hepatotoxins (liver), neurotoxins (nervous system), reproductive and developmental toxins
- *Use*, e.g. pesticides, solvents, food additives
- *Physical state*, e.g. solids, liquids, gases, dusts; size
- *Chemical nature*, e.g. metals, non-metals, acids and alkalis, organic
- *Source*, e.g. plant, animal, mineral, synthetic
- *Context*, e.g. air pollutants, occupation-related exposures
- *Mechanism of action*, e.g. cholinesterase inhibitor, endocrine disrupter
- *Type*, e.g. acute or chronic toxicity
- *Level of toxicity*, e.g. extremely toxic, very toxic, slightly toxic
- *Symptoms produced*, e.g. corrosion (e.g. sulfuric acid), irritation (e.g. lead), systemic (e.g. carbon monoxide). (e.g. Aleksunes & Eaton, 2021; Gupta, 2018; HESIS, 1986; NIOSH, 2007)

Some of these categorisations (and their combinations) allow a more general approach to reviewing toxicity than others. For example, considering the use and mode of action of pesticides, insecticides, herbicides, etc., allows comparison of the toxicity of particular chemical groups that may be used industrially (such as various organophosphates in agriculture[15])

Other more specific classifications may be used for toxins that can impact specific target sites. For example, the fish-borne toxins, ciguatoxin (section 2.2) and tetrodotoxin,[16] have opposing effects on the sodium ion channels involved in nerve conduction; ciguatoxin opens

[15] See *OHS BoK* 7 The Human as a Biological System.

[16] Fugu, a puffer fish consumed in Japan, is a known carrier of tetrodotoxin; it is prepared in such a way as to produce mild tingling in the lips, but can be fatal if incorrectly prepared (e.g. Kuda, 2015; Yong et al., 2013).

the channel while tetrodotoxin blocks the channels (mechanisms of action), and both disrupt nerve conduction (mode of action) with serious and often fatal consequences.

4 Examples of toxin groups affecting DNA and gene expression

This section reviews three groups of toxins – carcinogens, reproductive and developmental toxins, and teratogens. While there are many differences between these groups, they have properties in common; in each, DNA may be implicated either directly by alteration of the genetic code or by an *epigenetic process* in which the expression of genes is changed (i.e. switched on or off or altered) by a potential toxin.[17]

4.1 Carcinogens

Toxicity in which a chemical, biological entity or physical agent (radiation) either alters the DNA (deoxyribonucleic acid) in a target tissue, organ or individual or alters the expression of a gene is referred to as *genetic toxicity*. Genetic toxicology had its origins in mutation research, which began in the 1920s when American geneticist H. J. Muller induced mutations in the fruit fly, *Drosophila*, by irradiation with X-rays (Carlson, 2013). Following the 1953 publication of the structure of DNA (Watson & Crick, 1953), molecular biology began to play an important role in understanding occupational illness related to changes in gene expression and genetic mutation.

Mutations in DNA and altered expression of DNA are linked to cancer. The occupational exposure to certain chemicals and resultant cancer was first described in 1775 by English surgeon Percival Pott, who observed a high incidence of scrotal cancer in chimney sweeps and attributed this to their exposure from an early age to coal tar (soot) in chimneys (Brown & Thornton, 1957). More than 140 years later, Yamagiwa and Ichikawa (1917) established that coal tar produced a cancer when applied to the ears of rabbits. In 1933, the chemical responsible for cancer associated with coal tar, 1,2-benzopyrene, was isolated by Cook et al. (1933). Since then, many individual chemicals, mixtures of chemicals and processes involving chemicals have been linked to cancer.

[17] Detailed review of all the many subgroups of toxins is beyond the scope of this chapter. For further information, see, for example, *Casarett & Doull's Essentials of Toxicology* (Klaassen & Watkins, 2021) or *Principles of Occupational Health & Hygiene: An Introduction* (Reed et al., 2020).

A database of known carcinogens has been established by the International Agency for Research on Cancer (IARC). Consistent with its mission – *Cancer research for cancer prevention* – the IARC evaluates potential physical, biological and chemical causes of cancer and publishes monographs that:

> …identify environmental factors that are carcinogenic hazards to humans. These include chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and lifestyle factors. National health agencies can use this information as scientific support for their actions to prevent exposure to potential carcinogens.
>
> Interdisciplinary working groups of expert scientists review the published studies and assess the strength of the available evidence that an agent can cause cancer in humans. (IARC, 2023)

The IARC Monographs on the Identification of Carcinogenic Hazards to Humans[18] provide excellent guides to toxic agents that have been linked to the development of cancer. More than half of the 1000 agents that the IARC has evaluated since 1971 were identified as carcinogenic, probably carcinogenic, or possibly carcinogenic (IARC, 2023) as per the following classification scheme.

Group 1	Carcinogenic to humans
Group 2A	Probably carcinogenic to humans
Group 2B	Possibly carcinogenic to humans
Group 3	Not classified as to its carcinogenicity to humans

It should be noted that the IARC classification is about hazard and not risk. For example, exposure to a substance or process in Group 2A does not mean that an exposed person will develop cancer; rather, it indicates that use of the substance or process and the extent of worker exposure need to be carefully reviewed. Substances or processes in Group 1 need a much greater degree of surveillance and many jurisdictions require health monitoring of exposed workers to a range of Group 1 carcinogens.[19]

The process of classification is dynamic and regularly updated by the addition of new potential carcinogens or the reclassification of existing potential carcinogens. For example, in 2015, glyphosate (used in the weedkiller Roundup) was moved from 2B to 2A based on more published evidence (IARC, 2017). As might be expected, the number of established carcinogens increases over time as more suspected carcinogens are referred to the IARC

[18] Available at https://monographs.iarc.who.int/monographs-available/

[19] See, for example, https://www.worksafe.qld.gov.au/safety-and-prevention/hazards/hazardous-exposures/carcinogens

for evaluation. Table1 shows the increase in number of established carcinogens over a 26-year period.[20]

Table 1: Total number of classified toxic agents (1996-2022) (IARC, 2022)

IARC Classification	No. Agents	
	1996	2022
Group 1	70	122
Group 2A	57	93
Group 2B	224	319
Group 3	469	501

The difficulty with identifying occupational cancer is the fact that the 'biology' of an occupationally induced cancer is no different to a non-occupationally induced cancer. Cancer can be linked to occupation and described as an 'occupational cancer' when a worker has been employed in an industry in which exposure to a known carcinogen has occurred and the type of cancer has been associated with that industry and occupation. For example, few, if any, Australian OHS professionals would not have an appreciation of the devastating impact mesothelioma has had on many workers exposed to airborne asbestos fibres. While asbestos exposure of Australian workers peaked in the 1970s, the impact continues with exposure occurring during removal of asbestos from buildings and renovation of dwellings containing asbestos (Asbestos Awareness, 2021; Soeberg et al., 2018).

Rushton et al. (2010) estimated that, in 2005, 5.3% (8019) of cancer deaths in Britain were attributable to occupational exposures to a range of chemicals, mixtures or processes from IARC Group 1 and Group 2A carcinogens. While shift work and occupations such as painting and welding, as well as solar radiation, were implicated, most links to occupational cancer were chemical. Interestingly, Rushton et al. (2010) noted that there were 212 deaths related to occupational injury in Britain in 2005; the less-visible chemical-related workplace deaths are much more prevalent than workplace traumatic deaths. In Australia, it was estimated that 1.4% (68,500) of all cancers that would develop in the 14.6 million Australians who were of working age in 2012 would be occupationally induced, the majority of which would be lung cancers (26,000), leukaemias (8,000) and malignant mesotheliomas (7,500) (Carey et al., 2017). While acknowledging that this estimate is lower than other studies, the

[20] Current Group 1 carcinogens can be located at https://www.cancer.org/healthy/cancer-causes/general-info/known-and-probable-human-carcinogens.html

authors pointed out that it is “not directly comparable to past estimates of the occupational cancer burden because they describe…future cancers in currently exposed [workers] versus current cancers due to past exposures” (Carey et al., 2017).

As indicated above, the assessment of workplace versus non-workplace exposure in the development of a cancer may be difficult, hence any estimate of incidence is subject to a range of confounders. There are various models of cancer development, ranging from two-stage (initiation and promotion) and four-stage (initiation, promotion, malignant transformation, tumour progression) models (e.g. Weston & Harris, 2003) to a wide range of complex models and model systems (Breitenbach & Hoffmann, 2018).

DNA damage repair mechanisms can operate at the level of an organism, such that deleterious changes are not transmitted intergenerationally, or at the tissue or organ level, such that intragenerational damage is minimised or eliminated (Huang & Zhou, 2021). There are three possible outcomes to a genetic change in DNA at the cellular level that may lead to a mutation: successful repair without pathology; cell death, which eliminates the altered DNA; or incorporation of the altered DNA into the genome, leading to possible pathology (e.g. cancer).

Not all cancers are due to mutation in chromosomal DNA. *Epigenetic mechanisms* are now considered a cause of cancer (e.g. Baylin & Jones, 2016). Epigenetic processes can be altered by the effect of toxins on a range of biochemical and enzymatic mechanisms impacting the outcome of gene expression. These mechanisms include methylation of the bases in DNA, modification of histones that are the proteins associated with chromosomal DNA, non-coding RNA and micro RNA (Kumar et al., 2020). The switching on and off of genes is a normal process in all biological systems and is part of the development of each human during embryonic and foetal life.

4.2 Reproductive and developmental toxins

Reproductive and developmental toxins differ from other groups of toxins in that they may not only impact the health of exposed workers but can also affect the ability of workers to have children and increase the possibility of having children with birth defects. In the past, the inability of a couple to conceive was assumed to be a female issue. In the context of occupational exposure, many substances can have a range of effects on reproduction, including infertility in both males and females.

In males, primordial germ cells originate in the first three to six months of foetal life; these cells develop into spermatogonia and during puberty they undergo the first and second meiotic divisions[21] to produce sperm. Sperm are produced in large numbers through most of adult life. In females, the primordial oocytes develop during the first three to six months of foetal life and undergo the first meiotic division prior to birth. The total number of ova in females is set before birth. (See, for example, Marieb & Keller, 2022.)

Both male and female reproduction, including the cycles of gamete[22] production, are controlled by positive and negative feedback mechanisms with a range of hormones, including gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinising hormone (LH), testosterone, oestradiol and progesterone that form the hypothalamic–pituitary–gonadal axis (Figure 3).

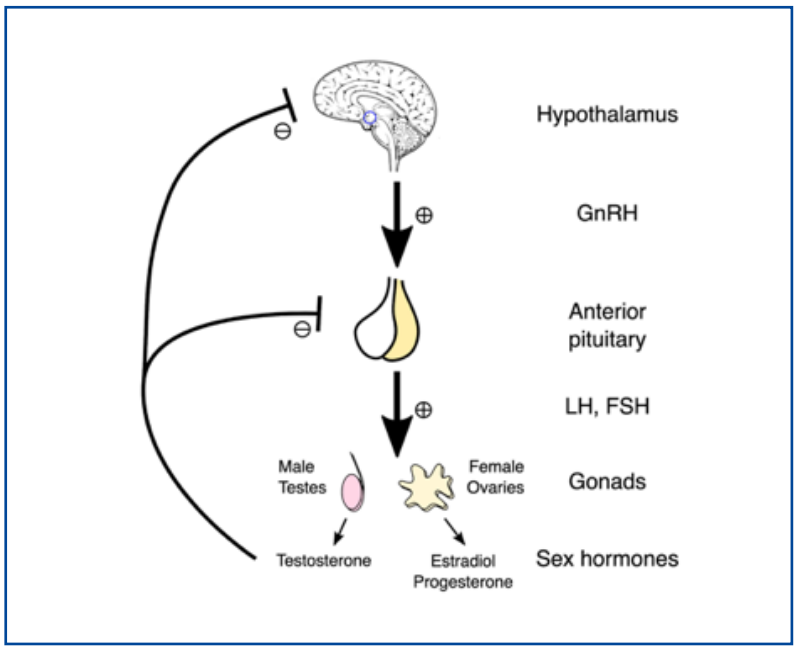

Figure 3: Hypothalamic–pituitary–gonadal hormonal axis (Kong et al., 2014)[23]

[21] Meiotic division – meiosis – is required to produce egg and sperm cells for sexual reproduction. It reduces the number of chromosomes in parent cells by half because it only packs one of each type of chromosome into the gamete.

[22] Gametes – reproductive cells (eggs and sperm) produced during meiosis – are haploid cells that carry only one copy of each chromosome, unlike diploid body cells that carry two copies of each chromosome.

[23] Reproduced in Wikimedia Commons: https://commons.wikimedia.org/wiki/File:Hypothalamic%E2%80%93pituitary%E2%80%93gonadal_axis_in_males.png

This hormonal control of reproduction by the endocrine system of the body involves many complex biochemical processes that can be influenced both internally (within the body) and externally (by the environment). Disruption of these processes may cause changes to gamete production. For example, in 1977, dibromochloropropane (DBCP) – a compound used extensively as a nematicide for crops – was associated with infertility in the male workers involved in its production at a California pesticide manufacturing plant. These workers had elevated incidences of azoospermia (no sperm in the ejaculate) or oligozoospermia (low sperm count in the ejaculate) (Whorton et al., 1977). Eight years later, a study of 15 of the exposed workers (eight with azoospermia, seven with oligozoospermia) found that only three of the azoospermia group and four of the oligozoospermia group had improved reproductive status; for the remainder, their semen would be unlikely to fertilise an ovum (Potashnik & Yanai-Inbar, 1987). It was noted that the five workers with non-improved azoospermia had elevated levels of follicle-stimulating hormone eight years after the initial observations (Potashnik & Yanai-Inbar, 1987).

Endogenous chemicals that cause such hormonal disruption are known as **endocrine-disrupting chemicals (EDCs)**, which can be natural or synthetic chemicals that come from a source external to the body (xenobiotics). EDCs may mimic or interfere in various ways (e.g. block hormone receptors, block the synthesis of hormones) with the expression of the hormones of the endocrine system. EDCs will be encountered in both work and non-work environments. A review of studies of the effects of EDCs on male reproductive health identified 20 such EDCs (Sharma et al., 2020) (Table 2). Table 2 is essentially a hazard list that may alert OHS professionals to the potential for risk to exposed workers' reproductive health and to a need for prompt assessment of the use of these EDCs. Any assessment needs to consider specific safety data sheets, the exposure (dose) and frequency of exposure as well as biological variability as indicated in the dose-response curve (Figure 1). While exposures to EDCs will not necessarily result in any reproductive dysfunction, prolonged exposure or exposure to a range of EDCs may need to be assessed.

Table 2: Summary of postulated EDCs affecting male reproduction and their common use (Sharma et al., 2020)

Postulated EDC	Common uses/exposure
Bisphenol A	Manufacture of polycarbonate plastics; used in food packaging, water containers, dental sealants
Phthalates	Plasticisers; used in packaging, personal care products, industrial plastics, medical devices, pharmaceuticals
Parabens (e.g. butylparaben)	Preservative; found in food, cosmetics, toiletries, medications
Nonylphenol ethoxylates	Detergents, paint, pesticides, personal care products, plastics
Tributyltin chloride	Consumer goods and industrial products

Postulated EDC	Common uses/exposure
Genistein	Soy-derived products
Silver nanoparticles	Antibiotics, burn wound dressings, surgical devices, prosthetic bones
Perfluoroalkyl compounds	Carpets, textiles, paper
Triclosan	Personal care, household, industrial and veterinary products
Octylphenol	Sewage, farm animals' tissues grazed on sewage-contaminated ground
Microcystin-LR	Fresh water
Chlorotriazine herbicides (e.g. atrazine)	Herbicide, ground water
Insecticides	Fresh produce, bioaccumulation in the environment
Glyphosate	Herbicide
Dichlorodiphenyltrichloroethane	Pesticide
Vinclozolin	Fungicide used in fruit and vegetables
Benzo[a]pyrene	Formed from incomplete combustion of organic material, e.g. diesel exhaust, cigarette smoke, charcoal cooked food, cooking oil fumes, industrial waste by-products
Polycyclic aromatic hydrocarbons	Environmental pollutant from incomplete combustion of coal, petrol, oil and wood
Polybrominated diphenyl ethers	Flame retardants used in building materials, furnishings, electronics
Dioxins	By-products of chlorine bleaching of pulp and paper, manufacture of certain pesticides, and incineration of medical waste and plastics

In California, Proposition 65 (i.e. the *Safe Drinking Water and Toxic Enforcement Act of 1986*) is a law that:

> …protects the state's drinking water sources from being contaminated with chemicals known to cause cancer, birth defects [teratogenicity] or other reproductive harm…[It] requires the state to maintain and update a list of chemicals known to the state to cause cancer or reproductive toxicity. (OEHHA, 2022)

The 2022 iteration of the Proposition 65 list is summarised in Table 3. While the listed EDCs are primarily related to contamination of drinking water, they may be present in workplaces, with potentially an additive or synergistic effect with respect to their toxicity. Note the larger number of EDCs implicated in male reproductive health in Table 3. Many EDCs have oestrogenic and anti-androgenic properties and combinations of these may have 'greater-than-additive' adverse effects on male reproductive health (De Falco et al., 2015) in comparison to EDCs that affect female reproductive health. Kortenkamp (2020) suggested that when considering male reproductive disorders that originate in foetal exposure, mixtures

of chemicals rather than single chemicals should be considered (e.g. phthalates, androgen-receptor antagonists and inhibitors of steroidogenic enzymes, dioxin-like pollutants and pain killers such as paracetamol, aspirin and ibuprofen).

Table 3: Number of EDCs on California's Proposition 65 list in 2022 (OEHHA, 2022)

Total Listed EDCs	861
EDCs implicated in male reproduction issues	321
EDCs implicated in female reproduction issues	58
EDCs implicated in developmental issues	289
EDCs implicated in cancer	621

A range of EDCs may diminish sperm production, with an obvious effect on fertility, and cause damage to sperm that affects the viability of an embryo and/or foetus. In response to a paucity of infertility data, in 2012 the World Health Organisation began an evidence-gathering process; outcomes of this included the acknowledgement of research challenges associated with the diagnosis of male infertility (Barratt et al., 2017). Assessing the reproductive consequences in males exposed to potential EDCs in the workplace is complicated by the sensitive nature of the subject, the considerable reliance on self-reporting, and a range of personal and ethical issues that make the identification and study of reproductive toxicity in males difficult (Schrader & Marlow, 2014).

In terms of intergenerational birth defects associated with sperm quality, Pastuszak et al. (2019) suggested that the quality of sperm may not increase the risk of birth defects (congenital malformations) in offspring, while others stated that further research is required before definitive conclusions can be made (Hanson et al., 2017). Consequently, the issue of the involvement of sperm affected by EDCs and possible consequences for intergenerational anomalies resulting from DNA damage or epigenetic mechanisms remains open.

As stated in section 4.2, the total number of ova in females is set before birth; however, a range of female reproductive health issues – including altered reproductive development and fertility and the onset of menopause – may be related to EDC interference (Fowler et al., 2012). Also, many EDCs can impact the development of a foetus and, in extreme cases, may lead to severe physical and/or mental disorders in offspring. EDCs and other chemical groups that can produce serious consequences for affected children are known as teratogens (section 4.3).

In 2018, the United Nations produced a list of 45 EDCs[24] that can alter the functions of the endocrine system and, consequently, lead to adverse health outcomes. The list met with considerable controversy; while some concerned parties thought it was inadequate given the number of known EDCs, others thought it was too extensive.

Ten groups of EDCs most commonly associated with human reproductive disorders are listed in Table 4 along with summaries of their physiological and pharmacological effects. The information was compiled as part of a process of developing a job exposure matrix to assist epidemiological studies in the correlation of exposure and adverse reproductive health outcomes (Brouwers et al., 2009).

Table 4: Chemical groups of substances with endocrine-disrupting potential (Brouwers et al., 2009)

Chemical group	Subgroups	Description	Reported endocrine-disrupting effects
1. Polycyclic aromatic hydrocarbons	None	Formed by incomplete combustion of carbon-containing fuels Constituents in tar	Anti-oestrogenic effects in vitro
2. Polychlorinated organic compounds	2.1 Polychlorinated biphenyls (PCBs) 2.2 Dioxins, furans, polychlorinated naphthalene (PCN) 2.3 Hexachlorobenzene (HCB) 2.4 Octachlorostyrene (OCS)	Produced as by-products during waste incineration and industrial processes involving carbon and chlorine (e.g. during metal, solvent or pesticide manufacturing) PCBs: until 1970s widely used as insulating and cooling fluids	PCBs, dioxins, furans, PCN: interfere with steroid synthesis through aryl hydrocarbon receptor binding (CDC) HCB: affects male and female fertility in animal studies OCS: metabolites possibly interfere with thyroid homeostasis through binding with plasma proteins
3. Pesticides	3.1 Organochlorines 3.2 Carbamates 3.3 Organophosphates 3.4 Tributyltin 3.5 Pyrethroids 3.6 Other pesticides	Used in agriculture Other purposes include wood preservation, anti-fouling, parasite treatment and public hygiene	Oestrogenic or anti-androgenic effects in vitro, reproductive toxicity in animal models, and subfertility or endocrine alterations in human studies

[24] The *UN List of Identified Endocrine Disrupting Chemicals* is available at https://www.chemsafetypro.com/Topics/Restriction/UN_list_identified_endocrine_disrupting_chemicals_EDCs.html

Chemical group	Subgroups	Description	Reported endocrine-disrupting effects
4. Phthalates	4.1 Di-2-ethylhexyl phthalate (DEHP), di-isononyl phthalate (DNP), di-n-hexyl phthalate (DHP) 4.2 Benzyl butyl phthalate (BBP) 4.3 Dibutyl phthalate (DBP) 4.4 Diethyl phthalate (DEP)	Many industrial applications High molecular weight phthalates (DEHP, DNP, DHP) primarily used as plasticisers in polyvinyl chloride (PVC) Low molecular weight phthalates (BBP, DBP, DEP) used as solvents and plasticisers in cosmetics, adhesives, ink, dyes and plastic packaging	DEHP, DNP, DHP, BBP, DBP: affect the development of male reproductive organs in animal studies DEP, DBP, BBP: possibly interfere with male reproductive hormone levels in children
5. Organic solvents	5.1 Ethylene glycol ethers (EGEs) 5.2 Styrene 5.3 Toluene 5.4 Xylene 5.5 Trichloroethylene (TCE) 5.6 Perchloroethylene (PCE)	EGEs, toluene, xylene: widely used in, for example, paints, adhesives, thinners, lacquers and resins Styrene: used for producing polystyrene plastics and resins TCE, PCE: used for metal degreasing and other industrial cleaning purposes	EGEs: reproductive toxicity in animal studies and possibly reduced fertility and menstrual length variability in women Styrene: styrene dimers and trimers bind to oestrogen receptors in vitro Toluene, xylene, TCE: possibly interfere with reproductive hormone levels in humans PCE: dry cleaning has been associated with menstrual disorders, infertility and delayed conception in women
6. Bisphenol A	None	Used in the production of polycarbonate plastic and epoxy resins	Oestrogenic effects according to various in vitro and in vivo studies
7. Alkylphenolic compounds	7.1 Alkylphenolic ethoxylates (APEs) 7.2 Alkylphenols (APs)	APEs: commonly used surfactants in, for example, detergents, pesticides and cosmetics APs: primarily used to produce APEs	APE metabolites, which include APs and short chain APEs, interact with oestrogen receptors in vitro
8. Brominated flame retardants	8.1 Tetrabromobisphenol A (TBBPA) 8.2 Hexabromocyclodecane (HBCD) 8.3 Polybrominated disphenyl ethers (PBDEs)	Widely used in the polymer industry; for example, in the production of PVC, epoxy resins, polyester and rubber	TBBPA, HBCD, PBDEs: interfere with thyroid hormone levels TBBPA, PBDEs: possibly interfere with oestrogen metabolism through oestrogen

Chemical group	Subgroups	Description	Reported endocrine-disrupting effects
			sulfotransferase inhibition
9. Metals	9.1 Arsenic 9.2 Cadmium 9.3 Copper 9.4 Lead 9.5 Mercury	Used in, for example, the electrical/electronics industry, for construction, in batteries, dyes, pesticides and dental amalgam, and as chemical intermediates	Arsenic: inhibits glucocorticoid gene transcription in vitro and thought to have similar effects on other steroid receptors Cadmium, coppers, lead, mercury: testicular toxicity in animal models or altered hormone levels and/or male subfertility in humans
10. Miscellaneous	10.1 Benzophenones 10.2 Parabens 10.3 Siloxanes	Benzophenones: UV screens used in cosmetics and the plastic industry Parabens: widely used preservatives in cosmetics and the pharmaceutical industry Siloxanes: intermediates in the polymer industry and ingredients in personal care products and precision cleaning agents	Benzophenones: bind with oestrogen receptors in vitro and exert oestrogenic effects in animal studies Parabens: oestrogenic activity in vitro and in animal studies Siloxanes: oestrogenic and anti-oestrogenic activity in animal studies

Common adverse reproductive outcomes in males and females are presented in Table 5.

Table 5: Male and female reproductive disorders for which EDC exposure is a risk (Marlatt et al., 2022)

Disorder	
Fertility	Capacity to establish a clinical pregnancy
Infertility	Failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse
Decline in fertility	Increase of 0.37% and 0.29% per year in age-standardized prevalence of infertility for females and males, respectively, for the period from 1990 to 2017 2009-2010 Canadian Community Health Survey: infertility prevalence ranges from 11.5% to 15.7%, significant increase compared with previous national estimates of 5.4% (in 1984) and 8.5% (in 1992)

Disorder	
Miscarriage	Loss of pregnancy before viability 23 million miscarriages per year worldwide; pooled risk of miscarriage of 15.3%
Men	
Cryptorchidism	Non-descent of one or both testicles in the scrotum at birth
Hypospadias	Congenital malformation of the penis where the opening of the urethra is in the underside of the penis instead of its tip
Testicular cancer	2019 Canadian Cancer Statistics Annual Report: 1.3% yearly increase in its incidence between 1984 and 2015
Decrease in sperm count and quality	Decline of 52.4% in sperm concentration between 1973 and 2001 in western countries
Decrease in testosterone levels	Age-independent decline in total serum testosterone
Women	
Early menopause	Entry to menopause age 40–45 years old
Primary ovarian insufficiency	Prior to age 40 cessation of ovarian activity Oligo/amenorrhea (for at least 4 months) Elevated serum follicle-stimulating hormone (FSH) levels (>25IU/l) on two occasions >4 weeks apart
Polycystic ovarian syndrome	Oligo/anovulation, hyperandrogenism, polycystic ovarian morphology, as well as metabolic dysfunction Increase of 1.45% from 2007 to 2017 in global age-standardized incidence rate
Endometriosis	Ectopic endometrium (presence of endometrial glands and stroma outside the uterus)
Uterine fibroids	Benign tumors of the female reproductive tract Cause of menorrhagia, pelvic pain, and pregnancy complications

4.3 Teratogens

Teratogens are toxic agents that may cause embryonic or foetal malformations (e.g. Butler & Als, 2020). Much of our understanding of teratogens and their serious ramifications for those exposed at a critical stage of embryonic development has resulted from methyl mercury poisoning in Japan in the 1950s and 1960s (Hachiya, 2006; Ekino et al., 2007) and the use of the drug thalidomide to treat morning sickness in pregnant women in the late 1950s and early 1960s (Vargesson, 2015).

Exposure to methyl mercury became known as Minamata disease because the first well-documented outbreak occurred in Minimata, Japan (Ekino et al., 2007). Caused by daily

consumption of seafood contaminated with methyl mercury (MeHg), the severe neurological disease resulted in both acute and chronic poisoning cases characterised by neurological symptoms.

> Acute adult cases of MeHg poisoning present the following manifestations: blurred vision, hearing impairment, olfactory and gustatory disturbances, ataxic gait, clumsiness of the hands, dysarthria, and somatosensory and psychiatric disorders. Children born to mothers exposed to MeHg show extensive spongiosis of the cerebral cortex. … [Affected children demonstrated] serious disturbances in mental and motor developments [and] showed significant impairments in chewing, swallowing, speech, gait, other coordination and involuntary movement. … Thus, MeHg was recognized as being highly neurotoxic to the human brain, and most especially to the developing brain. (Ekino et al., 2007, pp. 134, 136)

A chemical company in Minimata was responsible for the poisoning; it used mercury as a catalyst in the production of acetaldehyde, an intermediate in the production of a range of plastics (Ekino et al., 2007; Hachiya, 2006). For many years, the factory's wastewater containing the organic methyl mercury had been discharged into Minimata Bay, where it accumulated in the marine environment before poisoning was recognised in the local population.

Thalidomide – developed by a German pharmaceutical company – was marketed in 46 countries and became one of the world's largest selling drugs, resulting in "the biggest man-made medical disaster" (Vargesson, 2015, p. 140). A range of disabilities occurred in the surviving children of women who took thalidomide to treat morning sickness; these included shortening and absence of limbs, malformation of hands and digits, sensory impairment, facial disfigurement, eye and ear damage, and nerve and central nervous system damage. Although many victims of thalidomide lead full and productive lives, "many of the survivors are experiencing early onset age related issues, such as osteoarthritis, joint mobility issues and coronary heart disease" (Vargesson, 2015, p. 141). Thalidomide is a powerful teratogen with epigenetic effects (Shortt et al., 2013), but it does not have any intergenerational effects as the children of thalidomide victims show no signs of the condition of their parents.[25]

Exposure during pregnancy to a range of chemicals, including EDCs (section 4.2), can influence embryonic and foetal development, especially during the first trimester. Exposure during early pregnancy to workplace chemicals that are teratogenic or potentially teratogenic can have dire consequences for the developing embryo when major systems, including the nervous, cardiovascular and renal systems as well as limbs, eyes, ears, teeth, palate and external genitalia are developing. Maternal exposure to EDCs can lead to urinogenital (urinary) anomalies of the kidney and urinary tract in the offspring (Spinder et al., 2022).

> In utero sexual differentiation and urinogenital tract formation begin…very early in pregnancy, around the 4th gestational week, and continue until the 15th week. For the

[25] For more information, see The Thalidomide Trust at https://www.thalidomidetrust.org/about-us/about-thalidomide/

> majority of working women, pregnancy is detected only after the 5th or 6th gestational week. We also know that socioeconomically disadvantaged women tend to have important delays in pregnancy detection and first access to prenatal care. (Messerlian et al., 2022)

Messerlian et al. (2022) found that late detection of pregnancy by workers in industries in which EDCs are common (e.g. agriculture, cleaning) can have lifelong consequences for affected embryos/foetuses and suggested that such job areas (Table 6) be targeted for primary, secondary and tertiary prevention strategies. Although broad categories, the "prioritised" occupations may have relevance for OHS professionals working in or across these areas. As noted previously, it is important to make appropriate use of safety data sheets and assessment of the extent of real and/or potential exposure, bearing in mind biological variability. Importantly, when considering use of a 'three-prong' approach of primary, secondary and tertiary intervention,[26] primary prevention strategies to eliminate or reduce exposure should always take precedence. By comparison, secondary and tertiary prevention strategies (such as management and remedial support, respectively) generally have relatively limited value but may be useful in, for example, instances of accidental exposure that are not part of workers' usual activities.

Table 6: Prioritised occupations and their exposure to EDCs for preconception and prenatal primary, secondary and tertiary prevention strategies (Messerlian et al., 2022)

Prioritised occupations	Example EDCs implicated in potential teratogenesis
Agricultural workers	Pesticides, organic solvents, alkylphenolic compounds
Beauticians, hairdressers, cleaners	Phenols (e.g. bisphenols, triclosan, benzophenones), parabens, phthalates, siloxanes, alkylphenolic compounds
Laboratory technicians, medical/chemistry industry	Organic solvents, alkylphenolic compounds, heavy metals, polychlorinated organic compounds, perfluorochemicals
Metallurgic, electronic, and other industry	Heavy metals, polycyclic aromatic hydrocarbons, brominated flame retardants

[26] Cooper and Cartwright's (1997) "three-prong intervention strategy" for reducing workplace stress included: *primary prevention*, involving taking action to eliminate or modify sources of stress (stressor reduction); *secondary prevention*, involving prompt detection and management to limit damage (stressor management); and *tertiary prevention*, which is concerned with the treatment, rehabilitation and recovery process (remedial support) (Cooper & Cartwright, 1997).

5 Measures to protect workers

As discussed in section 2, exposure to many and varied workplace chemicals can result in acute and/or chronic health conditions. Any worker may react in a unique way to a chemical exposure that is related to the extent and duration of the exposure and their genetic makeup, which highlights the concepts of dose response and human variability. Consequently, protecting workers is a complex endeavour.

Figure 4 summarises the pathway from occupational exposure (via inhalation and dermal routes) and the aspects that influence whether a worker remains healthy or succumbs to an adverse health effect.

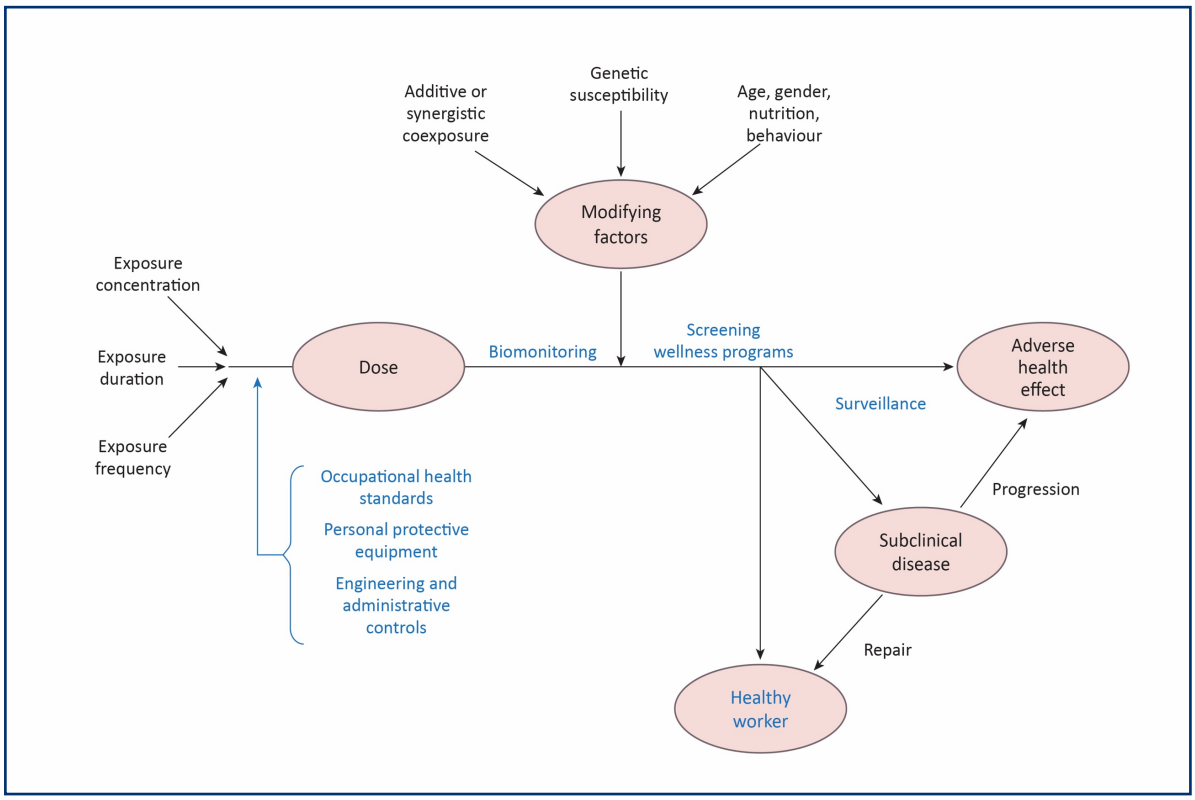

Figure 4: Pathway from exposure to disease, showing modifying factors and opportunities for intervention (Thorne, 2021, p. 582)

Measures to protect workers have been developed in most Australian jurisdictions over many years; these include work-specific legislation, monitoring work environments (occupational hygiene), monitoring workers' health status (biological/health monitoring) and

health promotion interventions (public health methodologies), all of which have contributed to safer and healthier workplaces. In Australia, professional bodies associated with the scientific protection of workers' health include the Australian Institute of Health and Safety (AIHS) (formerly the Safety Institute of Australia), the Australian Institute of Occupational Hygiene (AIOH), the Australian Faculty of Occupational and Environmental Medicine (AFOEM) and the Australian and New Zealand Society of Occupational Medicine (ANZSOM). The AIHS, AIOH, AFOEM and ANZSOM all have a basis in science and support workplace monitoring of adverse exposures to chemical, physical, medical and wellbeing issues within individual workplaces.

OHS BoK 17.1 Managing Hazardous Chemicals outlines a systematic and systemic approach to worker protection via the chemical management stages of hazard identification, risk assessment and control, monitoring and product stewardship. *OHS BoK* 17.3 Dusts, Fumes and Fibres addresses prevention and control of worker exposure to dusts, fumes and fibres, and provides information about exposure monitoring strategies.

5.1 Future directions for worker health surveillance

Currently, two potential tests for the type of genetic damage that may precede the development of cancer exist. These tests are based on the formation and monitoring of DNA adducts[27] that are known to increase in the presence of mutagens (Totsuka et al., 2020). Association between changes in telomere length[28] and adverse health have been shown to be linked to the development of occupational exposures to chemicals (Shoeb et al., 2021).

To date, health surveillance and monitoring have been based on what might be called pre-genetic toxicology. Perhaps the way of the future in protecting the health of workers exposed to known toxicants or potential carcinogens (IARC Group 1 and Group 2; section 4.1) will leverage advances in molecular biotechnology to develop tests for genetic damage to supplement or replace current hygiene and health monitoring. For example, tests based on the polymerase chain reaction (PCR) such as those widely used during the Covid-19

[27] A DNA adduct is a segment of DNA that is bound to a carcinogen. The adduct may be removed during DNA repair within the cell nucleus. If the DNA adduct is removed, it can be used as a biomarker for exposure to carcinogens. Various techniques are available to identify and quantify the amount of DNA adduct present in tissue samples; currently, however, these processes are complicated and expensive.

[28] A telomere – the word derived from the Greek *telos* (end) and *meros* (part) – is the terminal part of a chromosome. A telomere is made up of a unique sequence of repeated nucleotides and a group of proteins (shelterins). Changes in the length of the telomere and the shelterin protein complex have been shown to be associated with chemical exposures and hence have potential use as biomarkers of exposure.

pandemic could be developed to assess damage or changes to DNA due to life's various exposures, including those at work.

6 Implications for OHS practice

As stated by Thorne (2021, p. 591), "The working environment will always have the potential to overexpose workers to toxicants." Risk assessment and development of effective controls to manage hazardous chemicals requires specialist expertise. As explained in *OHS Bok* 17.1 Managing Hazardous Chemicals and 17.3 Dusts, Fumes and Fibres, generalist OHS professionals will need to take a collaborative approach to managing hazardous chemicals. However, knowledge of the general principles of toxicology will enable OHS professionals to make informed observations, recognise triggers for action and effectively engage with specialists to reduce the risks of adverse health effects of hazardous chemicals.[29]

7 Summary

Toxicology has been referred to as the 'science of safety.' Chemical exposure in both the non-work and work environments can increase the cumulative dose and/or response to toxic chemicals. Understanding the potential health effects of the multitude of chemicals used in industry, complicated by the constant appearance of new chemical compounds, presents a great challenge for generalist OHS professionals.

This chapter provides an overview of how exposure to occupational chemicals can have adverse health effects. Drawing on OHS-relevant examples, it explains some general principles of toxicology – the dose-response relationship, LD_{50} values, acute and chronic toxicity, absorption, distribution, excretion and biotransformation. Various classifications of toxins are introduced, with an emphasis on examples of carcinogens, reproductive and developmental toxins, and teratogens. The chapter briefly considers measures to protect workers (as this topic is addressed in other chapters of the *OHS Body of Knowledge*) and future directions for worker health surveillance. Armed with knowledge of toxicological principles, the generalist OHS professional can effectively contribute to chemical hazard identification, risk assessment and control, monitoring and product stewardship.

[29] See also *OHS BoK* 35 Mitigation of Health Impacts, *OHS Bok* 36 Emergency Management, *OHS BoK* 31.1 Risk and *OHS BoK* 34.1 Prevention and Intervention.

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