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Environmental Toxicology

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Guest Editorial

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The use of toxicology in the protection of public health has a long history. There is a clear societal desire to benefit from the scientific discipline inherent in toxicological investigation, and to apply the data generated to quantitative risk assessment of potential toxicological outcomes following exposure to a range of materials in the modern environment. The set of papers presented in this issue of the Bulletin shows the range of interests currently associated with the use of toxicology.

David Simon's paper is a condensed yet very readable description of the history of toxicology – what it is, where it comes from and what its value is to society. Toxicology essentially evolved from the nascent material sciences of the 19th century, especially that of the organic chemical industry, and from discoveries in medicine, which drove the development of the science of toxicology. Importantly, this paper also forecasts toxicology's trajectory into the future and the importance of the science for society. Ian Delaere, Jim Fitzgerald and David Simon's paper is somewhat of a primer on toxicology, providing the readership of the Bulletin with a reference framework in which the subsequent articles can be placed. It outlines the fundamentals and principles of toxicology and the tools used in addressing toxicological problems. It explains the breadth of the science – the wide range of disciplines it encompasses in studying the interactions of poisons on biological systems. Maintaining population health is a multi-faceted endeavour in which toxicology has a central role.

One of the primary roles of toxicology is in guiding public health risk perception. Common fears such as the impact of pesticides and commonly used materials (e.g. bisphenol A) on modern society are a reflection of the greater public's level of understanding of the benefits, detriments and risks associated with the use of such materials. In the past such fears have been well founded, as is clearly



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seen in consideration of mistakes made in the use of materials such as asbestos and dioxin-containing pesticides. Brian Priestly's paper shows the reader that a logical framework exists to conduct environmental health risk assessments (EHRAs). The concepts used in EHRA are constantly being updated as science progresses. The guiding principles of EHRA have been applied to addressing toxicological problems and providing more competent datasets, as outlined in some detail in subsequent articles in this issue. As part of this assessment of risk, we need to recognise that analytical competence allows us to measure smaller and smaller concentrations of compounds. However, just because we can measure at this level does not mean that vanishingly small concentrations of toxins present a risk. It is for this reason that the concept of the 'threshold of toxicological concern' has been developed, as described by David Simon in his article.

There are definitional issues when one talks about some aspects of toxicology. For example, environmental toxicology is a public health rather than an ecological health discipline. Environmental toxicology might be described as the impact of the environment on humans, while ecotoxicology is arguably the impact of humans on the environment. Increasing demand for training and appropriate levels of registration of practitioners of toxicology has led to the recent establishment of the Australasian College of Toxicology and Risk Assessment (ACTRA). Its role in training, education and registration is starting to be accepted by most practising qualified toxicologists in Australia. Although toxicology is a component of pharmacology, the role that toxicologists fill is quite different to that of pharmacologists. There is also a need to recognise that toxicology has a quite different role to play.

In Australia there are direct economic consequences from toxic compounds and organisms in several sectors. For example, pesticides in the agricultural sector and the presence of marine stingers (e.g. the Irukandji jellyfish) in the burgeoning tourism sector are putting bounds on economic expansion. In agriculture, the need to restrict pesticide residues in agricultural products below prescribed maximum residue limits is just as critical to their marketability internationally as is the presence (and regulation) of other undesirable components (e.g. heavy metals). In the article on shellfish toxins, David Cunliffe draws attention to the need for quality control in one such area of fisheries. Naturally derived toxins in seafood such as ciguatera in tropical marine fish are a particular issue – because of

a lack of understanding of not only the toxins involved but also their mode of action and derivation. The same applies when we attempt to deal with envenomation by a range of poorly characterised jellyfish and the consequences of encounters with them by visitors and locals alike.

No two humans are identical. Our individual capacity to deal with toxicological insult varies enormously. The background to toxicogenomics, presented by Jorma Ahokas, explains why we respond differently to toxins. Typical of the susceptible populations are those listed by Peter Sly and Jim Fitzgerald, who discuss two vulnerable subpopulations with unique susceptibility to chemicals — children and multiple chemical sensitivity (MCS) sufferers. Children are more vulnerable to environmental exposures, receiving a higher 'dose' from a given level of exposure. Thus, they require special consideration when framing environmental standards, and deserve to be protected by legislation.

To ensure a nationally consistent approach to the assessment and management of the environment, a number of National Environment Protection Measures (NEPM) have been adopted through legislative frameworks developed by the Commonwealth Government. Local jurisdictions are responsible for implementation of NEPMs, and an example is given in the paper by Richard Evans and his team on the Clovelly Park contaminated site.

Maintenance of consumer product safety is typical of the role that toxicology plays in Australia. A number of agencies are involved in product control, such as Food Standards Australia and New Zealand, the Australian Competition and Consumer Commission, the Australian Pesticides and Veterinary Medicines Authority, and the Therapeutic Goods Administration. Extensive information on this involvement is provided in the article on product safety by Adam Capon and Vicky Sheppeard. Medicines are normally considered to be above reproach because of the complex regulatory environment in which they are registered. However, as indicated by Ian Delaere and Carolyn Lewis, although 'complementary medicines' are regulated as medicines under the *Therapeutic Goods Act 1989* in Australia, there is ample evidence of adulteration of some of these compounds, and of the toxicological consequences.

There are a number of new challenges in toxicological investigation, for example the implications of the use of very small, particulate materials. Sam Bruschi's

elegant paper on nanotoxicology, which deals simply with a complex topic, concludes that in the face of the number of products that now incorporate nanoparticles, caution is needed to ensure we get the benefits and not the adverse effects of these materials. Application of the precautionary principle and a conservative approach is required.

The greatest challenge that toxicology faces is an appropriate attribution of levels of toxin exposure. In many circumstances measurements are not or cannot be taken of exposures. The toxicologist has to turn to imperfect models, which invariably overestimate exposure, to provide some protection in measurement of risk. This is inevitable in a multidisciplinary topic that aims, within the public health sphere, to prevent detriment rather than cure the outcomes of toxic exposures. In the absence of competent datasets, there are and have been opportunities to skew perceptions of risk—often in an alarmist fashion. Toxicologists can introduce a balanced perspective and generate the necessary exposure data to allay public fears. Toxicology will thus continue to play a major role in the protection of public health.

A brief history of toxicology

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Why a history?

If one records history, one must presuppose that someone will read it. The question could be, 'Why read history?'¹ For a scientist or public health practitioner, does reading history help in one's endeavour to better the health of people, especially a population? Some maintain that both the explanation and the understanding of events are transmitted through historical narrative. History may be important if the reader can extract 'lessons' – if it teaches us something of practical relevance for the present and future, it is of use. Notwithstanding, we know that many scientists dismiss history because 'science is revolutionary', as Claude Bernard (1813–1878) is purported to have stated. On the other hand, toxicological history can provide entertainment, particularly if it involves the intrigue of poisoning. However, history must be more than this. In Tolstoy's portrayal of history, which he regards as an aggregate of finite time events, humans cannot separate themselves from history because it intrudes into life.² Chemicals have intruded into everyone's life, in all generations – whether extracted from plants or ore, or manufactured as single entities or mixtures; whether used in attempts to prevent or alleviate illness or for cosmetic purposes, or to cause illness and death. Indeed 'one cannot escape history', and without it one will become insular from the very society the science is endeavouring to help.³

The history of toxins says as much about the behaviour of humans and their communities as it does about the science. From the antiquities until today, the need to deal with poisoning – both poisons and remedies – has been a major endeavour. However, despite the past millennia, toxicology is really only a recent science that has been advanced through revolution, crises and war.⁴

Toxins and remedies: the dose

One should not dismiss the endeavours of those Renaissance thinkers who, in their attempts to find remedies, mixed pragmatism with philosophy, mysticism and superstition, but began to understand the actions of chemicals on the human body. This early science of toxicology had three aspects — chemicals as remedies, chemicals as toxins, and remedies as toxins (or toxins

as remedies), all being differentiated, according to Paracelsus (Theophrastus Philippus Aureolus Bombastus von Hohenheim) (1493–1541), by the dose.⁵ The science of chemicals as remedies ultimately became pharmacology, and the science of chemicals as poisons, toxicology.

The indigenous populations of South America, and of many other countries, resorted cleverly to extracting poisons from species such as *Strychnos toxifera* (whose fruit looks like an apple⁶) and injecting the poison into their enemies using arrows as instruments. The identity of this plant was first made by Alexander von Humboldt (1769–1859), who also realised that different plants produced different toxins. Furthermore, he found that the poison contained curare, and that it would not deteriorate as rapidly if transported in hollow bamboo tubes. This is the origin of the common name ‘tubocurare’,⁶ and how the word *toxicus*, from the Greek *toxikon*, meaning ‘bow poison’, entered the vocabulary. More properly, the bow is the *toxon* and the *toxikon* the viscous organic plant extract that was applied to the tips of the arrows. The etymology of the word ‘toxin’ deserves much more credit than given here – like the history of toxicology, it is convoluted and full of intrigue. (A short history of toxicology by Watson and Wexler makes a great read, delving into the ancient history of arrows as a dose-delivery system.⁷) Words used to describe poisonous substances were obviously not limited to the Greeks, with the word ‘poison’, from the Latin *potionem* (being a drink), also entering the English language⁸ along with others such as *venom*.

In addition, the healers of illness, once alchemists, apothecaries and barbers, also cleverly resorted to injecting arrow tip poison, albeit somewhat more purified (as d-tubocurarine), into humans to relax the muscles of patients undergoing the rigors of tetanus in 1932 and later into patients undergoing general anaesthesia and surgery. This usage was first trialled by Griffith and Johnson in 1942.⁹ Indeed, the history of curare and its role in expanding the knowledge of the action of drugs is a fascinating read, including principal characters such as Claude Bernard. He demonstrated that animals could provide adequate data from which inferences on the effect or otherwise of toxins on humans could be derived, provided ‘appropriate differences [are] noted’.¹⁰

Toxicology as a science rises from the antiquities

It was scientists of the calibre of Claude Bernard who advanced the exactness of science as a tool in order to shake off, once and for all, the element of mysticism from whence medicine and the art of poisoning arose. He famously wrote, ‘When we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted’.¹¹ This was indeed a challenge to the immense volume of scientific and philosophical work that preceded this period, and to the mind-set change required to allow data from animals to be applied to humans. Indeed, Bernard’s family was to suffer as a consequence of his pursuit of experimental medicine – it is reported that matrimonial bliss was forgone for the pursuit of knowledge. The innovation of experimentation, although not new, required as its basis a thorough understanding of physiology, which Bernard, in particular, advanced under the umbrella of medicine, publishing some 14 volumes on the subject.¹²

The development of the science of toxicology followed the shift in the fundamentals of the way people and society thought and explained themselves and their environment. The birth of modern medicine required the elimination of the link between mysticism and superstition, and illness and disease. Some have suggested that it was after the death of Galen (129–200), a surgeon and skilled physiologist, that there followed a long transitional period into modern medicine, although the beginning of this period did nothing to further the science.⁷ Until this time, medicine had travelled a route that was little unchanged from the days of ancient Egypt and Mesopotamia, where illness was believed to be uncontrollable by humans. Notwithstanding, the use of poisons such as hemlock (loved by the Greeks), opium and lead had been discussed in writings as early as circa 1500 BC, suggesting knowledge of substances as being either harmful or beneficial.⁴ Although Hippocrates (c. 400 BC) added to the knowledge, he did not reduce the confusion through his philosophy. The Greeks who followed merely carried on with the theory of the internal imbalances of ‘humours’ being the manifestation of all ills.¹³ The monastic period and the Middle Ages contributed little, and in the end toxicology only moved swiftly from an empirical science after the emergence of the analytical sciences, and in particular chemistry.¹⁴

Its beginnings are found in the work of Paracelsus. Although being an alchemist (from where the discipline of chemistry arose), he used the notion of spiritual substances (mercury, sulphur and salt),¹⁵ so making chemistry the key to explain causality.¹³ However, the forces of history sifted these notions, leaving behind the important facts that heavy metals can poison, occupational settings can expose one to toxins, and the greater the exposure (i.e. dose) the larger the effect, whether adverse or not.¹⁶ Indeed, his words linger today: 'Alle Ding sind Gift und nichts ohn Gift; allein die Dosis macht, dass ein Ding kein Gift ist' (loosely translated as 'All things are poison and nothing is without poison; only the dose permits something not to be poisonous').¹⁵ Paracelsus also deserves better recognition for introducing the need for experimentation, to understand the effect of chemicals on living organisms, and for the fact that he distinguished therapeutic from toxic properties.⁵

Forces that shaped the science

History shows that it was essentially material sciences, especially the organic chemical industry, that drove development of the science of toxicology. The need for new and better materials, manufactured more efficiently and in large quantities, shaped the Industrial Revolution and created an abundance of chemicals that quickly spilled over into the workplace and the environment. By 1880 there were 10 000 new compounds synthesised, including phosgene, mustard gas, chloroform, diethyl ether and carbonic acid.⁴ Nearly 130 years later the American Chemical Society boasts that 12 000 new chemicals are added to their database daily (this number includes genomic sequences).¹⁷ Although occupational issues were in the minds of some, such as Ulrich Ellenbog (1440–1499), who wrote of occupational requirements to avoid lead and mercury poisoning in metalworking, their importance was very slow in coming to the fore, even in the Industrial Revolution, where the dictum was maximum output—which required a well workforce.¹⁸ Eventually, the Germans saw this and implemented the first worker insurance laws in 1893, followed by England and, some 28 years later, the USA.¹⁸ However, along the way some edifying observations were made. For instance, epidemiology solved the issue of scrotal cancer among London chimney sweeps—a very observant Mister (being a surgeon) Percival Pott (1714–1788) matched occupation with disease, and therefore exposure with outcome. However, in the main it was the Industrial Revolution followed by war that created a crisis that quickly advanced toxicology.^{4,7}

Although there were large achievements in toxicology following World War II, it was not until Rachel Carson (1907–1964) had a vision of a chemically scorched earth, where birds were ravaged by the persistence of DDT, that toxicology found a new avenue—ecotoxicology or that pertaining to ecosystems, although the term was a later invention and much broader than Carson's vision. To some extent this is where toxicology entered the public's imagination, activated by Carson's work *Silent Spring*.¹⁹ This book has a place at both the table of history and that of the industrialist—a salient reminder that toxicology is about more than the poisoning of humans to gain revenge.

One cannot speak of the history of toxicology without mentioning the role of toxins in literature, whether the Book of Job²⁰ or Agatha Christie (1890–1976), who poisoned at least 41 victims in her 85 books, or Alice's experience in the work penned by Lewis Carroll (a.k.a. Charles Dodgson, 1832–1898), who also describes the characteristics of the occupational hazard of softening felt with mercury.²¹ And so it goes on, with Martha in *Arsenic and Old Lace* (a play by Joseph Kesselring), who takes elderberry wine with arsenic, strychnine and a 'pinch of cyanide',²² and, of course, Shakespeare's *Romeo and Juliet*.

Conclusion

This essay is not even a glimpse of the realm of toxicology. It does not include key dates and, more importantly, contributions from the giants of toxicology such as Socrates, Hippocrates, Moses Maimonides, James Marsh, Paul Ehrlich or Louis Lewin. The chemicals themselves—lead, arsenic, mercury, sulphanilamide, thalidomide and 51 million others—are missing, as are the great discoveries such as oxygen or the circulatory system or drug receptors (considered hypothetical 25 years ago²³). Nor are the innocents mentioned, such as Cleopatra, or the people of Minimata Bay in Japan (mercury poisoning), Bhopal (methyl isocyanate poisoning), or Bangladesh (arsenic poisoning). And the essay does not explore the broadness of the topic, whether forensic, clinical, environmental, or ecological, and has not divided the history by discovery or technology. However, it is hoped that a whetted appetite will encourage an examination of the past in order to better direct the future.

The current trajectory of knowledge is clear—toxicology has entered the realm of genetics, in particular its effect on the storage and transcription of information. We now acknowledge the sequenced human genome and have entered the age of 'omics'—toxicogenomics along with proteomics²⁴ etc. and their respective flock of journals, which always accompanies a maturing science.⁴ The development of new technologies, such as nanotechnology, will bring about new challenges. One lesson that this history has taught is worth listening to—the asbestos story, which is still unfolding but is highly relevant to potential health problems from carbon nanotubes. The toxicology may be different but society's reaction to these potential toxins should not mimic those of asbestos. On another level, populations of interest need to be assessed; protecting the most vulnerable groups is laudable but these groups are currently crudely defined only by age and economics. Current definitions of population exposure are minimalistic at best, and nearly always lacking at the level of the individual's medical history. Toxicology needs to keep up with the tools at its disposal. Developing whole-of-life medical histories including accessible occupational exposure data will help complete the loop between exposure and hazard, and allow better management strategies to be developed. We have much to look forward to in the future.

Further reading

The good texts of toxicology begin with a history; for example, see references 4, 7, 25 in the list below

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Fundamentals, principles and methodology of toxicology

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Introduction

Current activity in toxicology is largely concerned with determining the potential for adverse effects from chemicals on humans and other biota. Toxicologists are specially trained to examine the nature of these adverse effects and assess the probability of their occurrence. The variety of potential adverse effects and the diversity of chemicals present in our environment combine to make toxicology a very broad science¹ with a number of subspecialties, as outlined in Table 1.

Table 1: Major subspecialties of toxicology

Specialty	Major functional components
Clinical	Causation, diagnosis and management of established poisoning in humans
Veterinary	Causation, diagnosis and management of established poisoning in domestic and wild animals
Forensic	Establishment of the cause of death or intoxication in humans, by analytical procedures, with particular reference to legal processes
Pharmacological	Assessment of the toxicity of therapeutic agents
Ecotoxicological	Assessment of the toxicity of chemical exposure on the environment
Regulatory	Administrative functions concerned with the development and interpretation of toxicological information, with particular reference to controlling chemical exposures
Experimental	Design and conduct of in-vivo and in-vitro toxicology testing programs

Fundamentals and principles

General classification of toxic effects

Before toxicity can develop, a substance must come into contact with a body surface such as skin, eye or mucosa of the alimentary or respiratory tract.² Other routes of exposure, in experimental or therapeutic situations, include subcutaneous, intravenous, intramuscular and intraperitoneal.

Harmful effects that occur at the sites where a substance comes into initial contact with the body are referred to as local effects. If substances are absorbed from the site of contact, they, or products of their metabolism, may produce toxic effects in cells, tissues or organs remote from the site of exposure. These remote responses are referred to as systemic effects. Many chemicals may produce both local and systemic effects.² In general, the injury depends upon the physicochemical properties of the potentially toxic substances, the exact nature of the exposure circumstances (e.g. temporary or persistent), and the health and developmental status of the person or organism at risk.³

Also, since the nature and probability of toxicity depend on the number of exposures, this forms an additional general means for classifying toxic effects into those developing after either a single (acute) exposure or multiple (repeated) exposures. Repeated exposure toxicity can cover a wide time span; however, it is descriptively convenient to refer to it as short-term (not more than 5% of lifespan), subchronic (5–20% of lifespan) or chronic (entire lifespan or greater proportion of it).²

In general, a description of toxicity from a chemical requires inclusion of the following: whether the effects are local, systemic or mixed; their nature and (if known) mechanism of toxicity; the organs and tissues affected; and the condition of exposure resulting in toxicity (including species, route, duration and magnitude of exposure).

Spectrum of adverse effects

The spectrum of undesired effects of chemicals is broad.¹ They may take the form of tissue pathology, aberrant growth processes, altered or aberrant biochemical pathways, or extreme physiological responses.² Additionally, the adverse reaction may result from a hypersensitive or idiosyncratic reaction to a chemical. The term 'hypersensitivity' is most often used to describe an allergic state. Because allergic reactions

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usually occur at low doses of chemicals, dose-response curves have seldom been obtained. Individuals that display chemical idiosyncrasy demonstrate genetically determined abnormal reactivity to a chemical.¹

Dose response

A fundamental principle of toxicology is that, for a chemical administered to a genetically homogeneous population of animals from the same species, the proportion exhibiting a particular toxic effect will increase as the dose increases. For many toxic effects, except genotoxic carcinogens, there is a dose below which no effect or response can be elicited—referred to as the ‘threshold dose’. The threshold concept, a corollary of the dose-response relationship, is important. It implies that it is possible to determine a ‘no observed effect level’ (NOEL), which can be used as the basis for assigning ‘safe levels’ for exposure.²

Factors influencing toxicity

With animal studies and human poisoning, the nature and severity of toxicity depend on a large number of exogenous and endogenous factors.² Some of the more important are as follows:

- > Species and strain differences in susceptibility may be due to differences in rates of absorption, metabolic conversions, detoxification mechanisms and excretion.
- > Age may significantly affect toxicity, probably owing to relative metabolising and excretory capacities.
- > Nutritional status may significantly influence the expression of toxicity by altering biochemical and physiological response mechanisms.
- > Time of dosing (e.g. effects that might be observed by diurnal and seasonal variations) may alter biochemical, physiological and hormonal responses and affect the overall toxicological profile of the challenge.

Absorption, distribution, metabolism and excretion

The magnitude, duration, frequency and route of exposure will determine the amount of a chemical to which an organism is exposed, and hence the amount that can be absorbed; this then determines the amount available for distribution and toxic metabolite formation, and hence the likelihood of a toxic effect.²

Toxicokinetics is the study of the movement of chemicals around the body. It includes absorption (transfer from the site of administration into the general

circulation), distribution (via the general circulation into and out of the tissues) and elimination (from the general circulation by metabolism or excretion). The toxicokinetics of a chemical are determined by measuring its concentration in plasma or blood at various times following a single dose.⁴ Additional useful information can be obtained from measurements using different exposure scenarios (inhalation, dermal, oral) and durations (single, chronic).

The interpretation of toxicokinetic data requires an understanding of (a) the biological basis of the processes of absorption, distribution and elimination and (b) the way in which simple measurements of plasma or blood can be converted into useful quantitative parameters that relate to these processes. The mathematics used to define and describe the movement of a chemical around the body can display various levels of complexity.⁴

Evaluation of mixtures

Evaluation of the hazards from exposure to multiple chemicals can be much more demanding than is the case for a single chemical.² In assessing toxicity from mixtures it is important to consider (a) the chemical and/or physical interactions of the individual chemicals; (b) the effect that one chemical may have on the absorption, metabolism and pharmacokinetic characteristics of another; and (c) the possibility of interaction between parent compound and metabolites.

The International Programme on Chemical Safety (IPCS), through its project on harmonisation of approaches to assessment of risk from exposure to chemicals, is investigating the development of a framework for the risk assessment of combined exposures to multiple chemicals.⁵

Methodologies

The professional activities of toxicologists fall into three main categories—descriptive, mechanistic and regulatory.¹ The descriptive toxicologist is concerned directly with toxicity testing. The mechanistic toxicologist is concerned with elucidating the mechanisms by which chemicals exert their toxic effect on living organisms. The regulatory toxicologist has the responsibility of deciding, on the basis of available information, if a chemical poses a risk to the community. Some of the studies commonly used by toxicologists are outlined below.

Major in-vivo toxicity tests

In-vivo toxicity studies are particularly useful for hazard identification and characterisation of chemical agents when conducted according to standard protocols.⁶

The following types of studies are defined:

- > Acute toxicity studies investigate the effects of single doses of a substance. The LD₅₀ test, or medium lethal dose test—which records gross toxicity and mortality data over a 14-day post-dosing period—has been commonly employed, but newer tests ('limit' tests and 'up-and-down' dosing methods) are now favoured as they reduce the numbers of animals required and the suffering seen in the classical LD₅₀ test.
- > Standard acute toxicity studies include tests for acute oral, dermal and inhalational toxicity; eye irritation; skin irritation; and skin sensitisation. Such studies may serve as the basis for classification and labelling of a particular chemical or mixture, as an initial guide to possible toxic modes of action, and in establishing a dosing regimen for subchronic toxicity studies.
- > Subchronic toxicity studies are short-term repeat-dose tests. The main purposes of subchronic testing are to identify any target organs and to establish dose levels for chronic toxicity studies.
- > Chronic toxicity studies, or long-term studies, are defined as those lasting for the greater part of the lifespan of the test animals, usually 18 months in mice or 2 years in rats. The protocol for these studies may cover the investigation of chronic toxicity or carcinogenicity, or both.
- > Reproductive toxicity studies are designed to provide general information about the effects of a test substance on reproductive performance in both male and female animals, for example mating behaviour, gonadal function, oestrous cycling, conception, implantation, parturition, lactation, weaning and neonatal mortality. These studies may also provide some information about developmental or teratogenic effects of the test substance.
- > Developmental toxicity studies examine the spectrum of possible in-utero outcomes for the conceptus, including death, malformations, functional deficits and developmental delays. Exposure during sensitive periods may alter normal development, resulting in immediate effects, or may subsequently compromise normal physiological or behavioural functioning later in life. Since some developmental processes can occur peri- or postnatally, protocols for

developmental studies are being reviewed, with the possibility of extending the dosing period to cover not only major organogenesis but also the perinatal and early postnatal periods.

Genotoxicity tests

Genotoxicity studies are designed to determine whether test chemicals can perturb genetic material to cause gene or chromosome mutations. A large number of assay systems, especially in-vitro systems, have been devised to test the genotoxic or mutagenic potential of agents. Most authorities consider that a minimum set of data is required to define a mutagen/non-mutagen. These data usually consist of gene mutation tests in bacteria and mammalian cells, and in-vitro and in-vivo cytogenetics. Newer assays that could provide additional information include mutagenicity in transgenic animals and cell transformation.⁷

Epidemiology

Epidemiology is the analysis of the distribution and determinants of health-related states or events in human populations, and the application of this study to control health problems.³ It is useful for hazard identification and characterisation within a population and, in particular, in the study of air quality parameters on human health outcomes. The following are the main approaches that have been used in epidemiology:

- > Cohort studies use a component of the population whose characteristics can be ascertained as it enters successive time and age periods. The term 'cohort' has broadened to describe any designated group of persons followed or traced over a period of time.
- > Retrospective studies are used to test aetiological hypotheses in which inferences about exposure to the putative causal factor(s) are derived from data relating to characteristics of the persons under study or to events or experiences in their past. The essential feature is that some of the persons under study have the disease or other condition of interest, and their characteristics and past experiences are compared with those of other, unaffected persons. Persons who differ in the severity of the disease may also be compared.
- > Prospective studies investigate events or cases as they occur, or in which human subjects are identified and followed forward in time. This type of 'forward looking' study is designed with a specific goal (endpoint) in mind.

- > Case control studies start with the identification of persons with a disease or other outcome of interest, and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased groups with regard to how frequently the attribute is present.
- > Cross-sectional studies examine the relationship between diseases or other health-related characteristics of interest as they exist in a defined population at one particular time. Disease prevalence rather than incidence is normally recorded in a cross-sectional study, and the temporal sequence of cause and effect cannot necessarily be determined.

Predictive toxicology

Risk assessment

From an environmental health perspective, the main purpose of the toxicology tests described above is to provide a database that can be used to assess the risk (or evaluate the hazard) to humans associated with a situation in which a chemical agent, the subject and the exposure conditions are all defined.⁶ A flow diagram describing the components used for environmental health risk assessment is outlined in Figure 1.

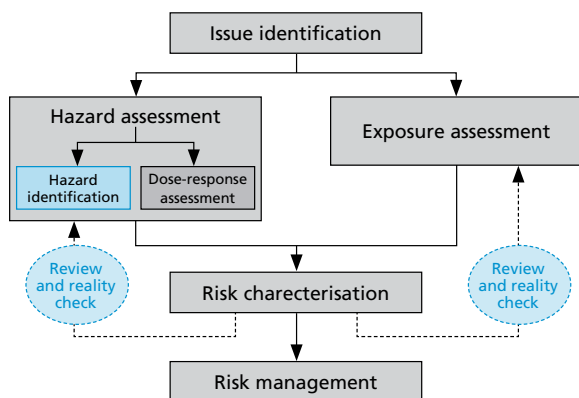


Figure 1: Australian environmental health risk assessment framework⁶

Ideally, to inform a risk assessment a toxicologist will review a series of chronic toxicity studies in laboratory animals to determine a lowest-observable-adverse-effect-level (LOAEL) as well as a no-observable-adverse-effect-level (NOAEL). The NOAEL is the highest dosage administered that does not result in adverse effects, and can be used to determine an approximate 'safe' level of a compound in the species tested. For many chemicals

associated with occupational exposure or environmental contamination, human data can form an invaluable component of the toxicological dataset. The ultimate objective of an environmental health risk assessment is to derive a 'safe' dosage for humans.

Threshold approach

The threshold approach is used to derive exposure limits such as an acceptable daily intake (ADI), a provisional tolerable weekly intake (PTWI), a tolerable daily intake (TDI) or a reference dose (RfD).^{8,9} The threshold approach makes no attempt to calculate a level of risk at low exposures. Rather, it derives a dose that is apparently without effect in a human population or suitable animal model, and then applies a factor to derive an exposure with a high likelihood that no effect will occur in the general human population.⁶

The traditional approach for establishing safe levels for chemical agents to which humans may be exposed is to reduce the NOAEL by a safety or uncertainty factor that takes into consideration both intraspecies and interspecies variation. When valid, chronic exposure data in humans are available, a safety factor of 10 is often applied as it takes into consideration the variability among humans. Most often, however, chronic exposure data in humans are not available for the chemical agent, and the toxicologist may extrapolate from chronic exposure studies in laboratory animals. A safety factor of 100 is often employed, 10 for extrapolation from laboratory animals to humans and 10 for variability among humans. When chemicals for which there are no good chronic exposure data available have to be regulated, additional safety factors are often used.¹

Non-threshold approach

This approach, which does not recognise the possibility of a threshold effect, is appropriate for radiation and some genotoxic carcinogens. It is, as a science policy decision, applied to all carcinogens by the US Environmental Protection Agency.⁶

Non-threshold models assume linearity between the lowest experimentally derived dose and the zero dose (the origin). This implies that there is a calculable probability of an adverse effect (risk) no matter how small the dose.

Numerical estimates of risk probabilities are generated by fitting one or more mathematical models to the data in the experimental dose range and extrapolating to

the low environmental exposure doses. For example, low-dose extrapolation using a linear model is a default approach for cancer risk assessment in the USA¹⁰ and is one approach used by the World Health Organization for genotoxic carcinogens in deriving drinking water guidelines.¹¹

The outcomes are estimates of either:

- > the dose at a predetermined acceptable risk level (note that this requires some judgement on what constitutes an acceptable level of risk); or
- > the risk level at any particular dose.

Benchmark dose approach

The benchmark dose (BMD) approach has been used in dealing with both cancer and non-cancer end points. It combines toxicological dose-response data (usually from animal studies) and conventional mathematical models to generate dose-response curves for the chemical in question, even in the sub-experimental region, and assumes a non-linear relationship in this region. In the NHMRC (1999) approach, the conservatism of other BMD models is avoided by relying on best-fit modelling rather than 95% lower confidence limits on a dose.

For the various mathematical models applied, the technique determines an average dose at which a 5% extra risk is incurred—this level of risk is near the lower limit of responses that can be experimentally measured. Modifying factors reflecting the degree of uncertainty in extrapolating from animal exposure are then applied to yield a guidance dose (or TDI) for human exposure.¹² This methodology has recently been used to propose PTDIs for benzo(a)pyrene (BaP), *N*-nitrosodimethylamine (NDMA) and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone, also known as mutagen X (MX).¹³⁻¹⁵

Threshold of toxicological concern approach

The threshold of toxicological concern (TTC) approach has its roots in the concept that 'safe levels of exposure' can be identified for individual chemicals with known toxicological profiles. The TTC approach aims to establish a human exposure threshold value below which there is a very low probability of appreciable risk to human health. For chemicals for which toxicological data are not available, the process is based on the chemical structure and toxicity data of structurally related chemicals.¹⁶

Starting with the generic approach ('exposure threshold') used by the US Food and Drug

Administration in the 1980s, the TTC concept has evolved over the years to take into account extensive analysis of available data, mainly on the oral toxicity of substances and the intake of / exposure to substances; and, on the basis of a structure-based decision tree, to find applications, mainly in the food area.¹⁶

The TTC approach has been used to evaluate flavouring substances,^{17,18} food contact materials^{19,20} and genotoxic impurities in pharmaceuticals;²¹ and for the risk assessment of chemicals. Recent publications have suggested that the TTC approach may also have uses in other categories of chemicals, more specifically on chemicals (or trace contaminants) in consumer products, food additives, pesticides and cosmetics.¹⁶

The TTC approach is discussed in more detail by Simon later in this issue of the Bulletin.

Conclusion

Toxicology is a broad science that encompasses a wide range of disciplines used to study the interactions of poisons on biological systems. The purpose of this article is to provide a brief overview of some of the fundamental principles and tools routinely applied to addressing toxicological problems, and be a point of reference for subsequent articles in this volume. Other articles in this issue will describe the individual application of toxicology to creating a better understanding of the outcomes associated with the 'real-world' interaction of chemicals in the community.

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Environmental health risk assessment: principles and guidance

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Background

Virtually all aspects of life involve exposure to potential risks.¹ Environmental Health Risk Assessment (EHRA) is an organised process for evaluating potential threats to human health from environmental factors (usually chemical or biological pollutants in air, water, soil or food). Its purpose is to:

- > evaluate the nature and magnitude of such risks and the factors that govern them, including an assessment of risks at a particular point in time, whether they exceed baseline or pre-existing risks, and the likelihood of changes in risk over time
- > determine who may be at risk and the pathways by which they may be exposed
- > characterise the risks and uncertainties that surround the EHRA processes
- > outline and prioritise processes that may result in risk mitigation (risk management)
- > underpin the development of health-based guideline values and standards that may be useful in regulating risk management and environmental clean-ups.

Risk assessment is a process that informs risk management, and it is important to understand the distinction between these two separate processes. It is equally important to understand how people actually perceive threats to their health and the emotive factors that govern that perception. This assists consultation with stakeholders about the ways in which risks occur and can be managed. Effective risk communication strategies are vital to developing appropriate risk management options.

Guidance on EHRA

There is an abundance of guidance on how to do EHRA on the websites of various national and international agencies. The US Environmental Protection Agency (EPA) collection is probably the most extensive, featuring specific guidance on cancer risk assessment (updated in 2005 after some 10 years of consultation),

aggregate and cumulative risk assessment, and assessment of health risks for children and other potentially susceptible population groups.

In the USA the National Research Council (NRC), working in conjunction with the EPA, National Institute of Environmental Health Sciences and National Academy of Sciences, has carefully enunciated the science policy decisions that underpin the use of threshold and non-threshold risk assessment approaches. The outcomes of this project were communicated through various consultations and reports, culminating in the release of the seminal report *Science and decisions: advancing risk assessment* in December 2008.¹

The key monograph on how to conduct EHRA in Australia is the enHealth Council guidance document, first published in 2002.² This document is currently being updated and a consultation draft should be released early in 2010.

What are the processes of EHRA?

The current enHealth definition of risk assessment is:²

'The process of estimating the potential impact of a chemical, biological, physical or social agent on a specified human population system under a specific set of conditions and for a certain timeframe.'

There are numerous models of EHRA to cater for the many contexts in which risk assessments are undertaken.² These range from relatively simple and rapid screening studies to complex multi-route, multi-hazard assessments.

Most EHRA models tend to be described by five stages:

1. issue identification
2. hazard identification
3. dose-response assessment
4. exposure assessment
5. risk characterisation.

These stages are closely linked and each is highly dependent on the preceding stages. The framework model (Figure 1) that encompasses these five stages, and their interlinkage with stages of risk management and stakeholder consultation, was first proposed for use in Australia in the enHealth Council guidance document.²

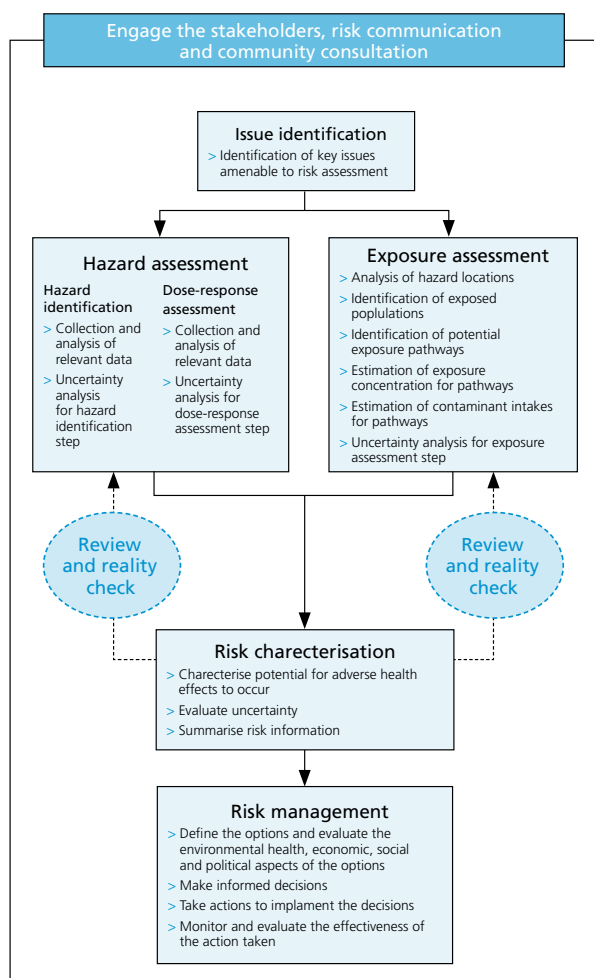


Figure 1: enHealth Council environmental health risk assessment mode

More contemporary models (e.g. NRC 2008¹) expand on these five stages with descriptions of their components. All models emphasise the importance of effective communication and consultation with stakeholders throughout the processes, in order to address their concerns.

Risk estimates derived by EHRA processes generally relate to defined groups or populations rather than individuals. The term ‘receptors’ is often used to designate people who may be exposed to an environmental hazard, and to whom the EHRA would be directed. Identification of ‘receptor’ locations and pathways by which they might be exposed is an integral part of any EHRA.

EHRA methodologies are inherently conservative and intended to be protective of public health under

all conceivable circumstances. This is especially true of ‘screening’ type risk assessments, or where the outcomes are intended to be used to establish environmental guidelines or standards. These tend to incorporate the most conservative assumptions about exposure, including the use of exposure estimates that represent ‘worst case’, or at least the upper percentiles of parameter distributions, rather than mean, average or typical values. Furthermore, exposure is usually considered to be constant over a substantial period of time (sometimes an entire lifetime), whereas many environmental exposures are episodic and may decline over time due to loss or degradation of the contaminant.²

Levels of risk may be qualitatively expressed using categories such as ‘high’, ‘medium’, ‘low’ or ‘negligible’. This is the generic approach outlined in the Australia/New Zealand Standard for Risk Management (AS4360:2004),³ although it is not necessarily suited to the more specific requirements of EHRA. It is also the approach taken in the risk analysis framework used by the Office of the Gene Technology Regulator to manage risks associated with GMOs.⁴ The problem with this approach is that such risk terms may have different meanings and interpretations for members of communities exposed to them, compared with those who formally assess the risks.

EHRA methodologies may result in quantitative estimates of risk relating to low levels of exposure to environmental hazards, but, because of the use of data extrapolation and the uncertainties inherent in such estimates, caution must be exercised in presenting such numerical estimates to communities, since they too are open to misinterpretation:

‘...a number is a number is a number...and yet exactitude should not be confused with accuracy.’⁵

Complexity of the exposure conditions, variability in the environmental agents and exposed populations, and any inherent limitations in toxicological data may all limit the accuracy and meaning of any numerical risk estimates. Gaps in knowledge or data are likely to be filled using scientific judgements and policies, which should be clearly identified and enunciated so that the basis for interpreting the evidence can be understood.

It is important to dispel the myth that the numbers derived from an EHRA process can be taken as a ‘bright line between possible harm and safety’¹ or, in other words, the separation between safe and

unsafe exposures. Part of the reason behind this lack of understanding of what the numbers generated in an EHRA really mean is the dichotomy that has developed in the approach to cancer and non-cancer endpoints. This division is elaborated further below.

Three contemporary challenges in EHRA

1. Dose-response assessment—threshold or non-threshold?

A longstanding convention in risk assessment has been the different treatment of dose-response relationships where a threshold relationship may be inferred, compared with that where a non-threshold relationship is assumed. Non-threshold assumptions are typically made for carcinogens, where zero risk is only assumed when there is no exposure and anything above zero is assumed to carry a small, but finite, risk. However, extrapolation methodology used to estimate the disease incidence (or risk) at dose levels well below the high doses actually used in animal studies may be quite model-dependent. Furthermore, numerical data derived from any one study may not be reproducible in another repeat study of the same design. It is important to acknowledge this fact, since there is a general belief that numbers generated in a toxicity study are inviolable or sacrosanct as inputs into a risk assessment.

Studies where the significant endpoint includes a neoplastic change (carcinogenesis) are usually assumed to represent a non-threshold dose-response relationship, especially where the chemical of concern has been shown to have genotoxic potential. For non-threshold dose-response relationships, the excess incidence (i.e. corrected for background) of induced cancer is assumed to be zero only at zero exposure.

In deciding between a threshold and a non-threshold approach to risk assessment, it is important to recognise that one is entering the dictates of science policy. While most government regulatory agencies continue to rely almost exclusively on non-threshold, low-dose extrapolation for cancer risk assessment, there is a growing acceptance that a threshold approach may be valid where the scientific data justifies an assumption of non-linearity at low dose (e.g. where cytotoxicity is a necessary precursor to the carcinogenic response). The fact that a distinction may be made between a genotoxic and a non-genotoxic mechanism for a carcinogenic response will be based on the available evidence. However, it does not mean that a non-genotoxic carcinogen does not affect the genetic

material of the cell under some circumstances, nor that a genotoxic effect is the only event required for the development of cancer by a genotoxic carcinogen.

The requisite knowledge or understanding of the toxicological mechanisms that account for nuances in the shape of the dose-response relationship at low dose may be incomplete. The recent review of HRA methodology by the US NRC¹ proposes harmonising approaches to low-dose extrapolation methods, including the use of benchmark dose (BMD) methodology to derive a point of departure (POD) for risk estimation. This approach would assign a finite risk estimate to both cancer endpoints and other toxicological endpoints, where it has been traditional to derive threshold-based guidance values, such as the reference dose/concentration (RfD/RfC) or the acceptable/tolerable daily intake (ADI/TDI). This new approach would result in risk-specific dose estimates that describe the proportion of a population likely to be susceptible below the adjusted no-observable-adverse-effect-level (NOAEL).

2. Exposure assessment—when to use default assumptions

Exposure assessment is one of the more critical and complex areas of risk assessment. It requires a determination of the magnitude, frequency, extent, character and duration of exposures in the past, currently and in the future, as well as identification of exposed populations and potential exposure pathways.² Environmental monitoring and predictive models can be used to determine the levels of exposure at particular points on the exposure pathways. An initial requirement for exposure assessment is an understanding of the presence (or absence) of an agent and its concentrations and distribution. Appropriate guidance on sampling and analysis of environmental media is another important component of exposure assessment.

In the absence of direct measurement of elements of potential exposure pathways, there may be an undue reliance on modelling and the use of default input values. The US EPA has recently published an updated version of its exposure factors handbook,⁶ which includes guidance on input parameters and extensive tables of anthropomorphic data (e.g. age-specific breathing rates, food ingestion, dermal exposure factors, growth and body-weights), which may be useful in exposure assessment modelling. An Australian exposure factor guidance handbook compiling similar Australian and internationally derived data tables will

be published as an appendix to the 2010 update of the enHealth guidance document on EHRA.

However, it is a firm principle that the use of exposure data based on valid measurement of parameters describing the exposure scenarios under consideration is always preferable to using default assumptions.

3. Risk characterisation—the concept of acceptable risk

For non-cancer endpoints, the approach taken in Australia (and most other jurisdictions) is to assign an acceptable (or tolerable) ADI or TDI, which is based on applying modifying factors (usually termed ‘safety’ or ‘uncertainty’ factors) to an estimated NOAEL of dosing from animal experiments. This carries no implication that it represents a finite level of risk. The operating definition is that an ADI or TDI represents an estimate of the intake of a chemical which, during a lifetime of exposure, appears to be without appreciable risk, on the basis of all facts known at the time.

When the risk assessment uses a non-threshold approach (as is the case for most quantitative carcinogenic risk assessments), it is implicit that any derived environmental standards will attempt to protect the community by minimising exposures to a point where a specified level of risk will not be exceeded. This may be termed an ‘acceptable’ or ‘target’ risk level.

The setting of the numerical value for such a risk level is a sociopolitical or policy-driven matter requiring extensive consultation. It is therefore important that all parties appreciate the real meaning of a ‘target’ risk level—often expressed as something like 1×10^{-6} or one in a million. It should not be taken to imply certainty that one person will get the disease if there are at least one million people exposed. It is simply a way of expressing risk, as a numerical expression of the likelihood of an event occurring under the defined conditions of exposure, based on extrapolation of dose-response data.

The origin of the 10^{-6} level has been attributed to US regulators designating this level as a negligible or essentially non-existent risk, from the legal point of view that *de minimus non curat lex* (the law does not deal with trifles)— 10^{-6} is a convenient quantitative expression of the *de minimus* concept.⁵

However, it must also be acknowledged that the target risk level has been varied upwards to between 10^{-5} and 10^{-3} in different types of risk management

situations. The higher risk levels are more commonly found in occupational exposure settings, or associated with evaluation of contaminated sites. For example, the Dutch ‘intervention levels’ for management of contaminated soils are based on a carcinogenic risk target of 10^{-4} .⁷

The ‘target’ risk level to which most Australian environmental regulatory authorities aim is 1×10^{-6} , although this may depend on whether the risk is associated with exposure to a single carcinogen or is the outcome of multiple chemical exposures, when a combined risk of 10^{-5} may be considered acceptable.

Irrespective of whether the outcome of the risk characterisation process is a finite risk estimate that may be compared with a ‘target’ risk level, or an estimate of the extent to which estimated exposures fall below an ADI/TDI, both approaches are subject to uncertainty. Such uncertainty is managed to some extent by the conservatism built into evaluation of toxicological and exposure data in the EHRA process. However, it is important that the level of uncertainty in EHRA is made transparent in the risk characterisation step. This may be assisted by applying a sensitivity analysis, where the impact of varying the values of input factors can be tested.

Summary

The enHealth guidelines on EHRA establish a logical framework for conducting environmental health risk assessments. The underlying concepts for EHRA are being constantly refreshed and updated with the availability of new scientific information. The recent US initiatives^{1,6} illustrate the application of new scientific information and principles, including reconsideration of how animal-based toxicological data may be better integrated with in-vitro and in-silico data sources.⁸

There remain some issues on how best to organise EHRA reports and communicate EHRA outcomes to concerned communities and other stakeholders, so that they may better understand the caveats and uncertainties reflected in the risk estimates. Application of newer scientific information and approaches to EHRA should enable some of the inherent uncertainties to be minimised or better managed. These issues are addressed in other articles within this Bulletin.

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An approach for dealing with chemicals for which no toxicological data is available: the threshold of toxicological concern (TTC)

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The issue of chemical contaminants and residues

In public health the usual practice is to apply the precautionary approach when the risk of a hazard is unknown, poorly quantified or impossible to measure. In essence, it places the safety of the population above the need to expose the population to the hazard. In this discussion the hazard is chemicals,¹ including contaminants of food, water or wastewater; and chemical residues in cosmetics, drugs or products such as toys etc. The practical application of the precautionary approach extends to using various means, often regulatory, to prevent the public from being exposed to the hazard.

Considerable effort is already made to characterise major hazards that are constituents of food, water, drugs, cosmetics etc., with the level of expenditure being based on risk. However, there is a plethora of minute chemical residues for which the production of adequate data would be extremely expensive if not impossible to produce. This arises because, whether the chemical is manufactured or extracted from animal or plant source, chemical constituents are never 100% pure. Even the simplest chemical reactions, such as creating an ester from an alcohol and carboxylic acid, lead to a number of products that, without expensive purifying steps, are impossible to separate out. The classic example is the production of the chlorinated phenoxyacetic acid herbicides (e.g. 2,4-D) used in Agent Orange, where the reaction creates a large number of products including a range of polychlorinated dioxins and furans.² In some cases the lack of knowledge of the chemical constituents goes beyond a small fraction of products, extending to the majority, for example substances that make up complementary medicines.

Introduction to the threshold of toxicological concern

Is there a tool that could be used to ensure that even minuscule quantities of chemical residues in products do not pose an unacceptable risk? And yet the tool must not create a burdensome economic barrier, nor create the need for expensive experiments that may consume large numbers of animals and are often very time consuming. This paper examines such a tool, called the threshold of toxicological concern (TTC). It uses the universal knowledge of the nature of the toxicology of chemicals and, more specifically, extrapolates to an unknown chemical the probable toxicological effect based on the chemical structural class to which it belongs.³

To make the discussion simpler, this paper speaks of chemicals in terms of their concentration in a product, whether drug, food or substance, but, in reality, the actual dose that humans will be exposed to must be estimated. For drugs and foods this is reasonably easy, but for environmental pollutants it may be somewhat more complex. The TTC approach has two elements: the setting of the TTC dose as the maximum human dose of a chemical per day expressed as micrograms per day; and the application of the TTC to an unknown chemical that will expose humans via a particular route. In the latter step the maximum allowable concentration in the substance in question is calculated based on estimated population exposures.

Defining the 'safe' concentration

The question being answered is: Is there a method of defining a 'safe' concentration of a chemical in a medium without knowledge of the toxicity of the actual chemical in question? This question is answered from the work of Robert Kroes and fellow workers, whose body of work underpins the TTC method.^{3,4} Actually, Kroes was not the first to propose this approach to toxicology, with the ideas evolving perhaps from the work of Munro^{5,6} and others, such as Cramer.⁷

We begin by assuming that there is a safe level of exposure. This requires that there is a level or concentration of chemical from which *no effect is observable*, either in the short term or long term, and whether from a single dose or from multiple doses, even for a lifetime (see paper by Delaere et al., in this issue of the Bulletin). Using this notion, a generalised question can be asked: Is there a generic level or concentration for most commonly known chemicals

for which no observable effect can be defined? This generic question was first proposed by John Frawley in 1967⁸ and Alan Rulis in 1986.⁹ This level would mostly be impracticable for common use because it would need to be set very low in order to capture the entire spectrum of toxicities. However, it has been found that chemicals can be placed into *classes*, mostly based on structure, where members have similar toxicological profiles.

Based on the most likely structural relationship that chemicals have to their toxicological properties, it is possible to compare an unknown chemical with chemicals of the same class for which we have data, and in particular the most toxic of these.¹⁰ This means there is a method to define a generic, no observable effect level for a class. However, before this can be done there are a number of other parameters that need to be solved first. Two major parameters are: the generic or TTC concentration that defines the highest acceptable dose; and the safety margin that needs to be applied. The first parameter will be discussed in more detail below. In regard to safety margin: although (say) the 5th percentile level is often chosen from a list of the most toxic chemicals available in the domestic (non-warfare) realm, the data is usually from non-human experiments or from certain subsets of human data, such as the occupational setting. To account for this and the fact that the data is not from the actual chemical in question, a safety factor is applied. The calculation and application of safety margins or uncertainty factors is discussed in more detail in this issue (see paper by Delaere et al.), but they are usually in the numeric order of 10–1000.¹¹

The TTC approach is therefore a pragmatic risk assessment device that is based on the principle of establishing a human exposure threshold value for all chemicals below which there is a very low probability of appreciable risk to human health.¹²

How is the TTC concentration defined?

There are a number of elements to be considered when defining the TTC. Of importance are: the definition of the effect (i.e. what is being protected); the exposure period—acute or chronic; and the dose that would be allowable without appreciable health risk if consumed daily over a lifetime (which takes into account exposure level and route of exposure).⁴

There is clearly a scale of impairment from normal (whereby the human adjusts to the toxin by its own

homeostatic processes) through to complete failure of the physiological processes of the body. This scale correlates with no effect through to death. Through this continuum of effect there are a range of specific endpoints that must be considered. These are usually split into two groups—non-genotoxic and genotoxic. The non-genotoxic effect endpoints that need consideration are: neurotoxicity and developmental neurotoxicity, developmental toxicity, teratogenicity, immunotoxicity, endocrine activity and allergenicity.³

It has been found that these toxicity endpoints are influenced by the structural class of the chemical, which is obvious for the organophosphates (neurotoxic). Cramer and his co-workers in 1978 defined three classes of compounds into which most chemicals fall. The classes range from simple through to complex, based on data from the most sensitive species, sex and toxicological endpoint.⁷ It was found that, if a 100-fold safety margin is applied to the 5th percentile of the no effect levels of a class of chemicals, there is a high level of confidence that any other chemical with a similar structure to those in that class will also show no observable effect.⁶

Protecting against more complex endpoints

Using the scheme thus described, it has been found that chemicals that have neurotoxicity and developmental neurotoxicity also display a similar cumulative distribution as those in Cramer structural class III (the most complex class). However, some neurotoxins, as a class, were found to be different from this class, leading some to postulate setting aside neurotoxins per se. However, of this group, it is the organophosphate esters that are most different (being more toxic) and clearly identifiable, and these were justifiably removed as a group. So the scheme now asks the question: Is the chemical an organophosphate; if not, which Cramer class does it belong to?¹¹

What of the other endpoints? Data suggests that immunotoxicity, endocrine activity or allergenicity generally are not distinct from the most sensitive effect found in a class of chemicals as a whole. However, in the latter case there are some subsets of susceptible individuals that may require additional devices to protect them. Most consider teratogenicity need not be a separate class because the doses required to cause these endpoints are not lower than defined by the 5th percentile of the most complex class.

Using this approach, the International Life Sciences Institute (ILSI Europe) Threshold of Toxicological Concern Taskforce reported that neurotoxicants, immunotoxicants and teratogens are adequately dealt with by the TTC approach. However, ILSI Europe also suggested that endocrine-disrupting chemicals, including steroids, should not be evaluated using TTC. Finally, the class of chemicals used to construct the tool does not take into consideration polymers and other high molecular weight chemicals or proteins, and therefore cannot be used for these chemicals.¹¹

Dealing with genotoxic chemicals

What about chemicals that have the potential to cause cancer and, specifically, are genotoxic? These can be handled in a number of ways, one of which is very similar to the way other forms of toxicity are handled. Cheeseman showed that chemicals that cause tumours generally cluster linearly about a large concentration range. There are some exceptions, which can generally be identified by specific structural moieties within the compound.¹⁰ Hence, the TTC approach asks the following questions: (1) Is the chemical a polyhalogenated-dibenzodioxin, -dibenzofuran or -biphenyl, or an aflatoxin-like substance? If so, compound-specific toxicity data is required (i.e. the TTC approach cannot be applied); and (2) Does the chemical contain azoxy or N-nitroso moieties, because these point to a potential to cause neoplastic disease, and the TTC approach cannot be applied.¹¹

The setting of a level based on the TTC approach

The setting of a concentration level based on the TTC approach is therefore a step-wise process. The chemical structure is often acquired using a combination of mass spectrometry and nuclear magnetic resonance technologies. The process follows a dichotomous tree-like structure, beginning with excluding or including certain classes of chemicals (e.g. polymers or metal-containing compounds that have no physiological benefit). The chemical is also examined for 'structural alerts', such as moieties that could give rise to genotoxicity. Non-genotoxic chemicals are placed into their corresponding class (organophosphate or Cramer class I, II or III). For each class there is a TTC that defines the maximum daily intake.

The lowest TTC is 0.15 µg/day, which satisfies a risk of better than 1 in 1 000 000 for potentially genotoxic chemicals (excluding those with specific structural

alerts). For all other compounds a TTC of 1.5 µg/day can be applied. This level can be raised based on the class of chemical. For example, if the chemical is an organophosphate, a TTC of 18 µg/day can be applied, while a chemical with a Cramer structural class II has a TTC of 540 µg/day. A full decision tree is given in Kroes et al.¹²

Lastly, the regulator needs to ask the question: Does the chosen TTC make sense based on any other available information? For example, for therapeutic classes of agents, it would be prudent to compare the chosen TTC with the no effect levels of others in the class for which data is available. In the case of therapeutics, there is often a large range of human data available for the same class of chemical.

Limitations to using the TTC approach

In practice the TTC must be applied in the context of knowledge of toxicology or pharmacology—it is not a tool to be used by the naïve or unskilled. Being a pragmatic tool, the most important question is: Does the chosen concentration, along with information about the specific population being exposed, make sense toxicologically?^{3,12}

Limitations to the approach are fairly apparent and some are mentioned here. The classes are defined by a small subset of chemicals (less than 1000) out of some 50 000–70 000 in common use, although much work is being done to expand the underlying database. Thus, there are chemicals that are too different to be adequately classified using this tool. The tool also assumes oral ingestion, although much of the data may be from the intraperitoneal (IP) route in animals. Contamination of injectables may require further exploration should the bioavailability be believed to be somewhat different to either the oral or IP route.

The TTC approach is not the panacea for all chemicals or products, and should not reduce the impetus to gather chemical-specific toxicological data appropriate for the exposure scenario. However, the usefulness of TTC has been apparent for some time, especially for risk assessment of low molecular weight molecules at low levels, beginning with migratory chemicals from packaging materials and food flavours⁴ and extending to genotoxic impurities in pharmaceuticals.¹³ The European Medicines Agency recently published a TTC-based guideline on the assessment of genotoxicity of complementary herbal remedies,¹⁴ and recommendations for other products are expected in

the future. Recent considerations include extending its application to food residues from veterinary medicinal products, wastewater for the purpose of recycling (see paper by Cunliffe in this issue), and perhaps to pesticide breakdown products in potable ground or surface water.

TTC is probably of most use for newly discovered chemicals, with many being found as a result of enhanced analytical techniques that now routinely measure at the level of 10⁻¹⁵ gram, for example odorous compounds in water.¹⁵ However, there is a plethora of commercially available chemicals for which little toxicological data has been collected. Therefore, if not for setting regulatory standards, the TTC has a place as a screening tool and for the setting of priorities, especially where chronic intake is likely. To inform the tool, there is a need for continual updating of the underpinning database—with a view to broadening the classes of chemicals and endpoints examined, the routes of exposure, and the inclusion of data from mixtures.

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Toxicogenomics and what determines people's susceptibility to foreign chemicals in the environment

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Introduction

It should not surprise anybody that we score differently in the lottery of good health and ill health. Exposure to environmental factors is an important determinant in this lottery. This brief discussion focuses on chemical environmental factors only. Environmental exposure of humans encompasses a wide range of chemicals that includes constituents of foods, beverages, cosmetics, toiletries, therapeutic drugs, food contaminants, and environmental contaminants such as pesticides and products of combustion. Much has been done in our community to minimise unexpected exposure to contaminants, whether they are foodborne, environmental or chemicals in the workplace. Nevertheless, uncertainties in the level and nature of exposure make it difficult to identify specific causative agents for ailments that are thought to have an environmental aetiological component.

Individuals respond differently to the same dose

Therapeutic drugs serve as good examples of how we respond to many substances that we are exposed to. Therapeutic drugs are usually administered following well-established dosage regimens, yet it has been observed over many decades that some individuals have good therapeutic outcomes, some gain no benefit, and others suffer from serious toxicity. Why such a variability in response? This should not surprise us either. We are all different in appearance—why wouldn't we be different in our response to drugs? Indications of marked inter-individual variability emerged many years ago when it was noted that some people could not sense the distinctly bitter taste of phenylthiourea. This observation was preceded by the much earlier observation by Pythagoras (2500 years ago) that raw fava bean ingestion resulted in haemolytic anaemia. It is quite recently that the genetic basis of this problem has become apparent. It occurs only in individuals with

the hereditary glucose 6-phosphate dehydrogenase deficiency, which affects possibly some 200 million people.¹ It is now expected that a better understanding of genetic differences will be helpful in predicting adverse effects of this kind.

The full characterisation of the human genome has created a great deal of optimism that we will not only be in a better position to predict serious conditions resulting from exposure to foreign chemicals, but also prevent them. With a better understanding of the mechanisms of toxicity and appropriate genotyping and phenotyping, we may be able to answer questions like why ('only') 7–10% of all smokers die of cancer.

It is suggested that virtually all toxic responses are accompanied by changes in gene expression.² Accepting that this is the case, it is inevitable that, as we progress with the analysis of gene expression, the critical underlying processes will be uncovered. However, the day has not quite arrived when we can predict, individual by individual, one's sensitivity to specific toxic agents. Apart from the difficulties in analysing gene expression and relating the results to specific environmental exposures, unequivocal phenotyping is still wrought with obstacles.

The role of genetics in xenobiotic disposition

One area where we have made substantial gains is in the genetics of xenobiotic disposition and its impact on toxicity. In 1960 Evans³ described individuals who had difficulty in metabolising (by acetylation) common drugs used in the treatment of tuberculosis. A little earlier it had been observed that selected individuals suffered from prolonged respiratory paralysis when they were administered the muscle relaxant succinylcholine, and a genetic link was discovered underlying this drug toxicity.⁴ Phenotyping of individuals with respect to their acetylation status became possible soon after Evans's publication of the seminal paper³ relating to the acetylation of isoniazid, and it was possible to take the genetically determined acetylation status into consideration in clinical practice. On the other hand, prediction of plasma levels of drugs such as imipramine and nortriptyline (tricyclic antidepressants) and the appropriate dose adjustment remained a difficult problem for several years.

In the late 1960s Folke Sjöqvist's group reported up

to 36-fold differences in patient plasma levels of imipramine and nortriptyline. Their observations were extended to twins, highlighting that identical twins had very similar plasma levels of the antidepressant drug nortriptyline.^{5,6} The conclusion was clear that there was a genetic component involved, but it was not at all clear how to deal with this situation. There was no way of predicting what the resulting plasma level of a drug like nortriptyline might be when dosed at what was considered to be a standard dosage—until the discovery of multiple forms of cytochrome P450 (an important family of xenobiotic metabolising enzymes commonly referred to as CYP) and genetic polymorphism of some of the CYP isozymes such as CYP2D6.⁷ From these observations the pharmacogenetics of disposition of foreign chemicals has progressed to the stage where we can make practical decisions about drug dosages.

Table 1 illustrates plasma levels of nortriptyline in the general population and in sets of identical and fraternal twins. The plasma level reflects the rate of metabolism of nortriptyline. The identical twin sets show remarkable uniformity in their steady state plasma concentration of nortriptyline, whereas several fraternal twin sets show highly divergent plasma concentrations, similar to the variation observed in the extremes of the heterogeneous patient population. These early data are clearly hinting at the importance of genetic control in the elimination of drugs.

The discovery of the large number of cytochrome P450 isozymes has made it possible to understand the variability in the elimination and consequent plasma levels of many drugs. In particular, the relevance of CYP2D6 in the elimination of drugs has clarified the reasons for the staggering variability in the plasma concentration of drugs like the tricyclic antidepressants.⁸ This has resulted in the development of individualised dosing regimes; for example, instead of using the population-based nortriptyline dose of 150 mg/day, we may have to use as little as 50 mg/day for poor metabolisers (CYP2D6 deficient) and as much as 500 mg/ for ultrarapid metabolisers.^{9,10}

Ingelman-Sundberg estimates that in Europe there are 20–30 million people with no CYP2D6 and another 15–20 million people who have CYP2D6 duplications. When this information is combined with the estimate that CYP2D6 is relevant with respect to 15% of the drugs used, this emerges as a very significant

Table 1: Steady state plasma levels of nortriptyline in ng/mL in patients (1 to 15), identical twins (1a to 9b) and fraternal twins (10a to 21b). The patients received three times 25 mg of nortriptyline per day⁵ and twins were given weight-adjusted doses.^{5,6}

Non twins		Identical twins		Fraternal twins	
Patient ID	ng/mL	Subject ID	ng/mL	Subject ID	ng/mL
1	8.9	1aF	13.3	10aM	12.9
2	26.7	1bF	15.6	10bM	18.6
3	31.4	2aM	16.6	11aF	17.4
4	40.9	2bM	17.7	11bF	36.2
5	44.9	3aM	16.7	12aF	18.8
6	52.1	3bM	19.5	12bF	29.4
7	52.2	4aM	21.2	13aF	19.0
8	55.4	4bM	24.9	13bF	41.9
9	58.7	5aM	23.1	14aM	22.1
10	66.9	5bM	24.1	14bM	26.6
11	69.5	6aF	28.0	15aM	23.8
12	71.4	6bF	30.9	15bM	25.4
13	83.6	7aF	29.7	16aM	25.8
14	113.3	7bF	29.7	16bM	27.7
15	262.7	8aM	30.9	17aF	25.8
		8bM	30.9	17bF	29.7
		9aM	32.4	18aF	28.5
		9bM	35.1	18bF	30.6
				19aF	35.9
				19bF	36.3
				20aM	37.3
				20bM	38.5
				21aM	46.1
				21bM	78.4

M = male, F = female; 1a & 1b etc. represent twins.

problem.^{9,11} The role of these enzymes is not only related to elimination of drugs, but it is now clear that something like 10% of Caucasians do not get any pain relief from codeine simply because they lack CYP2D6. This enzyme converts codeine to its active metabolite, morphine.¹²

Dennis Smith of Pfizer has evaluated the dependency of 200 important drugs on various metabolic factors for their elimination, and CYPs emerged as highly important in this process.¹³ It has been shown that

~75% of all drugs can be metabolised by three CYPs (CYP3A4, CYP2D6 and CYP2C9),¹⁴ and a set of six to seven CYPs accounts for 90–95% of all drug metabolism.¹⁵ Figure 1 shows the relative importance of various routes of elimination and, in particular, the importance of the CYP enzymes.

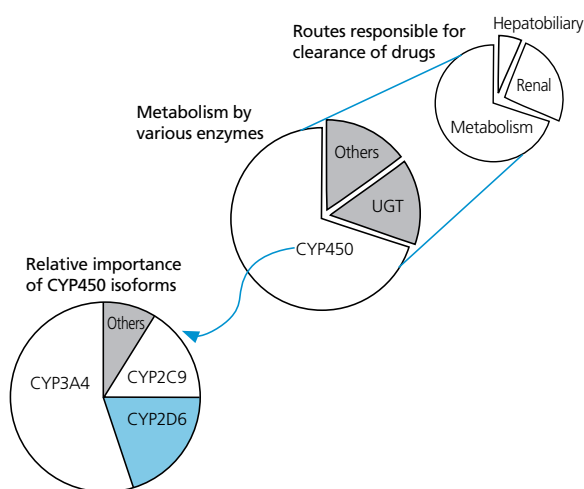


Figure 1. Role of various routes of elimination of 200 important drugs.

This highlights the dominance of metabolism, and particularly CYP enzymes, in the elimination of chemicals. It is expected that extrapolation of this analysis to other chemicals (cosmetics, agrochemicals, food additives and contaminants, herbal components etc.) will yield a similar outcome, with CYPs playing a dominant role in the elimination of a wide range of xenobiotics.

Drug metabolising enzymes are important not only in eliminating drugs but also in producing toxic intermediates of drugs. Consequently, the genetic variability of these enzymes sets the scene for the complex variability of drug toxicity from individual to individual. Bearing in mind that there are many other contributors to the disposition of drugs, such as the transport proteins, which also exhibit genetic polymorphism,¹⁶ the prediction of toxic outcomes is quite difficult.

Conclusion

Much of the above has focused on the kinetic behaviour of drugs, but a sound extrapolation can be made to include all small to medium molecular weight organic chemicals. These would include a large number of air and water pollutants as well as constituents of cigarette smoke, cosmetics and agrochemicals; food additives and contaminants; food constituents (particularly those of plant origin); and herbal components. Very little is known about the impact of genetic variability on our ability to detoxify or activate the wide range of environmental chemicals (perhaps with the exception of several constituents of cigarette smoke). Environmental chemicals are widely considered to be an important cause of disease, and there is overwhelming evidence that individuals respond differently to the same exposure to a specific

chemical.¹⁷ Current progress made in the area of genomics, drug metabolism and metabonomics¹⁸ will open many opportunities to resolve the questions relating to environmental toxicity.¹⁹

While the genetic basis for the pharmacokinetic determinants is becoming clearer, the mechanisms of toxicity also present examples of genetic variability with respect to receptors, ion channels and enzymes (other than those discussed above), and of immunity.¹⁶ We can expect to be able to predict toxicity much better in the foreseeable future, but there are still many obstacles associated with genotyping and phenotyping individuals¹⁷ and protecting specific individuals from toxicity.

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Vulnerable groups to chemical exposure

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Introduction

It is recognised that there are particular populations with unique susceptibilities to environmental agents and chemicals. In this paper we present two such populations—children and sufferers of multiple chemical sensitivity.

Children

Paediatricians recognise that children are not little adults and that they interact with their environment differently.^{1,2} In general, children are more vulnerable to environmental exposures than are adults; they receive a higher 'dose' from a given environmental exposure, are less able to detoxify many environmental toxicants and are more susceptible to the adverse effects of the exposure. The vulnerability of children to environmental exposures needs to be taken into account when developing exposure standards and environmental guidelines.

The exposure of any given child to hazardous agents is complex and differs with the life stage of the child. Conceptually, the child can be considered to be at the centre of an 'exposure universe', with exposures coming from the home, neighbourhood and ambient environments. A child's first exposure environment is the maternal womb during foetal development. Foetal exposures are determined by maternal exposures. After birth the home environment includes factors such as noise, housing quality, indoor air quality, nutrition and diet, waste disposal, sanitation and household chemicals. These factors can be influenced, to a large degree, by the family. The neighbourhood environment includes factors such as road safety, drinking water, food safety, drug abuse, child labour, crime and violence—factors which can be influenced to some extent by the local community. The ambient environment includes factors such as ambient air quality, insect-borne diseases, waste management,

natural hazards, radiation, hazardous chemicals, water (surface and ground) quality and climate. These are more national or global factors and less amenable to interventions by the family or local community.

Exposure pathways in children

Children often have different (sometimes unique) exposures to environmental hazards from those of adults, including trans-placental exposure, exposure via breastmilk, dermal exposure and non-nutritive ingestion. Exposures via these routes can occur for toxicants that adults are mainly exposed to by the inhalational route (Table 1).^{1,2} Exposures occur in utero to toxic environmental agents that cross the placenta. Such exposures can be chemical (pollutants and pharmaceuticals), physical (radiation, heat) or biological (viral, parasitic). In addition, maternal exposures that induce oxidative stress in the mother can adversely affect the developing foetus. Maternal exposures during pregnancy have the potential to impact on foetal growth and development, with perhaps the best understood examples being cigarette smoking, alcohol consumption and maternal consumption of prescribed and illicit drugs.³ There are increasing data to support a link between maternal exposure to ambient air pollution and decreased foetal growth.⁴ Foetal growth data obtained from 15 623 ultrasound examinations

performed between 13 and 26 weeks gestation were correlated with air pollution and meteorological data obtained from municipal monitoring stations in Brisbane.⁴ An estimate of pollution exposure for each day during pregnancy was calculated and correlated with various indices of fetal growth obtained from the ultrasounds. Hansen and co-workers reported that different pollutants caused restriction of several growth indices at varying times during gestation, consistent with the concept of windows of susceptibility.⁴

Latzin and colleagues in Switzerland⁵ studied 241 healthy newborn infants enrolled in a prospective birth cohort, and related lung function measured at 5 weeks of age to maternal exposure to air pollution during the pre- and postnatal periods. After adjusting for sex, postnatal age, season of birth, outdoor temperature and maternal smoking during pregnancy, they found significant impacts on the infants' breathing patterns, including increased minute ventilation, mean tidal expiratory flow, mean tidal inspiratory flow and respiratory rate, and decreased tidal volume, with increasing prenatal exposure to PM₁₀ (particulate matter with a mean aerodynamic diameter of 10 µm) and nitrogen dioxide (NO₂). There were no associations with exposure to ozone. There were also indications of increased airway inflammation in those with greater prenatal exposure to PM₁₀ and NO₂.

Table 1: Exposure pathways for various environmental toxicants at different developmental stages

Toxicant	Exposure pathway		
	Foetus	Young child	Adult
Ambient air pollution	Trans-placental	Inhalation Non-nutritive ingestion Dermal	Inhalation
Indoor air pollution	Trans-placental	Inhalation Non-nutritive ingestion Dermal	Inhalation
Household chemicals	Trans-placental	Inhalation Non-nutritive ingestion Dermal Breastmilk	Inhalation Non-nutritive ingestion Dermal
Maternal drugs	Trans-placental	Breastmilk	
Lead	Trans-placental	Breastmilk Inhalation Non-nutritive ingestion	Inhalation Non-nutritive ingestion
Tobacco smoke	Trans-placental	Inhalation Breastmilk	Inhalation
Persistent toxic substances	Trans-placental	Breastmilk Ingestion Non-nutritive ingestion Dermal Inhalation	Inhalation Ingestion

Adapted from WHO 2006.¹

Children are not little adults

Children’s physical differences also cause them to reside in a different location in the world, i.e. closer to the ground. Heavy pollutants such as mercury are concentrated in their breathing zone, and deliberate applications of pesticides and cleaning solutions at ground level make them more readily accessible to small children. Being small, children have a high surface-area-to-volume (SA:V) ratio and can have dramatically higher absorption through dermal contact than adults. In addition, children have a longer life expectancy, therefore having longer to manifest the adverse effects of environmental exposures and longer to live with toxic damage.

Exploratory behaviour is exemplified by hand-to-mouth activity, behaviour that is most prevalent in children between 1 and 3 years of age. Children often learn by putting things in their mouths, and can ingest significant quantities of contaminated soil, dust and dirt at early ages, leading to exposure by non-nutritive ingestion.

As children are in an active anabolic state to fulfil their growth requirements, they are often subjected to higher exposures to pollutants found in air, water and food. Relative to body size, children breathe more air (Table 2), drink more water, and have a higher caloric requirement and a higher body SA:V ratio than adults (Table 3). The larger SA:V ratio of a child means that dermal exposures may be greater. Except for premature infants and newborns, children’s skin presents the same barrier to dermal exposures as that of adults, but there is more of it on an SA:V basis. Babies have an SA:V ratio three times, and toddlers twice, that of adults (Table 3). Children also tend to have more skin exposed and more cuts, abrasions and rashes than adults, which can easily lead to increased dermal absorption as a proportion of body weight.

Table 2: Ventilation parameters relative to age

Age (years)	Respiratory rate (breaths per minute)	Tidal volume (mL)	Minute ventilation (mL/kg)
Birth	40–60	28	320–480
6 months	30–50	64	240–400
1 year	30–40	80	240–320
2 years	30	104	160
6 years	16	160	128
12 years	14	320	112
≥ 18 years	12	560	96

Adapted from Selevan et al. 2005.⁶

Table 3: Dynamic developmental physiology relevant to increased exposures in children

	Newborn	Young child	Older child	Adult
Surface area: body mass (m ² /kg)	0.067	0.047	0.033	0.025
Water requirement (mL/kg/day)	165	75	55	38
Caloric requirement (cal/kg/day)	100	90	45	35
Absorption of ingested lead (%)	42–53	30–40	18–24	7–15

Adapted from Selevan et al. 2005.⁶

The developmental component of a child’s physiology changes, maturing, differentiating and growing in phases known as ‘developmental windows’.⁶ These ‘critical windows of vulnerability’ have no parallel in adult physiology, and create unique risks for children exposed to hazards that can alter normal function and structure.

While many organ systems are mature either at birth or in the early postnatal period, the lungs, kidneys, immune system and brain are immature at birth and have prolonged periods of postnatal maturation. The lungs grow rapidly, forming new alveoli, in the first 2 years of life and then less rapidly until adulthood. The immune system does not reach full adult capacity until the teenage years. The brain continues to develop after birth, with myelination and development of higher intellectual functions not complete until early adulthood.¹ These prolonged periods of maturation throughout childhood mean that these organs are vulnerable to adverse environmental exposures.

Environmental toxicants generally need to be detoxified in the body. Two main detoxification systems exist: elimination or transformation of specific functional groups of toxicants (phase I); and conjugation of toxicants and their metabolites with endogenous co-factors such as UDP-glucuronic acid, sulphate and glutathione (phase II). Neonates and young children may be either better able or less able to deal with toxic substances than adults, due to differences in metabolic capacity. Some increased sensitivity of neonates may be related to their very low or, at times, unmeasurable metabolising capacity. The phase I metabolic enzymes

in the liver are present at lower levels during foetal life and increase to close to adult levels over the first 6 months after birth. Many aspects of the phase II detoxification capacity are immature at birth, especially in the lungs. Overall, the maturation state of these enzymes is likely to mean that infants have a lower capacity to handle oxidative stress than adults.

In summary, children are not little adults. They have unique exposure pathways and are generally more vulnerable to exposure to environmental toxicants than are adults. Children require special consideration when framing environmental standards, and deserve to be protected by legislation.

Sufferers of multiple chemical sensitivity

A second example of a particular vulnerable population is characterised by individuals with multiple chemical sensitivity (MCS). MCS has been defined as follows:

*'...an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms.'*⁷

People with MCS suffer a wide array of symptoms, the most frequently reported being headache, fatigue, confusion, depression, shortness of breath, arthralgia, myalgia, nausea, dizziness, memory problems, gastrointestinal symptoms and respiratory symptoms.⁸ Other reported symptoms include anxiety, irritability and sleep disturbance.⁹ As such, MCS can be a debilitating condition and one consequence is that sufferers can become socially isolated. To make matters worse, it is possible that the term 'multiple chemical sensitivity' actually adds to the disease burden, as applying this label to patients can result in a worsening of their condition.¹⁰ Partly for this reason, some physicians prefer to use the term 'idiopathic environmental intolerance'. Also, MCS may be a misnomer since it assigns causation to chemical exposure when the evidence for this is considered by some not to be firm.¹¹⁻¹⁷

One area of controversy regarding the above definition of MCS concerns the expression 'chemically unrelated compounds', as no toxicological paradigm that could accommodate such unrelatedness is apparent. However,

in recent treatises on toxicological mechanisms of action, Pall argues in favour of a range of chemicals acting via a variety of pathways to stimulate the NMDA (N-methyl-D-aspartate) receptor in neuronal tissues (in the central and peripheral nervous system), resulting in generation of nitric oxide/peroxynitrite and subsequent release of inflammatory cytokines.^{18,19} This range includes chemicals such as monosodium glutamate, organophosphate/carbamate pesticides, organochlorine and pyrethroid pesticides, organic solvents, mycotoxins, capsaicin, carbon monoxide, hydrogen sulphide and methyl mercury.

This suggests that a wide range of seemingly unrelated chemicals are related mechanistically, and indicates that they may best be referred to as 'chemically diverse compounds'.

At odds with this toxicogenic view of MCS are data suggesting a psychogenic aetiology. Exposure chamber studies with MCS patients^{14,16,17} have demonstrated in some instances a lack of reliable response patterns; for example, symptoms were instigated with sham control exposures (clean air challenge) or with anticipation of a chemical challenge. This is not unlike the phenomena known as Pavlovian conditioning,²⁰ the nocebo effect²¹ (opposite of placebo) and mass sociogenic illness.¹⁵ While there is considerable polarity in aetiological beliefs about MCS causation, perhaps there is interplay of both toxicogenic and psychogenic mechanisms.

There are two further points on the mechanistic aspect. First, it has been noted that drug addicts going through withdrawal suffer symptoms quite similar to those of MCS patients, leading to the suggestion that there could be some common mechanistic underpinning of these two phenomena. This has brought together MCS and drug addiction specialists.²² Second, it has been documented that three-quarters of MCS cases are female,^{8,23,24} suggesting an underlying gender-specific mechanism.

One important avenue of research has aimed at determining whether there is any genetic aetiology in MCS. Investigation of the genes for cytochrome P450-2D6 and N-acetyl transferase-2—enzymes involved in toxin activation/inactivation and arylamine bioactivation, respectively—has suggested that rapid metabolism of both enzymes may confer substantially elevated risk of MCS.²⁵ In this same study the odds for being heterozygous for the gene coding for paraoxonase-1 (i.e. less able to metabolise organophosphate compounds) were significantly

higher in MCS cases.²⁵ Other work has demonstrated a significantly higher prevalence of the panic disorder-associated cholecystokinin B receptor allele 7 in MCS subjects compared with control subjects.²⁶

What is known of the prevalence of MCS in the community? A recent publication of self-reported MCS in South Australia indicates a prevalence of about 1%,²³ although a potential impost of false negatives²⁷ suggests a range of 0.5–2%.²³ Various overseas surveys report a range of 1–6%.^{24,28–31} This then is not an insignificant public health issue. In the South Australian survey 36% of MCS responders indicated that their family or social life was greatly affected.²³

Unlike the related chronic fatigue syndrome, there are currently no clinical management guidelines for MCS in Australia. This is one area that needs urgent attention, and some work has commenced in this regard in South Australia through the MCS Reference Group (comprising representatives from the Department of Health, several other government agencies including local government, MCS advocacy groups and general practitioners).

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Shellfish toxins

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Introduction

Shellfish have long been part of the Australian diet. Shell middens are relatively common features of our landscape, with some being thousands of years old. In recent years there has been an increase in the consumption of shellfish, which are low in saturated fat and, like other seafood, high in omega-3 fatty acids.

While Australia produces an abundance of high-quality shellfish, assurance of safety is a constant challenge because popular filter-feeding shellfish such as oysters, scallops and mussels concentrate organisms and substances present in their environment. This can include pathogenic bacteria, viruses, protozoa, biotoxins and heavy metals. Probably the best known example of this causing problems is the Wallis Lakes outbreak of 1997, where 442 cases of hepatitis A were attributed to oysters contaminated by septic waste.¹ Worldwide, biotoxins accumulated in shellfish have caused large numbers of outbreaks, several thousand illnesses and more than 200 deaths.² This has included limited outbreaks of relatively mild illness in Australia.³

To respond to this challenge, Australia has introduced shellfish quality assurance programs that are predicated on growing shellfish in protected 'clean seas'. These programs are supported by both government and the shellfish industry. In South Australia only shellfish farmed from growing areas classified as safe are sold for human consumption. These areas are located in high-quality oceanic waters, with the majority being along the coastline of Eyre Peninsula and others off Yorke Peninsula and Kangaroo Island.

The focus of shellfish quality assurance programs is to ensure that oysters, scallops and mussels are grown in areas of high water quality that are not impacted by sewage, industrial discharges and urban stormwater. These programs are very effective in preventing contamination from land-based sources of pathogenic micro-organisms and chemicals. However, there is an ocean-based source of toxins that also must be considered for human health risk assessment, namely biotoxins produced by naturally occurring microalgae. While the frequency of microalgal blooms may be

lower in protected waters, they cannot be eliminated completely. Normal practice for assuring safety is to monitor growing areas for microalgae and to test for biotoxins when necessary. This can include monitoring for established biotoxins such as okadaic acid and also dealing with emerging toxins such as pectenotoxins.

Marine biotoxins

Marine biotoxins are produced by microalgae, including dinoflagellates such as *Alexandrium*, *Dinophysis* and *Gymnodinium*. In sufficient numbers these organisms can produce red tides, but at much lower concentrations they are significant sources of biotoxins in shellfish.

Biotoxins can cause a variety of symptoms ranging from rapid and short-lived diarrhoea to death. Internationally, the most significant of the biotoxins are the paralytic shellfish poisons (PSPs), which have caused over 2000 illnesses and 200 deaths since the first cases were identified in Canada in the 1700s.² In Australia human health impacts have been largely limited to outbreaks of diarrhetic shellfish poisoning.³

Internationally, at least eight groups of marine biotoxins have been identified.⁴ These are summarised in Table 1.

Detection of biotoxins

The traditional method for detecting biotoxins was to inject mice intraperitoneally and to monitor for toxicity, which typically occurs within 24 hours. The use of mice has been increasingly questioned in recent years for reasons of ethics but also because of lack of specificity, particularly as the number and range of marine biotoxins of potential concern has increased. As shown in Table 1, there are a number of toxins that are toxic to mice but have no reported impacts on humans.

Expert consultations on biotoxins for the joint FAO/WHO Food Standards Programme⁴ and the European Food Safety Authority⁶ have both identified significant shortcomings with the mouse bioassay method due to high variability, insufficient sensitivity and limited specificity. It has been recommended that the safety of shellfish from biotoxins should be based on an integrated shellfish and algal monitoring program, with decisions on safety being based on direct chemical monitoring of marine biotoxins.⁴

Emerging toxins

The Codex Alimentarius Commission (CAC) indicated that guideline values or standards should only be set where there is evidence of harm to humans, either

Table 1: Biotoxins and potential impacts on human health

Biotoxin	Human health impacts	Australian Standard ^a
Azaspiracid	Acute gastrointestinal effects but limited data available	None
Brevetoxins	Neurotoxic shellfish poisons (NSPs)—acute gastrointestinal effects with mild gastroenteritis	200 mouse units/kg shellfish
Cyclic imines	Includes gymnodine, spirolides, pinnatoxins, proocentrolide and spirocentrimine—fast acting and highly toxic in mice but no evidence of human toxicity	None
Domoic acid	Amnesic shellfish poisoning (ASP). In mild cases—vomiting, diarrhoea and abdominal cramps, extending in severe cases to include dizziness, hallucinations, confusion and short-term memory loss. In extreme cases—death	20 mg/kg shellfish of domoic acid equivalents
Okadaic acid	Diarrhetic shellfish poisoning (DSP)—rapid onset (30 minutes to a few hours) of diarrhoea, nausea, vomiting and abdominal pain; complete recovery within 3 days even in the absence of treatment	0.2 mg/kg shellfish of okadaic acid equivalents
Pectenotoxins	Toxic to mice but no evidence of human toxicity	None
Saxitoxins	The most significant biotoxins from a public health perspective. Paralytic shellfish poisoning (PSP) is caused by a broad range of related toxins including saxitoxin, neosaxitoxin, c-toxins and gonyautoxins. In mild cases—within 30 minutes a tingling sensation or numbness around the lips, gradually spreading to the face and neck; a prickly sensation in fingertips and toes; headache, dizziness, nausea, vomiting and diarrhoea. In severe cases—muscular paralysis; pronounced respiratory difficulty; a choking sensation. In extreme cases—death through respiratory paralysis within 2–24 hours. People who survive the first 24 hours recover fully within 3 days	0.8 mg/kg shellfish of saxitoxin equivalents
Yessotoxin	Highly toxic in mice but no evidence of human toxicity	None

^a Source: FSANZ 2009 ⁵

from clinical data, epidemiological investigations or animal voluntary feeding studies.⁴ However, the option of waiting for evidence of harm is not a satisfactory approach and creates a practical difficulty for preventive programs that are intended to be protective of human health. Animal feeding studies are expensive, require quantities of purified toxin and present ethical issues. The good news is that assessing emerging biotoxins is not unique—similar challenges are faced in assessing emerging chemicals in many sources, including food and water, and a strategy has been developed to deal with these compounds. The threshold of toxicological concern (TTC) approach is a risk assessment tool based on the concept of deriving concentrations for chemicals that represent a very low probability of adverse health effects. Safe levels are determined by comparing the chemical structures of new compounds with those of established chemicals with known toxicity. A decision tree has been established for determining safe levels for various classes of chemicals including mutagenic, carcinogenic and non-carcinogenic compounds.⁷

As discussed elsewhere in this Bulletin, the TTC approach has been used for a range of chemicals, is considered applicable to food and water,⁸ and has been included in the *Australian Guidelines for Water Recycling*.⁹

Application of the approach follows a number of steps:

1. identification of the compound
2. determination of its chemical structure
3. evaluation of mutagenicity/carcinogenicity
4. classification using the decision tree of Kroes et al.⁷

Management of marine biotoxins

As recommended by CAC, the current approach for assuring the safety of shellfish from biotoxins is to undertake routine testing for microalgae to monitor for the presence of known toxin-producing species.⁴ This is supported, where appropriate, by testing of shellfish flesh for the presence of biotoxins.

Harvesting areas can be closed on a precautionary basis if significant concentrations of known toxin-producing algae are detected, or if concentrations of toxin exceeding those prescribed in the Food Standards Code for PSPs, DSPs, NSPs or ASPs are detected.⁵

Conclusions

Shellfish eaten raw or cooked have long been a part of Australian diets, and improved availability has allowed Australian consumers to enjoy increasing amounts of high-quality shellfish. Due to the ability of filter-feeding shellfish to concentrate contaminants and naturally occurring toxins, rigorous quality assurance programs have been established to ensure the safety of products that are sent to market. The focus of these programs is prevention. In the case of land-derived contaminants, this includes preventing exposure of shellfish-harvesting areas. For marine biotoxins, monitoring programs are used to detect the occurrence of potentially toxic microalgae prior to harvesting and marketing of shellfish.

The South Australian Shellfish Quality Assurance program has been applied successfully by government and industry to ensure that South Australian shellfish are of international quality. The program has successfully addressed existing and emerging toxins to ensure safety. There have been no recorded outbreaks of toxin-related illnesses associated with commercial shellfish harvested in South Australia. Ongoing vigilance is required to maintain this record.

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Nanotechnology: future benefits and hazards

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Nanotechnology is the term used to describe many new and emerging technologies, many of which are already impacting on our lives. They have in common the predetermined manipulation and use of materials at the nanometre level. A more strict definition has been provided by Borm and others, who state that nanotechnology is 'the manipulation, precision placement, measurement, modelling or manufacture [..at least in one dimension] of sub-100 nanometre scale matter'.¹

As far back as 1959 the American Nobel Prize-winning physicist, Richard Feynman, was prescient in appreciating the possibilities of nanometre-scale materials. However, only in the last decade or so has an appreciation of the remarkable potential of nanotechnology been popularly embraced. The commercial applications of nanotechnology are now widely believed by many to be the next industrial revolution. Indeed, hundreds of different products incorporating engineered nanoparticles (ENPs) are being sold in many countries including Australia. In the Consumer Products Inventory there are currently 1015 products, produced by 485 companies, located in 24 countries.² As with any new technology, there are and will be benefits, but there will also be potential for harm and adverse health effects if ENPs are not adequately scrutinised prior to public release. In short, we may have a dark cloud on the horizon—but we are also aware that this cloud has many silver linings.

It can be difficult to fully appreciate the scale at which these new technologies operate. An example may serve to illustrate this. Amongst the smallest ENPs are the fullerenes. Consisting of at least 60 carbon atoms and arranged in a soccer-ball or ellipsoidal configuration, they were first discovered in 1985 by Smalley, Kroto and colleagues (also Nobel Laureates for their efforts). In comparison to fullerenes, a human epithelial cell is approximately 70 000 times larger. The human oocyte, admittedly the largest cell type of the body, is about 700 000 times larger than a C-60 fullerene (Figure 1). If we assume a fullerene to be 1 metre in diameter, then a human oocyte would be equivalent to the distance between Melbourne and Sydney. This size disparity serves to illustrate a dilemma that toxicologists

are now addressing in their evaluations of the hazard potential of ENPs. On a per mass basis all ENPs have an extraordinarily large surface area compared to biological structures. Large surface areas in chemistry typically equate to increased reactivity and potential for harm. Consequently, toxicologists now consider surface area as one of several useful dose metrics in their studies.³

Fullerenes are by no means the only ENPs. There are many different forms of ENP; some of the major classes are represented in Figure 2. Prominent examples include

single-walled carbon nanotubes (SWCNTs), multiple-walled versions (MWCNTs), 'quantum dots' and metal / metal oxide nanopowders. There are also naturally occurring nanoparticles (such as viruses and bushfire smoke) as well as man-made 'incidental' nanoparticles (e.g. cooking smoke, diesel exhaust particulates and welding fumes). Our exposures to ENPs are expected to increase considerably in the near future. However, unlike our generally intermittent exposures to natural and incidental nanoparticles, the exposures to man-made ENPs are set to become incessant.

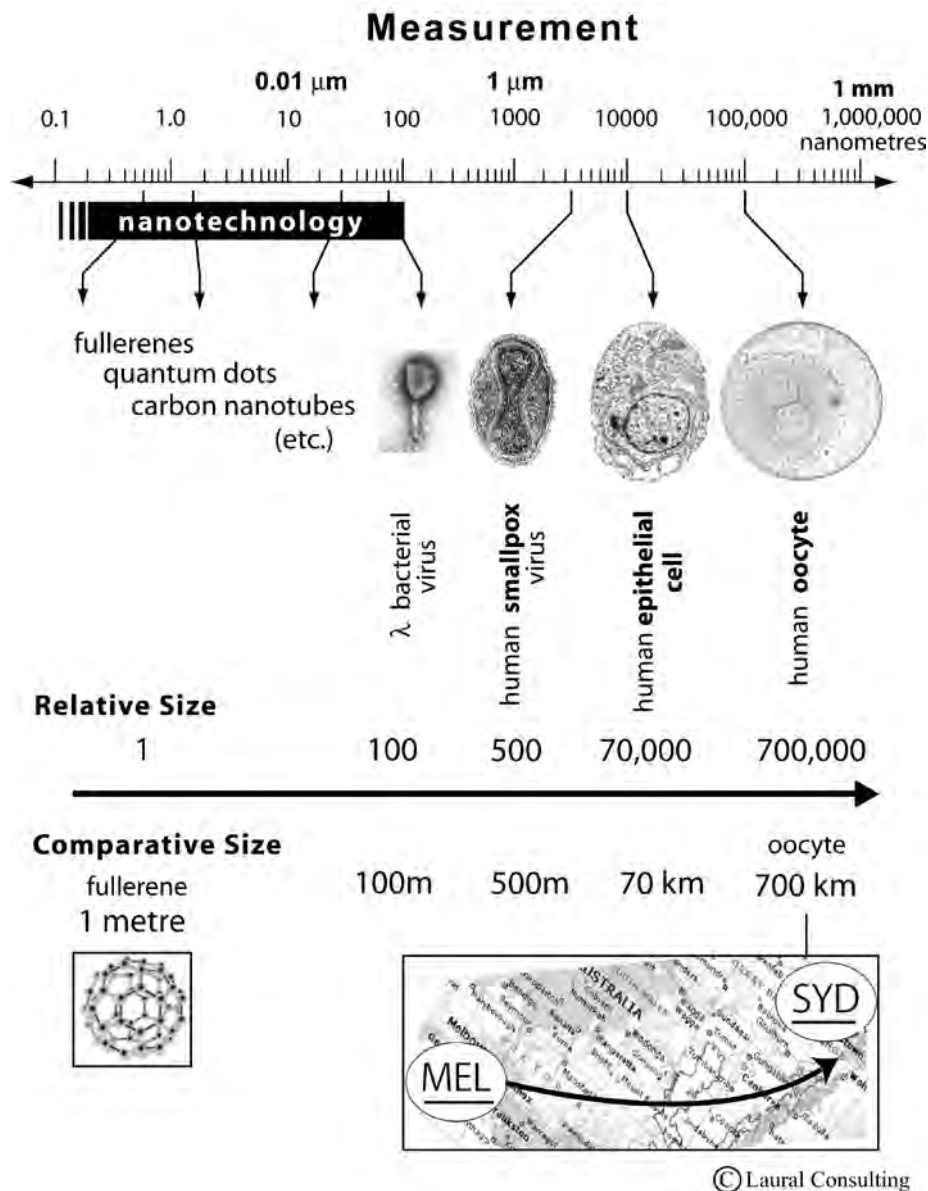


Figure 1: A comparison of the sizes of particles produced by nanotechnology with natural biological structures of interest. A 'real-world' comparative analogy of distance is provided for these chosen examples.

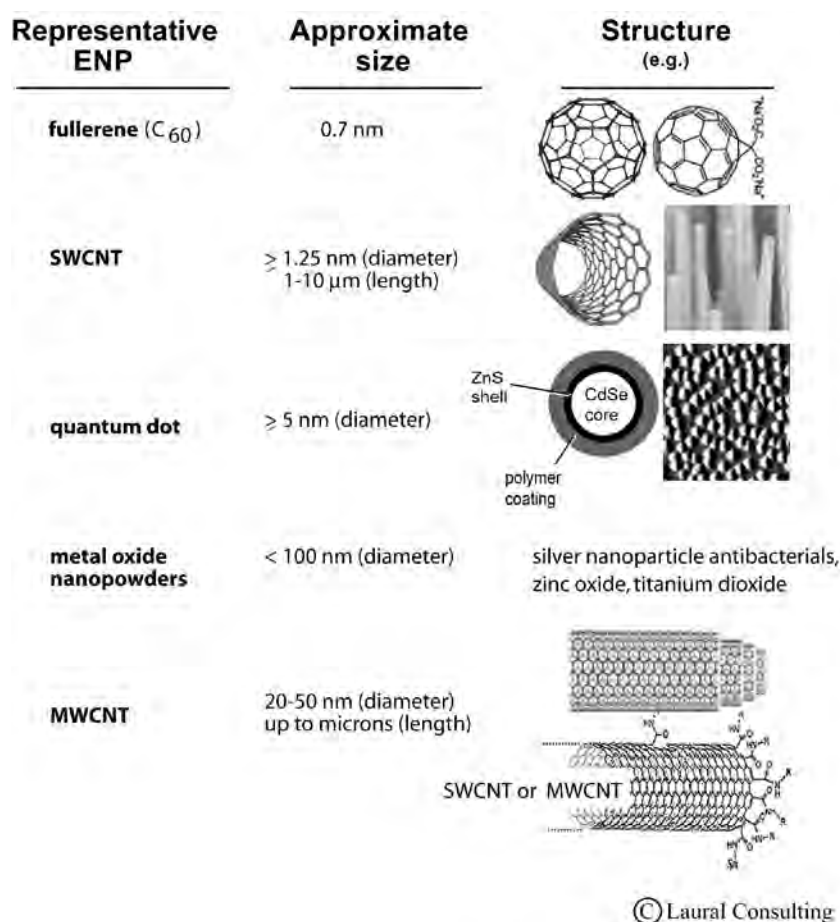


Figure 2: Some examples of major engineered nanoparticles (ENPs), their approximate sizes and structures.

The manufacture of ENPs is distinctive in another regard as well. In comparison to the natural and incidental nanoparticle versions, ENPs have predetermined nanometre size restrictions in at least one dimension. This ‘quantum squeezing’ can often lead to new and unexpected properties that cannot necessarily be predicted from the properties of the equivalent non-nanoscale material. For example, SWCNTs and MWCNTs are much stronger than carbon, having a per mass strength far greater than steel, and are also unusually conductive. This has created much enthusiasm; for example, SWCNT products have been synthesised that will improve power supplies for medical and portable electronic devices.⁴ There have also been substantial advances in the use of other ENPs across the board. Notable examples include those in primary diagnosis,⁵ biomedical and diagnostic imaging (e.g. quantum dots), targeted drug delivery and chemotherapeutics, solar cells, housing and construction (among many others).

In the meantime the goal posts have been shifted. Traditionally, toxicologists have viewed chemical structure and composition as two of the most important criteria in determining toxicity. Now, however, comes the realisation that ENP hazards can depend just as much on size and shape. A recent study by Poland and co-workers has provided an excellent example of this.⁶ In a well-conducted investigation, these authors were able to correlate MWCNT-mediated pulmonary inflammatory responses and downstream granuloma formation with the shape characteristics of administered MWCNTs in experimental animals. This study—and other prominent studies—support the belief that carbon nanotubes can resemble certain forms of asbestos fibres in that they are mechanically strong and, following aggregation, have a shape similar to some harmful forms of asbestos.⁷ Nonetheless, the toxicology community is still divided on the relevance of asbestos to carbon nanotube toxicity.⁸

Another level of complexity presents itself. Many ENPs can be chemically altered (i.e. 'tailored'), thereby considerably increasing the potential number of ENPs. Such 'functionalised' ENPs and their uses are only effectively limited by the power of the human imagination (Figure 2 provides two examples). The difficulty is that each individualised ENP will, by definition, have different properties to its parent—they may be either more benign or more reactive. A case-by-case evaluation of ENP product safety seems to be an inefficient if not totally daunting task. New thinking and approaches must therefore be embraced in order to test emerging ENPs on such a grand scale. For regulatory toxicologists charged with hazard evaluation and public safety, the answer should be readily apparent in the high-throughput, tiered systems of safety evaluations used for new drug development.

These sophisticated and established protocols now incorporate the best and most robust of in-vitro, genomic, proteomic, metabonomic, in-vivo and clinical pathology testing systems currently available. They function well because of the redundancies in the processes used and the integration of information across many different platforms. However, no single tier works in isolation. For example, although cell culture and model organism test systems can yield invaluable data on the mechanisms of chemical and drug toxicity, some toxicologists are still reticent to extrapolate directly to the human condition. In-vitro cell culture data are typically integrated with other tier data to provide a complete picture of the potential impact of unknown agents on human health. Nonetheless, many recognise that we are still falling short of the information required to do complete and thorough safety/risk assessments on most, if not all, ENPs.⁸

In the absence of such information, what are our options? Some information is already in the pipeline. The Australian Federal Government, through Safe Work Australia, has commissioned an analysis of the potential occupational exposures to nanomaterials in selected Australian workplaces. In the last year a major collaborative effort between the US and European governments has requested comprehensive profiles of ENPs from initial synthesis to eventual disposal (so-called 'life-cycle analysis' of ENPs). At this stage much of the data required to do comprehensive risk assessments are still being generated. In Australia we have the skills to do more to evaluate hazards. For example, an initiative to tier-test toxicity on a high-throughput level could—or perhaps must—be centrally supported. In the meantime, as the guardians of public

wellbeing, we must adopt a conservative approach to the adoption of nanotechnologies in the absence of definitive information regarding risk or hazard. This is often referred to as the 'precautionary principle'. Simply stated, it is a moral and political obligation that limits action in the absence of any scientific agreement with regard to potential harm. It is as your mother would have stated: 'best be careful' or better safe than sorry'. More specifically, others have already voiced their opinions on the matter. For example, Seaton has stated 'For the moment, it would be no bad thing if they [CNTs] were to be treated by those making and using them as though they were asbestos...'.⁹

Ultimately, it is important to recognise that the absence of any evidence of harm does not necessarily imply that there is no potential for harm. In lieu of us obtaining such evidence, it would be a shame that an otherwise bright and promising 'cloud' (i.e. nanotechnology) were to become dark and rain on our parade.

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Complementary medicines: the good, the bad and the ugly

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Introduction

In Australia medicinal products containing herbs, vitamins, minerals and nutritional supplements; homoeopathic medicines; and certain aromatherapy products are referred to as 'complementary medicines'. They are regulated as medicines under the Therapeutic Goods Act 1989, and include traditional (Chinese, Ayurvedic and Australian indigenous) medicines (Figure 1). Other terms sometimes used to describe these products include 'alternative', 'natural' and 'holistic' medicines.¹

The public is increasingly turning to complementary medicines for proven or perceived health benefits. A recent national population-based study reported that in 2005 complementary medicines were used by almost 70% of Australians, costing an estimated A\$1.86 billion per annum.² This prevalence has been steadily increasing across Western countries since the early 1990s.^{2,3} Complementary medicines are used widely by 'self-medicators' to treat specific medical conditions. More recently, these products are also being promoted to maintain or enhance health and wellbeing and prevent disease. Two important factors have driven this development in the market. First, consumers are

increasingly taking charge of their own health, which creates demand for health-related products and services. Second, scientific understanding of the health benefits of herbal preparations has improved and is being extensively communicated to the public.⁴

Protecting the public from potential harmful use of complementary medicines presents a significant challenge for health agencies and regulators. Australia has a two-tiered regulatory system for medicines, based on risk. Complementary medicines available for supply in Australia are included on the Australian Register of Therapeutic Goods (ARTG) as either Listed (low risk) or Registered (higher risk) medicines. Listed complementary medicines may only contain ingredients permitted by the Therapeutic Goods Administration (TGA) for use in low-risk products, and are not assessed individually for efficacy. Registered complementary medicines are assessed individually for quality, safety and efficacy. Post-market regulatory activities—reporting of adverse reactions, auditing of manufacturers, and laboratory testing—are important elements in ensuring the quality, safety and effectiveness of medicines regulated by the TGA.¹

In the current regulatory framework for complementary medicines in Australia, ensuring the safety of these medicines is hampered by uncertainty associated with toxicity (intrinsic and incidental), dose and the chemical composition of certain members of this class of products. Other contributing obstacles include general public perceptions of the safety of 'natural' products, inadequate regulatory controls, poor pharmacovigilance (e.g. under-reporting and lack of case details), insufficient scientific validation through clinical trials and toxicological assessment.

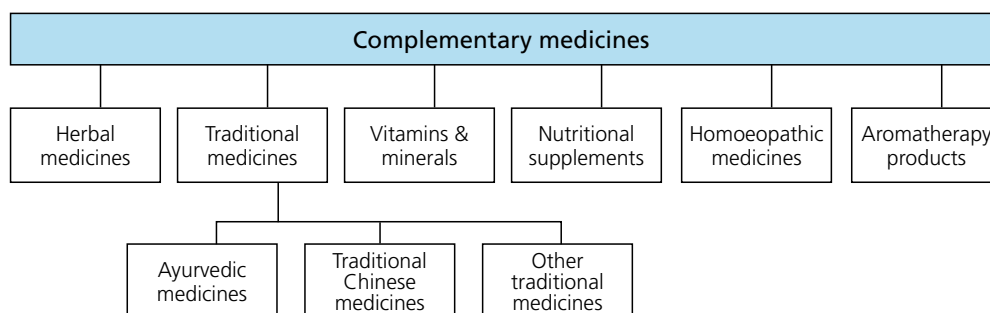


Figure 1: Classes of complementary medicines¹

This article focuses largely on herbal medicines. It contains a list of clinically relevant issues with complementary medicines from the peer-reviewed literature that challenge the common public perception that 'natural' products, in the form of complementary medicines, are inherently 'safe'. Some potential toxicity issues associated with three commonly used complementary medicine ingredients in Australia (black cohosh root, *Ginkgo biloba* extract and fish oil) are briefly reviewed. The activities or proposed refinements by the TGA to the regulatory environment associated with these ingredients to ensure the ongoing safety of products containing these ingredients are described.

It is 'natural', therefore it is 'safe'

There is a common belief in the community that natural products are 'safer' than products from other sources.⁵ In the case of complementary medicines this may not necessarily be true. The fact that many in the community believe that complementary medicines, in particular herbal medicines, are 'natural' belies the fact that many of these products are formulations of complex solvent extracts of herbal preparations containing multiple herbal ingredients. In some cases the transition from traditional use (i.e. teas and infusions) to Westernised formulations (i.e. solvent extracts) has altered, and in some cases worsened, the toxicological profile of complementary medicines. An overview of the peer-reviewed literature that highlights key factors contributing to the potential toxicity of some complementary medicines is presented in Table 1.

Table 1: Factors contributing to the toxicity of complementary medicines

Factor	Complementary medicine example	Toxicity/Quality
Intrinsic toxicity of naturally occurring plants	Comfrey herbal tea— <i>Symphytum</i> spp. ^{6,7}	Pyrrrolizidine alkaloid content leads to hepatotoxicity
Substitution with an incorrect part of the plant or misidentified plant species of greater toxicity	Aristolochia spp. inadvertently substituted for herbs with similar appearance or name in Chinese medicines ^{7,8}	Aristolochic acid is a nephrotoxic carcinogen
Plants of variable toxicity determined by: time and place of harvesting variation in metabolites between plants of the same species variable bioavailability inappropriate storage	Milk thistle fruit— <i>Silybum marianum</i> used for its hepatoprotective effect ³	Different preparations of the same herb produced different plasma concentrations and side effects (gastrointestinal, headache, skin reactions)
Actual concentrations differ from manufacturers' claims due to variable: extraction methods purity stability of active ingredients	Phyto-oestrogen soy supplements ⁹	Isoflavone levels in soy supplements can deviate from claimed concentrations depending on the starting materials used
Multiple active ingredients with different quality, safety and efficacy and no toxicological profile of mixtures	PC-SPES—a combination of 8 herbs used to treat prostate cancer ¹⁰	Promoted as a non-oestrogenic dietary supplement, but some ingredients have oestrogenic activity, with confounding effects on concurrent treatments, unknown clinical implications and the potential for adverse side effects
Adulteration with undeclared pharmaceuticals intended to improve the efficacy of the product	Chinese medicines used to treat inflammation and erectile dysfunction and to encourage weight loss have been found to contain: corticosteroids sildenafil <i>N</i> -nitrosufenfluramine ³	<i>N</i> -nitrosufenfluramine has been linked to hepatic failure and is a potential hepatic carcinogen

Table 1: Continued

Factor	Complementary medicine example	Toxicity/Quality
Chemical or microbial contamination	Ayurvedic and Chinese medicines contaminated with lead, arsenic and mercury arsenicosis in kelp <i>Aspergillus</i> sp. and <i>E coli</i> present in various herbal medicines	Neurotoxicity and other effects of heavy metal poisoning
Herb–drug interactions that reduce or increase plasma drug levels, or potentiate or antagonise therapeutic effects	St John's wort— <i>Hypericum perforatum</i> ⁶	Reduced plasma levels of many therapeutic drugs including digoxin, warfarin and theophylline; the mechanism is thought to be via metabolic enzyme activation by <i>Hypericum perforatum</i>
Non-traditional methods of preparation (including the use of non-traditional solvents) changing the toxicological profile	Kava kava— <i>Piper methysticum</i> ¹¹	Ethanol–acetone extracted preparations have been linked to hepatotoxicity, whereas there is no evidence to support the fact that the traditional aqueous-extracted preparation is hepatotoxic
Preparations compounded without reference to good manufacturing practice	PAN Pharmaceuticals ¹²	Poor manufacturing practices including substitution, falsified assay results, misidentification of raw ingredients and contamination led to the world's largest product recall
Consumer-related factors such as: age health status (e.g. liver and renal function) pharmacogenetics	Belladonna, <i>Digitalis lantana</i> and Ayurvedic herbs ³	Genetic differences in cardiac effects of digoxin and the belladonna alkaloid, atropine Genetic enzyme deficiency linked with haemolysis in patients using certain Ayurvedic herbs

Evaluation of ingredients permitted in Listed medicines: three case studies

In Australia the vast majority of complementary medicines in the market are Listed medicines, which may be supplied only if they contain active ingredients permitted under Schedule 4 of the *Therapeutic Goods Regulations 1990*. These are substances that have been evaluated by the TGA and found to be of low risk.¹ Given that, of 12 December 2007, the list of substances that may be used in Listed medicines in Australia ran to 169 pages, the process and the level of rigour that the TGA was able to provide to each of these evaluations is not entirely clear.

Despite improved scientific understanding associated with herbal medicines, there continues to be a paucity of documented mechanisms of action, toxicological assessments and clinical trials that meet the rigorous methodological and reporting standards of the

randomised double-blind placebo-controlled trials, when compared with the dataset that supports the safety assessment of conventional medicines. Where risks or potential risks are identified in association with the use of a particular substance (e.g. in its use by particular population subgroups, such as children or pregnant women, or in its interaction with other medicines), certain restrictions and/or controls may be imposed (such as the use of label advisory information) to manage the risk. However, the substance may still be eligible, with restrictions, for use in Listed medicines.¹

As a case study we have chosen to briefly review some toxicological hazards associated with three Listed ingredients commonly used in complementary medicines in Australia. We note activities or proposed refinements to the regulatory environment associated with these ingredients by the TGA to ensure the ongoing safety of products containing these ingredients.

Black cohosh

Black cohosh (*Cimicifuga racemosa*) is a herb that has a long history of traditional use (in North America) in Native American medicine. It has also been widely used in Western cultures since the early 1800s.¹³ More recently, solvent extracts of black cohosh root have been used for the relief of symptoms of menopause. Reported adverse events are rare; however, there have been a number of clinical reports describing hepatic injury associated with the use of black cohosh root preparations.^{14,15} In 2005 the TGA reviewed the safety of black cohosh following international and national reports of possible liver damage. At that time there were 47 cases of liver reactions worldwide, including nine Australian cases. Four Australian patients were hospitalised and two required liver transplantation. Some reports are confounded by concurrent medication use, multiple ingredients in black cohosh preparations, or pre-existing medical conditions. However, the TGA and the European Committee on Herbal Medicinal Products determined that there was sufficient evidence of a causal association between the start of treatment with black cohosh and serious hepatitis.^{13,16} Subsequently, the TGA announced new labelling requirements and consumer information for products containing black cohosh.¹³

While regulatory agencies in Australia and internationally were reviewing the case reporting literature, a mechanistic study investigating potential mechanisms associated with the hepatotoxicity of black cohosh root extracts was being conducted in experimental animals, hepatocyte cultures and liver isolates.¹⁷ The main finding, both in vivo and in vitro, was hepatic mitochondrial toxicity and inhibition of β -oxidation and the respiratory chain, eventually leading to apoptotic cell death. Relatively strong inhibition of β -oxidation appeared at low concentrations in vitro (starting at 10 $\mu\text{g/mL}$), suggesting that it represents the most likely mechanism of mitochondrial toxicity associated with black cohosh.

To assess whether toxic concentrations are within the range of plasma concentrations reached after ingestion of black cohosh tablets, a rough 'back of the envelope' estimate of maximal plasma concentration following a single dose has been made. Using the following crude assumptions—that a preparation containing 20 mg of extract (consistent with manufacturers' recommended doses of 20 mg twice a day) is ingested, rapidly absorbed and widely distributed (plasma volume 3.5 L); and that there is an absence of significant

metabolism—a maximal plasma concentration in the range of 6 $\mu\text{g/mL}$ could be reached following a single dose. This value, which does not include any assumptions regarding repeated dosing, approaches the concentration found to inhibit β -oxidation in vitro but is 30–150 times lower than the lowest concentration associated with cytotoxicity or apoptosis respectively.¹⁷ Therefore, the authors of the study stated that, while the inherent toxicity of black cohosh root extract was not clinically relevant for most patients, the results were compatible with idiosyncratic hepatotoxicity as observed in patients treated with Cimicifuga extracts.¹⁷

Ginkgo biloba

Ginkgo biloba is a deciduous tree native to China, Korea and Japan. Ginkgo leaves and seeds have a long history of use in traditional Chinese medicine for a range of conditions.¹⁸ More recently, standardised dried leaf solvent extracts of *Ginkgo biloba* characterise the Western use of this traditional herbal medicine to treat various non-specific cardiovascular disorders. Ginkgo leaf extracts are examples of modern non-traditional phytopharmaceutical herbal materials that have very little, if any, relationship to the original crudely refined, dried powder, tea form on which their 'traditional safety' was based.

It is worth noting that ginkgo leaf contains a number of compounds implicated in serious adverse health effects, specifically alkylphenols (ginkgolic acids) and 4-O-methylpyridoxine (ginkgotoxins). Processes used to manufacture ginkgo leaf extracts can concentrate these acids and toxins to levels that may cause harm.

Of particular concern is 4-O-methylpyridoxine, which is primarily found in *Ginkgo biloba* seeds but also at lower concentrations in the leaves. The presence of 4-O-methylpyridoxine in the seeds (nuts) of *Ginkgo biloba*, a food delicacy in China and Japan, led to its consideration as a novel food in Australia and New Zealand by Food Standards Australia New Zealand (FSANZ).¹⁹

Toxicological investigations have determined that 4-O-methylpyridoxine competitively inhibits the action of vitamin B6 (pyridoxine)—a co-enzyme in amino acid metabolism.²⁰ Ginkgo seed poisoning is characterised by repetitive seizures. It is thought that these convulsions are induced by the reduced synthesis of the inhibitory neurotransmitter γ -aminobutyric acid by 4-O-methylpyridoxine, and a concomitant increase in the production of the excitatory neurotransmitter,

glutamate. It is postulated that the repetitive nature of these seizures may be due to the repeated excretion of 4-O-methylpyridoxine via the enterohepatic circulation.²¹ The fatal dose varies as a poorly defined interaction between the serum concentration of 4-O-methylpyridoxine and the individual's nutritional state, particularly as it relates to pyridoxine storage.

Investigations of commercial liquor extracts of ginkgo leaf during the manufacturing process of dried leaf extracts have identified 4-O-methylpyridoxine concentrations of 4–10 µg/mL. This corresponds to a final concentration of about 100–250 ppm in the resultant dried extract.²² A pharmacokinetic calculation raises doubt as to whether standardised dried ginkgo leaf extracts containing 250 ppm of 4-O-methylpyridoxine are safe for consumers. A plasma concentration of 4-O-methylpyridoxine of 0.012 µg/mL after a single oral dose of leaf extract (240 mg/day) can be calculated using the following crude assumption—full absorption and uniform distribution (volume of distribution 5 L). This is less than an order of magnitude below plasma concentrations known to cause convulsions in vulnerable patients.

Recent case reports suggest a plausible association between 4-O-methylpyridoxine in ginkgo leaf extracts and serious adverse health effects, demonstrated by the onset of seizures in elderly patients within 14 days of commencing oral ginkgo leaf extract therapy.²³

In Australia, for regulatory purposes, the British Pharmacopoeia (BP) is currently the source of official standards.¹ The BP 2009 has two monographs for ginkgo: *Ginkgo leaf*²⁴ and *Ginkgo dry extract, refined and quantified*.²⁵ The *Ginkgo leaf* monograph describes the chemical content (\geq 0.5% flavonoids) and physical characteristics of the dried leaf of *Ginkgo biloba*.²⁴ The *Ginkgo dry extract* monograph has a more refined chemical specification, including for the flavonoids (22–27%), bilobalide (2.6–3.2%), the ginkgolides (2.8–3.4%) and the ginkgolic acids (maximum 5 ppm); however, there is no reference to 4-O-methylpyridoxine.²⁵

A recent alert by the TGA notes that there are currently more than 400 products that contain ginkgo on the ARTG. The TGA has recently conducted testing on 22 batches of medicines, covering 20 products, and a number of associated ginkgo extract raw materials. The testing focused on determining the quality of the ginkgo extract used in formulation of the medicines. In some of the samples tested, elevated levels of

quercetin and rutin (flavonoids) were noted (a quality characteristic). The TGA is currently working with its expert advisory committees and the complementary medicines industry associations to refine the quality standards for ginkgo extracts used in medicines available in Australia.¹⁸ Perhaps this review offers the TGA an opportunity to further investigate the appropriateness or otherwise of including a safety-based limit for 4-O-methylpyridoxine in these quality standards.

Contamination of fish oil supplements

Since the publication of pioneering studies in the 1980s demonstrating low rates of death from coronary heart disease among Greenland Inuit people, fish has been considered a healthy food. During the ensuing years, evidence has identified two long-chain n-3 polyunsaturated fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—as the likely responsible constituents. As a result, fish oils derived from the liver or tissue of fish are used widely as dietary supplements, with an ever-increasing range of purported health benefits including improved cardiovascular, renal, joint, immune and cognitive function.

One of the disadvantages of using fish oils as dietary supplements is the potential for increasing exposure to persistent organic pollutants, including dioxins, dibenzofurans and polybrominated diphenyl ethers. Many fish species bioaccumulate these contaminants, which are lipophilic and thus associated with lipid-rich tissues such as the liver and oil-rich muscle. Recent international studies indicate that some fish oils, when used in accordance with manufacturer-recommended doses, would exceed the provisional monthly tolerable intake of dioxins set by the Australian National Health and Medical Research Council, which is intended to protect against negative health implications, including cancer, endocrine and reproductive dysfunction.^{26–28}

A recent alert by the TGA in the form of a draft compositional guideline for fish oil intends to address the concerns associated with incidental constituents, such as the presence of dioxins, furans and polychlorinated biphenyls, by developing acceptance criteria similar to those set in other recognised pharmacopoeia.²⁹

Conclusions

Safety assessment of complementary medicines is a field where more information of a toxicological nature will be available to refine the safety profile of these products over time. The above case studies demonstrate how fragments of a toxicological database may be used to assist regulators in potentially responding to, and proactively improving the safety of, complementary medicines in Australia.

It is reasonable to conclude from reviews of clinical trial data and spontaneous reporting programs that adverse events associated with the use of complementary medicines are rare, generally mild and reversible. However, the potential for serious adverse effects exists, and is clearly highlighted by the case studies presented in this article. The unpredictable toxicity of complementary medicines remains a concern for practitioners, the public and public health regulators.

Improving the safety of complementary medicines requires combined efforts from scientists, health professionals, government and industry. Four key areas that need strengthening are:

- > a greater focus on investigating causal relationships between complementary medicines and adverse health effects through toxicological assessments
- > improved pharmacovigilance systems to enable relevant data to be collected
- > robust regulatory controls supported by adequate monitoring and enforcement
- > effective risk communication to consumers.

Injury prevention relies on these efforts increasing in tandem with the growing public demand for complementary medicines and their expanding role in health promotion.

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Consumer product safety and chemical contamination

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Introduction

The chemical contamination of consumer products is a public health issue that has serious and wide-reaching health consequences, which have increased over recent years with the globalisation of trade. From 1990 to 2007 Food Standards Australia and New Zealand (FSANZ) issued 786 recalls for food that posed a potential safety risk to consumers. Of these, 74 were for chemical contamination of the food product.¹ The Therapeutic Goods Administration (TGA) recalled 172 medicines and 1110 medical devices for the period 2006–09, of which 26 medicines and 33 medical devices were recalled due to possible contamination. For the period 1998–99 to 2007–08 the Australian Competition and Consumer Commission (ACCC) reported 1636 product recalls and the Australian Pesticides and Veterinary Medicines Authority (APVMA) reported 15 product recalls,² but the extent to which they were for chemical contamination is not publicly accessible. In the United States, during the 2-year period 2007–08, the Consumer Product Safety Commission (CPSC) reported almost 200 toy and children's products recalled due to lead contamination, and a further 4 products recalled due to other chemical contaminants.³

In Australia the chemical safety of products is regulated via a number of agencies and tools, leading to a complex web of regulation and responsibility. This outcome has arisen from historical approaches, societal changes and systems of local, state and federal governance within Australia. The public health response to chemically contaminated products requires an understanding of both the regulations and the responsible agencies. This paper describes this regulatory web, and documents four incidents of chemical contamination of products, and the regulatory and public health responses.

The web of regulation

The foundations of public health legislation throughout Australia were the British Public Health Act 1848 and the Nuisance Removal and Disease Control Act 1848. These pieces of legislation addressed the miasmatic view of disease causation, an influence that persisted in most Australian public health law until recently. Even now, most state public health legislation does not specifically address chemical contamination of consumer products, but rather concepts around 'nuisance' or 'risk' or 'harm to public health'.⁴ While these definitions may very well capture public health risk from unsafe chemically contaminated products, the New South Wales *Public Health Act 1991* has yet to be invoked for such a purpose. Indeed, it is acknowledged that, while they may not be recognised as public health laws, other pieces of legislation, such as the *Trade Practices Act 1974* (Cwlth), work to protect the health and wellbeing of the community. The penalties and administrative powers under several of these legislative instruments allow them to be more versatile and responsive to chemical contamination incidents.⁵

Subsequent to the first public health Acts, specific food safety Acts were developed in the early 1900s. Food safety has long straddled the realms of safe agricultural production and public health, but has historically been the charge of health departments in Australia. This remains the case, with the exception of New South Wales (NSW), where the *Food Act 2003* is under the jurisdiction of the Department of Primary Industries.

In the 1970s consumer protection laws came into effect following the growing acknowledgment by government that current common law solutions were inadequate. Developed under systems of village and single-merchant trading, the previous pieces of legislation were no longer applicable to the complex marketplace driven by a society of mass consumption and supplied by large corporations. This led to the development of the Australian *Trade Practices Act 1974* and associated state fair trading Acts.⁶ While these Acts cover many different topics with regard to trade, Part V of the *Trade Practices Act 1974* deals specifically with consumer protection and product safety. Various state legislation, such as the *NSW Fair Trading Act 1987*, Parts 3 & 4, further expand on this topic. This legislation deals with unsafe, defective and 'not to specification' products in the marketplace. Although these pieces of legislation do not specifically mention chemical contamination of products, the scope of the definition of product safety within the Acts is large enough to capture this concept.

In order to allow a more harmonised approach to consumer protection, a single national consumer law for Australia will be adopted by all states, territories and the federal government. Developed under the framework of Australian Consumer Law, it has been designed with the intent of improving consumer wellbeing, fostering effective competition and enabling confident participation of consumers in markets.⁷ Its full implementation is anticipated by 2011.

Other pieces of legislation may also be used to regulate products within the marketplace. The importation of goods into Australia may be subject to legislation including the *Customs Act 1901* and the *Quarantine Act 1908*.

Contaminated consumer products detected through clinical effects

Bindeez™ beads

Bindeez™ beads won the Australian Toy of the Year award in 2007. The toy consisted of numerous individual coloured beads approximately 5 mm in diameter. Children could create pictures or patterns with the beads and permanently fix the pattern by spraying water on the beads. The toy was manufactured in China and distributed to approximately 40 countries including the United States, United Kingdom, France, Germany, Spain, Italy, Australia and New Zealand.

On 5 November 2007 NSW Health was alerted that two children had been admitted to an intensive care unit with severe central nervous system depression. Both children had a history of recently ingesting and regurgitating a substantial number of Bindeez™ beads. Gamma-hydroxybutyrate (GHB) was detected in the urine of both children.⁸ Testing of several samples of Bindeez™ beads, including some from the affected children, revealed that the chemical used to coat the beads (that set the pattern when activated by water) was 1,4 butanediol instead of 1,5 pentanediol as required in the manufacturer's specifications.

Unlike 1,5 pentanediol, 1,4 butanediol is rapidly metabolised to GHB in the body. GHB is a central nervous system depressant that can induce effects ranging from drowsiness, disinhibition, nausea, euphoria and loss of consciousness to seizures.⁹ Effects occur quickly post ingestion, GHB is rapidly excreted and symptoms usually resolve within about 8 hours.¹⁰ It is for its overall effect that GHB has found a place in the recreational drug culture.

In response to these findings, NSW Health advised the NSW Department of Fair Trading. An interim ban was placed on Bindeez™ beads under the NSW *Fair Trading Act 1987*. All state and federal jurisdictions were notified of the situation, and all other states and territories imposed similar interim bans within the next 2 days. A voluntary recall of all Bindeez™ beads products by the Australian distributor was undertaken within 2 days of the initial NSW ban.

During 6–9 November 2007 clinical fact sheets were developed and distributed to emergency departments, general practitioners and paediatricians around Australia. Question and answer sheets were developed for the public and translated into 15 languages, and a technical fact sheet was developed for regulators. The World Health Organization was informed through an International Health Regulation notification regarding the situation, leading to worldwide dissemination of information about the problem. International recalls of the product were immediate: the US CPSC announced a voluntary recall on 7 November 2007, and in the same week France listed Bindeez™ beads on the European Union Rapid Alert System For Non Food Products as a voluntary recall by the importer.

Further batch testing of the products confirmed that the contamination was widespread. Active case identification in Australia and New Zealand discovered seven more cases—three occurred before 5 November 2007, one after that date, and three had no onset data. Newspaper reports in the US quoted the CPSC as identifying nine children that had been affected by the beads in early November 2007.¹¹

The issue led to a NSW Product Safety Committee Inquiry recommending that: a permanent ban be placed on bead toys containing 1,4 butanediol; testing methods for toys be reviewed; and warning labels be improved. The permanent ban, to replace the previous interim ban, came into effect in NSW on 18 December 2007, and in other states and territories shortly afterwards. The Australian Minister for Competition and Consumer Affairs placed an 18-month ban on the supply of bead toys containing 1,4 butanediol, effective from 7 February 2008.

The National Industrial Chemical Notification and Assessment Scheme (NICNAS) undertook a review of 1,4 butanediol to investigate its use and safety in Australia and the adequacy of current regulatory controls. In April 2008 NICNAS made recommendations to the National Drugs and Poisons Schedule Committee

(NDPSC) on the scheduling of 1,4-butanediol in the Standard for the Uniform Scheduling of Drugs and Poisons (the standard).¹² Subsequently 1,4 butanediol was banned for all domestic use through Appendix C of the standard; and is now listed as an illicit drug precursor under the Code of Practice for Supply Diversion to Illicit Drug Manufacture in several Australian states.

Toy beads have since re-entered the market, with commitments from the NSW Office of Fair Trading to monitor their reintroduction and ensure that they are free from contamination.

Bonsoy soy milk

Bonsoy is a soy milk product manufactured in Japan and exported around the world, including to Australia, where it is distributed through major supermarket chains and organic food suppliers. It contains kombu (sea kelp) that is said to enhance the flavour and texture.

On 23 December 2009 NSW Health was notified of a cluster of eight cases of people with thyroid conditions, including one of congenital hypothyroidism. Investigation by the attending physician revealed that all cases (including the mother of the affected infant) had consumed Bonsoy soy milk. Testing of several batches of Bonsoy revealed elevated levels of iodine within the product, to the extent that daily consumption of 30 mL by an adult or 5 mL by a child would exceed the safe upper limit for iodine intake. Sampling of other popular soy milk products on the market did not find elevated iodine levels.

Iodine is an essential mineral that is required to ensure normal hormonal function. However, excessive iodine intake can lead to thyroiditis, goitre, hypothyroidism, hyperthyroidism, and acneiform or other cutaneous eruptions. Symptoms of thyroiditis include a painful enlargement or distension of the gland, fever, malaise, anorexia, dysphagia, palpitations, weight loss and tremors.¹³ Symptoms of hyperthyroidism include palpitations, fatigue and weight loss,¹⁴ whereas hypothyroidism can cause fatigue, weight gain, depression and slow mental processing.¹⁵ Excessive iodine exposure during pregnancy is especially dangerous because the foetal thyroid is less able to escape the inhibitory effects of iodine on thyroid hormone formation.¹³

NSW Health notified the NSW Food Authority, FSANZ and other state health departments, and a national

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recall of the product occurred on 24 December 2009. Investigations are underway to determine the national health impact of this event and the exact cause of the contamination.

A similar cluster of thyrotoxicosis associated with a particular brand of soy milk was reported in New Zealand in 2005. The authors note that, while this product was also demonstrated to have elevated levels of iodine, no regulatory action was taken as the manufacturer cooperated and reformulated the product.¹⁶

Contaminated consumer products detected through surveillance

Lead in toys

Global attention focused on the hazard of lead in toys in 2007 with the recall of over 6 million toys.¹⁷ Prior to this there had been recent evidence of harm to children from lead in toys, with a death in 2006 and a poisoning in 2003 in the US.^{18,19}

In March 2007 routine testing by the US CPSC detected levels of 5000 ppm lead in the paint of Elite Operations action figures, resulting in 130 000 toys being recalled.¹⁷ In response to this incident, the US toy industry undertook voluntary lead testing of their products during June, leading to the recall of 1.5 million Thomas & Friends toys in the US alone. Similar voluntary recalls were announced in Australian states. In August 1 million Fisher Price character toys and 250 000 Mattel die-cast cars were recalled internationally. Recalls continued into September with more Mattel, Fisher Price and Thomas & Friends products being withdrawn worldwide.

In most cases the lead was present in the bright durable paint coatings of the toys, although in some cases it was incorporated in the matrix of soft plastic toys, or in the chief component of toy jewellery, charms and magnets.

These lead contamination incidents occurred in the context of a toy industry that had shifted from predominantly US or local manufacture to one in which 87% of toys in the US were imported, 74% from China.¹⁷ Leaded paint is still widely available in some Asian countries—for example, in 2005, 66% of new house paint in India, China and Malaysia still had lead concentrations over 5000 ppm.²⁰ In comparison, the Australian domestic paint standard of maximum lead concentration of 1000 ppm (0.1%) has been in place since 1997.²¹

In 2007 the Australian regulatory environment was unprepared for this challenge. Customs (Prohibited Import) Regulations relating to lead content were based on health standards from 1956 and relied on voluntary compliance by importers.²² A more stringent standard (AS/NZS 8124.3:2003) for the content of lead in toys (90 ppm migrateable lead) was in place but was not enforceable.

Following multiple voluntary product recalls based on overseas (mainly US) testing, the Customs Regulations were updated in August 2007 to reflect AS/NZS 8124.3:2003. In September the ACCC and individual states enacted temporary bans for all toys that did not comply with the standard. These bans became permanent in states at later dates, and commencing nationally in 2010. Bans were supported by blitz inspection programs by fair trading agencies in several jurisdictions.

In this incident the role of public health agencies was mainly in providing information to parents about the potential health effects and mitigative actions.

Piranha Vege Crackers

Piranha Vege Crackers are a packet chip or crisp food product, which is made in NSW from imported cassava and distributed around Australia and exported to Japan. Cassava is a starch-filled root plant known to contain potentially toxic compounds called cyanogenic glycosides. Before cassava can be consumed, it requires proper processing to remove these compounds. If not removed, they will be metabolised into hydrogen cyanide after ingestion. Hydrogen cyanide affects the energy cycle in the body, and acute cyanide intoxication can induce nausea, vomiting, giddiness, palpitations, convulsions and coma.²³

On 11 January 2008 NSW Health was informed by the NSW Food Authority that testing on Piranha Crackers by Japanese authorities had detected high levels of cyanogenic glycosides. The NSW Food Authority and the federal Department of Agriculture, Fisheries and Forestry had already undertaken a screening risk assessment that identified a potential risk from moderate to high consumption of the product. On 12 January the company agreed to an Australia-wide voluntarily recall of the product.

On 13 January general practitioners and hospitals were informed of the issue, and on 24 January the NSW Public Health Real Time Emergency Department Surveillance System (PHREDSS) database was

interrogated to determine if an excess number of cases of cyanide poisonings were presenting at NSW hospitals. No excess in cases was identified.

On 23 January testing of another brand of cassava chips manufactured in another state revealed similar high levels of cyanogenic glycosides. FSANZ undertook a risk assessment and commenced development of a new limit for hydrogen cyanide levels in ready-to-eat cassava chips. Advice was provided to the public in the interim on the safe level of consumption for cassava chips.

Piranha Crackers are now back on the market, and a new limit of less than 10 mg/kg hydrogen cyanide has been set in the Food Standards Code for ready-to-eat cassava chips.

Conclusion

The protection of consumers from products with chemical contamination poses unique challenges for public health practitioners because, while they are well-equipped to investigate acute problems, the identification of contaminated products and the legislative powers to correct these problems can fall outside their portfolio. Further, the systems of governance within Australia may hamper the effective implementation of corrective measures. The current web of regulation that surrounds this issue is complex, and practitioners need an acute understanding to ensure that they can respond quickly and effectively to such incidents.

The above four examples also demonstrate the mechanisms of detection of chemically contaminated products in Australia. These mechanisms are in part reliant on astute observation by medical professionals, and in part on surveillance and notification. It is critical that jurisdictions effectively disseminate findings of chemical contamination within Australia and internationally.

At present very little has been published on the health impact and costs associated with chemically contaminated products in the marketplace. This limits the ability of public health agencies to develop effective policies around these issues, including the justification of regulatory and surveillance mechanisms within the marketplace.

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Vapour intrusion in suburban dwellings

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Introduction

Risks to human health from site contamination are managed in Australia at a state and territory level by the local environmental protection and relevant health authorities. To ensure a nationally consistent approach to the assessment and management of sites, a National Environmental Protection Measure (NEPM) has been developed by the Australian Government that local jurisdictions implement through their legislative frameworks.

The NEPM provides nationally accepted guidance, with the goal of ensuring equivalent protection for communities from air, water or soil contamination, regardless of where they live.¹ In Australia environmental health risk assessments (EHRAs) are conducted with reference to the model of risk assessment adopted by the Environmental Health Council of Australia.^{2–4} Site-specific EHRAs are intended to provide a thorough appraisal of the nature and magnitude of the risks to human health (onsite or offsite) arising from contamination at a site; this process is complementary to that of ecological risk assessment. Both tasks are often undertaken concurrently in contaminated site assessments.

As part of the current NEPM review, a recent discussion paper⁵ identified deficiencies in the guidance provided for the assessment of volatile organic compounds (VOCs) in soils and groundwater. Currently, there is no guidance available in the site contamination NEPM relating to the migration of volatile compounds into buildings (vapour intrusion) from underlying contaminants in groundwater and/or soil.

The deficiencies identified in the NEPM were attributed by the authors to the rapid pace of development in the field and the relatively immature state of vapour intrusion science worldwide. As such, significant research effort has been focused on improving the scientific understanding of the vapour intrusion exposure pathway.⁶⁻¹¹ In the absence of guidance from the NEPM, risk assessors in Australia use information from international sources, such as the US Environmental Protection Agency (EPA), or other jurisdictions that have significant experience in addressing vapour intrusion issues, including the Californian EPA, New York State Department of Health and the New Jersey Department of Environmental Protection.

This paper summarises salient features of an EHRA conducted during the past year by SA Health and the Environment Protection Authority South Australia (EPA). The EHRA was initiated in response to a report provided by a consultant that demonstrated the presence of high concentrations of trichloroethylene (TCE) in groundwater and shallow soil vapour at an industrial site immediately adjacent to public housing in Clovelly Park, Adelaide. The paper also describes investigations conducted to address concerns that vapour intrusion may pose a risk to the long-term health of residents at a number of properties in this suburb. In the absence of appropriate guideline values, especially for TCE, guidance criteria were developed from primary toxicological data and are also reported briefly here.

Identifying the issues

In Australia, as elsewhere in the industrialised world, commercial, manufacturing and heavy industries in urban areas are often situated in close proximity to residential development. Contamination of soil and groundwater by volatile organic compounds can be a consequence of past disposal practices¹² and/or spills and leaks from storage tanks¹³ at these industrial and/or commercial sites. A recent study of US aquifers revealed the presence of volatile organic compounds in groundwater resources in 90 of 98 of the aquifers studied, with those in industrialised areas being particularly vulnerable.¹⁴ It is relevant, in this context, to note that investigations of the vapour intrusion exposure pathway at contaminated sites reveal that volatile contaminants in groundwater and/or soil may diffuse through pores or cracks in soil and building foundations, migrate into overlying buildings, and pose a risk to the health of residents or other site users.

Clovelly Park is a suburb of Adelaide that has a history (dating back to the early 1950s) of automobile-related manufacturing. The auto industry is one of many industries that make use of significant quantities of volatile organic solvents. As part of routine environmental assessments associated with the decommissioning of a vehicle manufacturing plant, a consultant noted that onsite TCE concentrations of > 5 mg/L in groundwater and > 60 mg/m³ in soil vapour had been reported for an area adjacent to a number of residential properties. On this basis SA Health concluded that an EHRA should be conducted to address the potential for vapour intrusion into these dwellings.

What is trichloroethylene (TCE)?

TCE is an industrial solvent mainly used for vapour degreasing and cold cleaning of fabricated metal parts. It has also been used as a carrier solvent for the active ingredients of insecticides and fungicides; as a solvent for waxes, fats, resins and oils; as an anaesthetic for medical and dental use; and as an extractant for spice oleoresins and for caffeine from coffee. TCE has been used in printing inks, varnishes, adhesives, paints, lacquers, spot removers, rug cleaners, disinfectants and cosmetic cleansing fluids.¹⁵

The major use for TCE in Australia is metal cleaning¹⁶ and it was used for this purpose by manufacturing industries in the suburb of Clovelly Park. At the time of writing, a search of the national pollution inventory (NPI) revealed 17 industrial sites in greater metropolitan Adelaide using >10 tonnes/year of TCE (facilities using less than 10 tonnes/year are not required to report to the NPI).

A prominent route of TCE release into the atmosphere of cities is via evaporation of the used or stored solvent from factory premises. Once in the atmosphere, the predominant degradation process is reaction with hydroxyl radicals; the approximate half-life for the process is 7 days.¹⁷ If disposed to soil, the portion of TCE not lost to the atmosphere can migrate into porous subsurface soils and be transported by diffusion, advection or dispersion of the pure liquid; as a solute in water; or by gaseous diffusion throughout the soil spaces. TCE also partitions to soil particles of high organic content, reducing its mobility, and in some subsurface soils the sorption and desorption of TCE is slow. Thus, subsurface liquid TCE may continue to contaminate groundwater aquifers and soils long after sources have been eliminated.

In groundwater, biodegradation may be the most important transformation process for TCE, although it is usually slow, with half-lives ranging from months to years, depending on ambient conditions and remediation measures. The major products resulting from biodegradation of TCE in groundwater are dichloroethylene, chloroethane and vinyl chloride. High concentrations of TCE are frequently observed in contaminated groundwater where volatilisation and biodegradation are limited, where there are point sources or where releases are small but continuous over time. Relatively constant concentrations can therefore exist for decades.¹⁶ In the case of Clovelly Park, given the potential duration and magnitude of the onsite contamination, it was postulated that substantial percolation to subsurface regions had occurred and was no longer confined within the boundary of the industrial site.

Is TCE a problem?

As discussed elsewhere in this Bulletin, the magnitude, duration, frequency and route of exposure all play an important part in determining if an exposure to a chemical may present a problem to the community. With respect to TCE, the toxicological literature is extensive and there have been a number of high-level reviews of the TCE toxicological database.^{16–18} In Australia there is no NEPM guidance on how jurisdictions should manage vapour intrusion contamination issues associated with TCE. Therefore, SA Health was compelled to review the scientific literature and derive an interim inhalation guideline value to inform potential risk management actions; an abstract of this consideration is presented below.

Hazard assessment of Clovelly Park

Toxicological endpoints

Non-carcinogenic effects

Human and animal data show that TCE can cause non-carcinogenic effects in a variety of organ systems. The most prominent, well-recognised and sensitive targets for the non-carcinogenic effects of TCE include the central nervous system (CNS), liver and kidney. Recent evidence suggests the male reproductive system may be also be affected by TCE. Studies on endocrine and immune toxicity provide suggestive evidence that TCE can also adversely affect these systems; however, the studies were not considered adequate to support derivation of a guideline criterion.

The CNS is clearly an important endpoint for TCE toxicity by inhalation. TCE was once used as an anaesthetic, and short- and long-term exposure to elevated levels have produced CNS symptoms in humans, including headaches, drowsiness, confusion, dizziness, nausea, loss of facial sensation, nerve damage and reduced scores on various tests of neurological function.

Carcinogenic effects

Available epidemiological studies provide evidence for a positive association between occupational TCE exposure and several types of cancer, most notably liver/biliary cancer, kidney cancer, non-Hodgkin's lymphoma, oesophageal cancer and, to a lesser extent, Hodgkin's disease and cervical cancer. The International Agency for Research on Cancer states that TCE is a multi-site carcinogen in animals.¹⁹ However, the human dose–response data on TCE carcinogenicity are insufficient to derive regulatory criteria, primarily because of uncertainties in the exposure estimates and the lack of clear dose–response relationships.

Development of criteria values for TCE to aid management of the site

For the purpose of managing the Clovelly Park site, SA Health developed a pragmatically derived criterion for TCE for indoor air of residential properties, based both on health criteria and other factors. These included detection limits of TCE, analytical methods and uncertainties in the toxicological database, including gaps in the Australian database, especially in regard to TCE in ambient and indoor air. In essence the criterion developed was a 'ceiling' air concentration to guide decision-making and efforts to manage and reduce TCE exposure.

Using first principles, a criterion for indoor TCE levels of $37 \mu\text{g}/\text{m}^3$ was proposed, with an 'investigation level' set at $3.7 \mu\text{g}/\text{m}^3$. This was based on pharmacokinetic and toxicological data derived principally from chronic exposure studies that found small but significant changes to CNS functions in humans and animals. The criterion was written in terms of a graded response, prioritised such that levels above $37 \mu\text{g}/\text{m}^3$ were dealt with immediately and effectively, and those below $3.7 \mu\text{g}/\text{m}^3$ were deemed satisfactory for the time being. In the latter case the future remediation and management of the entire site should address low-level exposures. For values between the action and investigation level, a full and thorough health based

investigation was undertaken which fully characterised the exposure levels and their uncertainties, along with vulnerabilities in the exposed population. (A more formal examination of this criterion with a view to publication has commenced).

Exposure assessment

Soil vapour testing

The first phase of the field investigation consisted of the placement and backfilling with sand of vapour probes (radiello®) into boreholes (up to 2 m deep, 50 mm in diameter) drilled in publicly accessible areas in close proximity to residential properties. The qualitative soil vapour data, obtained using this simple method, confirmed that VOCs were present in soils at three depths (2 m, 1 m and 0.5 m). On this basis it was considered likely that TCE vapour in soil was in contact with building foundations and the in-ground services typical of the area (e.g. sewers, pipes and cables). The data were of sufficient spatial resolution to show the presence of a significant soil vapour plume of TCE beneath approximately 50 dwellings in Clovelly Park. Given the magnitude of the TCE plume and its proximity to residential properties, the decision was made to progress directly to indoor air testing in order to clarify the potential for vapour intrusion within an acceptable timeframe.

Indoor air testing

Traditionally, an investigation of site contamination such as this proceeds through a variety of stages, such as a full delineation of the groundwater and soil vapour plume, derivation of a risk estimate, followed by consultation with the community and, generally, as a last step in the data collection process, indoor air testing of residential properties.¹⁰ The rationale for this approach is that the weight of evidence should be sufficient to provide a reasonable suspicion that residents may be at risk prior to undertaking indoor air testing, which can be very stressful to the community.

In Clovelly Park all residential property owners within the defined zone were given the opportunity of having their indoor air quality assessed with respect to the levels of common VOCs including TCE. These measurements were repeated in cases with equivocal results, poor detection limits or where TCE was detected. Over three rounds of testing in a 3-month period, using both 24-hour active sampling and integrated 7-day passive sampling, a total of

38 dwellings were tested, along with a number of 'control' homes located in other suburbs of Adelaide. Results clearly indicated that the TCE was intruding into the living spaces of some dwellings located on the immediate boundary of the industrial complex.

Risk communication

Prior to the commencement of indoor air testing, considerable consultation with the community, including media and relevant local officials, was required. Ideally, as an organisation, one needs to gain the trust of the community and become a respected intermediary.²⁰ This appears to have been achieved in Clovelly Park by initiating an extensive community engagement process involving letter drops and one-on-one meetings with residents in their homes, along with briefing of community leaders and the media. The process confirms the need for effective two-way communication with residents and other stakeholders in all environmental investigations that impact directly on residents in a community.

At the commencement of the investigation in Clovelly Park approximately 300 property owners adjacent to the affected area were informed of potential groundwater contamination associated with the TCE. It was recommended that householders refrain from extracting groundwater unless the water had been tested and shown to be fit for purpose. This is standard advice for much of Adelaide, which sits above a number of shallow unconfined aquifers that are invariably contaminated with TCE and other chemicals.²¹

Risk characterisation/management

Results of the indoor air testing demonstrated a clear dichotomy of results—either very low (or not detectable) or high. For a majority of dwellings TCE concentrations were found to be well below the investigation criterion of 3.7 µg/m³. However, several dwellings located on or near the boundary of the industrial site exceeded the upper criterion of 37 µg/m³, which necessitated relocation of residents. With the assistance of Housing SA, the residents of these dwellings were provided with alternative accommodation.

Conclusions

The immediate management of exposure to high levels of TCE in residential dwellings has been addressed, with some residents needing relocation. This was fortunately

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relatively easy to achieve since the dwellings were not privately owned and the residents were within the public housing system. The relevant authorities are currently in the process of addressing the entire site and its complex site contamination issues. Overall, the EHRA process was found to be a useful tool for developing a management plan in order to reduce the exposure of an affected community to industrial chemicals present in soils and groundwater.

The Clovelly Park EHRA provides an example that highlights the critical importance of investigating the potential for migration of contaminants in soil, air or water across contaminated site 'boundaries' and into adjacent residential areas. Without such information it is not possible to ensure that risks to the health of adjacent residents are appropriately understood and managed. EHRAs that do not thoroughly address off-site impacts for the adjacent communities are therefore inadequate.

In the absence of a convenient 'look-up' table approach for environmental assessment—an assessment style that is perhaps too common in Australia—this investigation required expert judgment, inter-organisational cooperation and extensive community engagement. Strong organisational support was critical for the investigation to proceed.

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Young worker injury experience in South Australia 1998–2007

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Preface

This special report has been compiled by The University of Adelaide and provides an overview of young worker injury claims experience for a 10-year period. It aims to highlight occupational injury epidemiology and time trends, and will be of interest to public health practitioners dealing with adolescents and young adults.

Summary

WorkCover SA injury claims by 15–24-year-old workers in the period 1998–2007 were combined with Australian Bureau of Statistics (ABS) census and workforce participation data to estimate injury rates. The information included minor injuries as well as serious injuries (i.e. those involving 1 week or more of lost work time).

The data show significant differences between males and females, as well as a steady temporal decline with respect to all injuries and a less obvious decline in serious injuries. The majority of injuries were associated with the fingers, hands and upper limbs.

The incidence of injury continues to be of concern, with an average of 1 in 15 young male workers making an injury claim each year.

Introduction

Injuries among young people represent a significant burden to society in terms of potential long-term costs and lost opportunity. Young workers are over-represented in workplace injury statistics, and this has been attributed to a range of factors such as lack of experience, incomplete physical and mental development, and risk-taking behaviours.¹ As part of the National OHS Strategy 2002–12, all Australian jurisdictions set a target of reducing workplace injuries by 40%, with a reduction of 20% to have been achieved by 30 June 2007.² With respect to young workers, interventions have included secondary school safety education initiatives, regulatory campaigns in the hospitality industry, and young worker websites. The purpose of this report is to characterise young worker injury claims experience in South Australia (SA) in the context of the national objectives.

Methods

The number of SA workers in the age range 15–24 years in the period 1998–2007 was estimated from ABS census data and workforce participation data.³ The age- and gender-specific working populations were interpolated when data for individual years were not available. Claims data were provided by WorkCover SA, and serious injuries, involving 1 week or more of lost time, were considered separately. Claims rates are expressed as the number of claims per worker, as there were no data on full- or part-time employment or the number of hours worked. There was no adjustment for multiple claims for the same individual in any one year, but, in general, such multiple claims represent a very small proportion of the total. Industry-specific data are expressed as absolute claims across the period 1998–2007. Claims by body location are presented from 2007 statistics, but other years are similar. In order to assess the experience of teen workers, young workers were stratified as 15–19-year-olds and 20–24-year-olds.

Findings

Serious injury claims

Rates of serious claims over the period 1998–2007 show a weak decline in both age strata (Figure 1), with a steeper decline during 2004–07. Rates in the 20–24 years age group are about twice those for the 15–19 years age group.

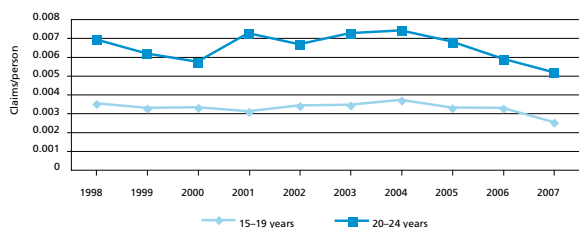


Figure 1: Serious claims by age group and year

Data for male and female workers for the same period also show a temporal decline (Figure 2). Rates for males are approximately double those of females.

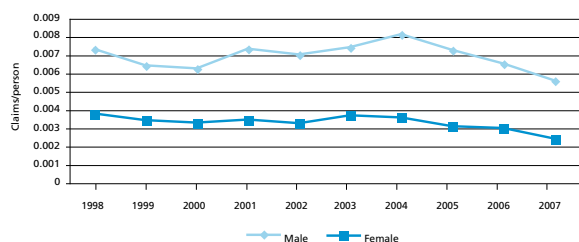


Figure 2: Serious claims by gender and year

All injuries

When all injuries are considered, there is a more noticeable decline. Figure 3 shows consistent declines for 15–19-year-olds as well as 20–24-year-olds.

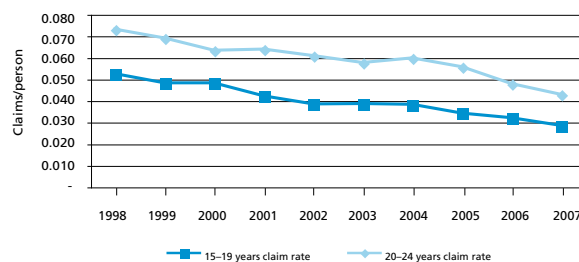


Figure 3: Injury claims over time by age group

Injury claims by gender (Figure 4) show markedly higher rates for male workers compared to female workers. However, the rates are clearly falling in both cases.

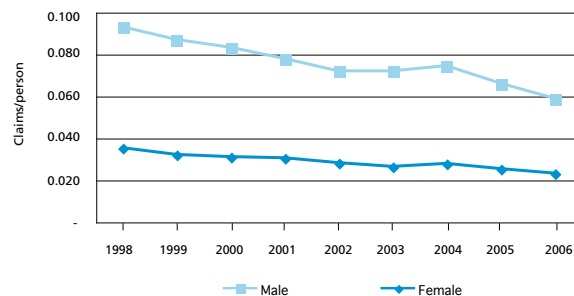


Figure 4: Injury claims over time by gender

Figure 5 shows the percentage of injuries by body location during 2007 for young workers aged 15–24 years. Fingers, thumbs, hands and wrists account for about 31% of the claims. One in 10 claims was for lower back injury.

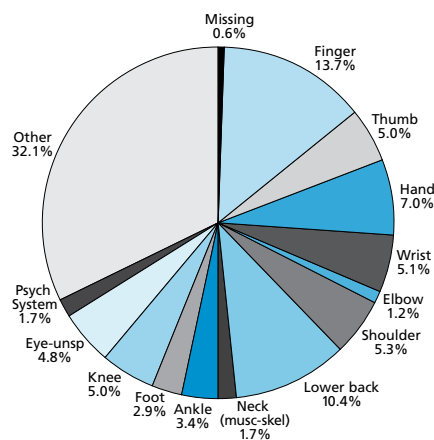


Figure 5: Young workers' injury claims by body location, 2007

Figure 6 shows the absolute number of injury claims by five major industry categories. The highest numbers of claims were found in manufacturing, but these decline rapidly over time. A slight increase in claims in community services is apparent from 2000.

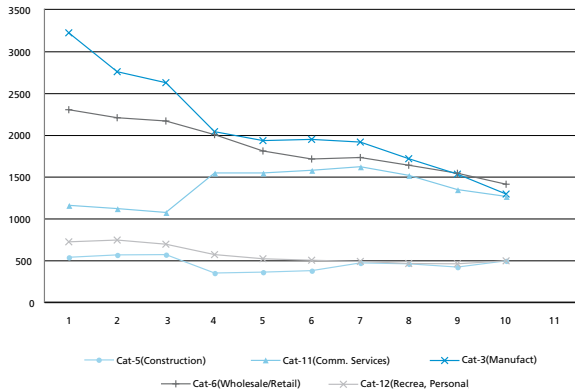


Figure 6: Young worker injury claims for five major industry categories

Figure 7 shows the absolute number of injury claims over time for two industry categories with a high proportion of young workers. A significant reduction has occurred for wholesale and retail trade, which includes supermarkets. The reduction is less apparent for recreational, personal and other services.

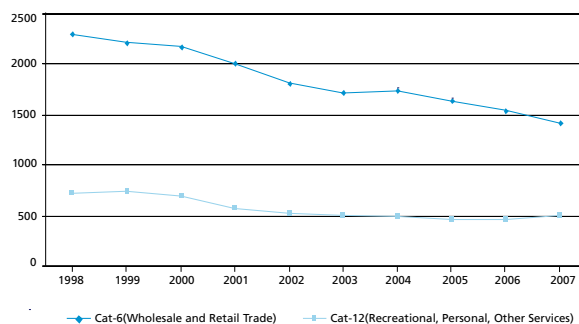


Figure 7: Injury claims over time for two industry categories with a high proportion of young workers

Interpretation

This analysis indicates that young worker injury rates in SA are declining with time. However, the decline is less obvious for serious injuries.

Those in the older age group (20–24 years) and males are more likely to lodge a serious injury claim. This is

consistent with the national statistics for the period 2000–01 to 2005–06, which shows that the number of serious claims decreased by 16%.⁴ However, there has been little change over this period in the proportion of serious claims lodged by male employees compared to female employees (67% and 32% respectively), which is similar to Figure 2.

In terms of all injuries, 15–19-year-olds were less likely to claim than the older age group (20–24-year-olds), and overall injury rates are higher among male compared with female workers. However, there is the distinct possibility of under-reporting and claims lodgement of the more minor injuries. A recent report by Safe Work Australia suggests that young females are the least likely to make a claim.⁵

Although the time trends are encouraging, a significant gap exists between males and females, and the decline in serious injuries is weak. The overall incidence of injury continues to be of concern, with an average of about 1 in 15 young male workers making an injury claim each year.

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Communicable Disease Control Branch

Disease Surveillance and Investigation Report 1 July to 31 December 2009

The Disease Surveillance and Investigation Section (DSIS) of the Communicable Disease Control Branch (CDCB) conducts statewide surveillance for notifiable diseases enabling analysis of health data and initiation of specific public health actions to prevent further spread of disease. Specified data are provided regularly to the National Notifiable Diseases Surveillance System.

Weekly summaries of notifiable diseases in South Australia (SA), as defined in the *Public and Environmental Health Act 1987*, are published on the SA Health website. Included are counts of notified infections, information about current cluster and outbreak investigations as well as historical data.

Some investigation and control activities are conducted in conjunction with partner agencies that provide additional expertise and authorities under other Acts in South Australia. These agencies include OzFoodNet Australia, SA Pathology, Primary Industries and Resources SA (PIRSA), and Environmental Health Officers (EHO) from local government, as well as other areas of SA Health including SA Infection Control Service, Food Policy and Programs, Applied Environmental Health, and Scientific Services.

Summary

Between 1 July and 31 December 2009 the DSIS collected a total of 15 853 reports of notifiable diseases, including 9545 cases of influenza and 1591 reports of gastrointestinal diseases. Pandemic influenza (H1N1 2009) numbers began to decline by September, leaving pertussis dominating respiratory disease.

> Investigation and control activities included:

- > 9545 cases of influenza
- > 3384 pertussis cases
- > 17 cases of hepatitis A infection
- > 30 cases of Shiga-toxin producing *E. coli* infection
- > 8 cases of invasive meningococcal disease

- > 2 cases of mumps
 - > 1 case of typhoid fever
 - > 54 outbreaks of gastroenteritis in aged care facilities
 - > 2 linked cases of Q fever.
- > In partnership with OzFoodNet, foodborne disease investigations included:
- > 5 outbreaks of illness due to *Salmonella*
 - > 1 outbreak of Shiga Toxin producing *Escherichia coli* infection
 - > 2 outbreaks of hepatitis A
- > In partnership with Applied Environmental Health Branch investigations included:
- > One cluster investigation in to 5 cases of *Legionella pneumophila* serogroup 1 in metropolitan Adelaide.

Vectorborne disease

Ross River virus and Barmah Forest virus are both arboviruses, that is, viruses spread by arthropods, in these cases mosquitoes. These infections usually demonstrate cyclic patterns of disease, peaking in summer months. A media release by SA Health on the first day of summer raised awareness of mosquito borne disease. A prevention program, the *Fight the Bite* campaign, has operated in SA since December 2004.

Common symptoms of local arboviral diseases include arthralgia, rash, flu-like symptoms and swollen glands, ranging from mild to disabling. Severe complications occur rarely. Blood tests confirm the diagnosis, usually by demonstration of specific arboviral antibodies in acute-phase sera.

Barmah Forest infection

In the second half of 2009, 16 cases of Barmah Forest virus infection were reported compared to 23 in the same period of 2008. Cases comprised 5 males and 11 females, with an age range of 14–76 years.

Ross River infection

Between July and December 2009 inclusive, 200 cases of Ross River virus infection were reported (59 males, 141 females), compared to 97 in the same period of 2008. Although low compared to epidemic year case numbers, these data are higher than the background level of Ross River virus infections reported in previous inter-epidemic periods. For example, only 17 cases were reported for the same period in 2004 (Figure 1).

This may partly reflect increased awareness of the disease resulting in increased testing.

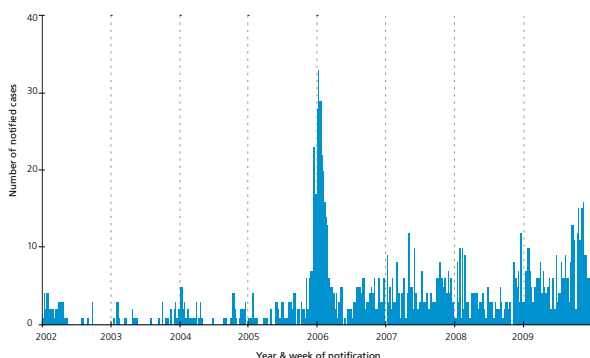


Figure 1: Ross River virus infections in South Australia by year and week of onset, 1 January 2002 to 31 December 2009

Dengue fever

During the second half of 2009 seven cases of dengue fever were recorded (four males, three females), compared to 13 cases in the same period of 2008. Cases were adults aged 25-58 years. All infections were acquired overseas in south-east Asia.

Malaria

Of 19 cases of malaria reported in the second half of 2009, 18 were acquired overseas and one case had no exposure details obtainable at the time of report. Cases comprised five females and 14 males; aged 12–69 years.

Eight cases caused by *Plasmodium falciparum* reported exposure in Africa. Nine cases were caused by *P. vivax*; three acquired the infection in India; three in south-east Asia; two in Africa and one further case has no exposure details obtainable at the time of report. One case of *P. malariae* was reported with acquisition of infection in India. The remaining case was reported to be a mixture of both *P. vivax* and *P. malariae* with exposure in Papua New Guinea.

Zoonoses

Hydatid Disease

Hydatid disease, caused by the larvae of the tapeworm *Echinococcus granulosus*, is now rare in SA. Hydatid cysts, which usually appear in the liver or lungs but can occur in other viscera, are a result of this infestation. Over the last seven years an average of five cases per

year has been recorded in SA.

Three cases of hydatid disease were reported in the second half of 2009; these represented new diagnoses of past infection and *not* recently acquired infection. All were incidental findings in medical investigation of the patients. Cases comprised one male and two females with an age range of 49–76 years. One case was born overseas, two were Australian born. All cases had potential exposure risks many years ago.

Ornithosis

Ornithosis (also known as psittacosis) is caused by a bacterium, *Chlamydia psittaci*, and humans can become infected by contact with birds. Symptoms include fever, headache, rash, myalgia, and cough.

Two cases of Ornithosis were reported between July and December 2009 in males aged 15 and 68. Both cases had contact with birds.

Q fever

Q fever, caused by infection with *Coxiella burnetii*, often results from direct exposure to animals that are natural reservoirs for this agent. Typically, cases are males aged between 15 and 60 years with occupational exposure to animals, commonly sheep, cattle or goats, in meat and livestock industries. An average of 20 cases per year has been reported for the last 10 years; 24 cases were recorded in 2007 and 16 in 2008.

Eight cases of Q fever comprised of five males and three females aged 19–59 years were reported in the second half of 2009, compared to five in the same period of 2008. All cases had obvious risk factors for this infection through occupation or direct animal contact.

Two cases of Q fever were reported in employees in a pathology laboratory. The cases shared a working space with a person conducting studies on *C. burnetii*. An investigation was conducted and environmental control measures were implemented including extensive immunoserology testing of pathology employees. No further cases were identified.

Vaccine preventable diseases

Influenza

In addition to the collection of influenza data through the state notifiable diseases system, since May 2008 when influenza became a notifiable disease, the DSIS

Public Health Bulletin

has undertaken syndromic surveillance by collating datasets from laboratory and clinical sources to describe influenza-like illness in SA.

SA Pathology laboratories and medical practitioners report positive influenza tests to the DSIS. Clinical diagnoses of influenza-like illness are collected from two sources: Royal Australian College of General Practitioners members participating in the Australian Sentinel Practice Research Network (ASPREN), and emergency departments of several public hospitals. These combined data provide a weekly picture of confirmed influenza infections and influenza-like illness activity across the state.

In the second half of 2009, 9545 influenza cases were recorded, compared to 475 in the same period of 2008 (Figures 2, 3). Among these, 9539 cases were caused by influenza A virus, and 8 were due to infection by influenza B virus. Cases comprised 4711 males and 4834 females aged from <1–98 years.

Among cases of influenza A, 8702 cases were further characterised as influenza A H1N1 2009 virus, the pandemic strain. These cases comprised 4306 males and 4396 females with an age range of <1–98 years. However, only 2.8% of the total number of pandemic cases were aged 60 years or over compared to 14.5% of cases being aged 60 years and over in cases of seasonal influenza in 2008 (Figures 4, 5).

Public health information was released on 1 July and 12 August 2009 on the 'Protect' phase of the pandemic response. Public health information on the proposed National Pandemic H1N1 (2009) Influenza Vaccination program was released on 25 August 2009. An announcement was made on 22 September 2009 regarding the commencement of the vaccination program on 30 September 2009, with the prioritisation of vulnerable and high risk groups in the community. A public health alert issued on 4 December 2009 informed all medical practitioners of Therapeutic Goods Administration approval of a children's H1N1 flu vaccine for children aged 6 months to less than 10 years of age.

Figure 2 illustrates the difference in diagnoses per week from 2001 to 2009 for laboratory confirmed cases of influenza.

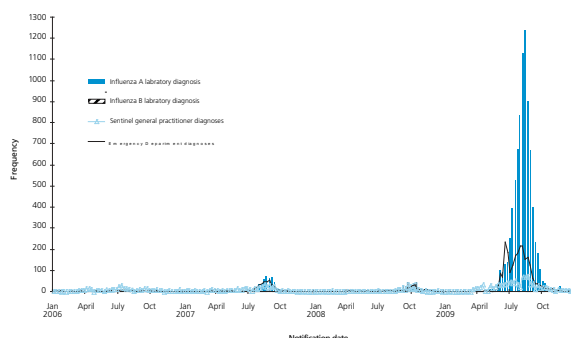


Figure 2: Laboratory influenza diagnoses in South Australia, 1 January 2006 to 31 December 2009

Information about influenza and respiratory diseases is available at: www.health.sa.gov.au/pehs/ & www.flu.sa.gov.au.

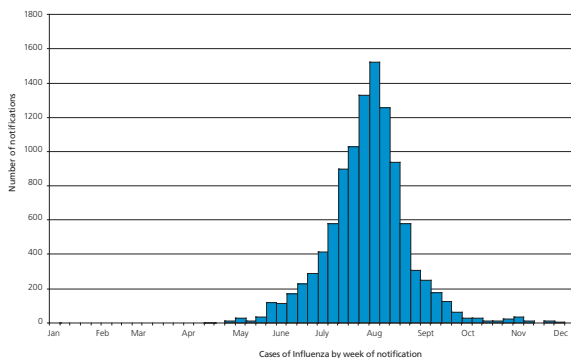


Figure 3: Influenza cases in South Australia by week of notification, 1 January 2009 to 31 December 2009

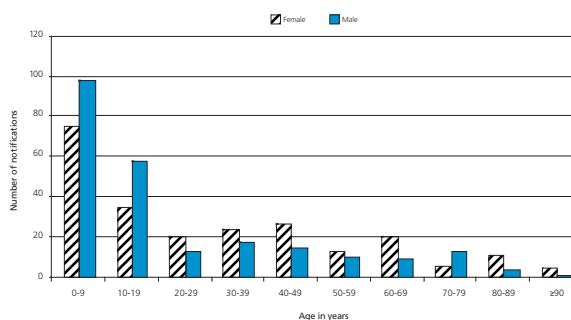


Figure 4: Influenza cases in South Australia: sex by age-group, 1 July 2008 to 31 December 2008

Graph depicts age distribution of seasonal influenza cases seen from 1 July to 31 December 2008. Although most cases were seen under the age of 20 years, 14.5% of cases were aged over 60 years.

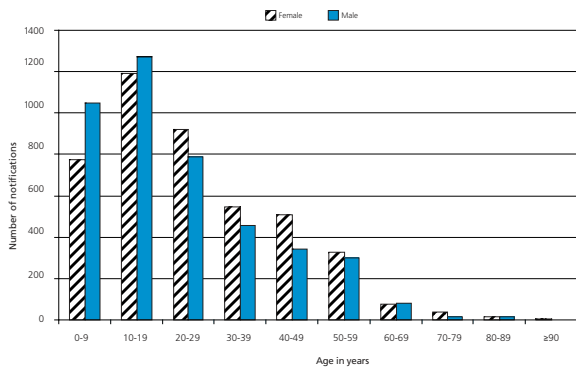


Figure 5: H1N1 influenza cases in South Australia; sex by age-group, 1 July 2009 to 31 December 2009

Graph depicts age distribution of pandemic influenza cases seen from 1 July to 31 December 2009. Most cases were seen under the age of 30 years, with only 2.8% of cases aged 60 years and over.

Invasive Haemophilus influenzae

The introduction of Hib vaccine in 1997 resulted in a reduction in the number of cases of invasive disease in children due to *Haemophilus influenzae* type b. However, cases of disease continue to occur in adults and unimmunised or partially immunised children. The last case of *H. influenzae* type b in a child was a 5 month old unvaccinated Indigenous child in August 2007.

Six cases of invasive *H. influenzae* disease were reported during the second half of 2009, two males and four females with an age range of 30–92 years. Five cases were hospitalised. All *H. influenzae* isolates were unencapsulated strains (untypeable), that is, not type b.

Invasive pneumococcal disease

Streptococcus pneumoniae is the cause of invasive pneumococcal disease and many individuals carry the organism in the respiratory tract without symptoms. *S. pneumoniae* is a frequent cause of otitis media in children, and pneumonia in all age groups. Two vaccines help protect against some of the 90 identified serotypes of *S. pneumoniae* infection. A 23-valent vaccine is commonly used for adults; and a seven-valent vaccine for infants and children.

Between 1 July and 31 December 2009, 93 cases of invasive pneumococcal disease were reported, compared to 78 cases in the same period of 2008. Cases comprised 49 males and 44 females, with an age range from <math><1-94</math> years; of these, 11 were less than 5 years of age (Figure 6). Cases were residents in a

range of locations across the state and eight were reported as Indigenous. Most cases were hospitalised (91 of 93), and one death was attributed to the disease.

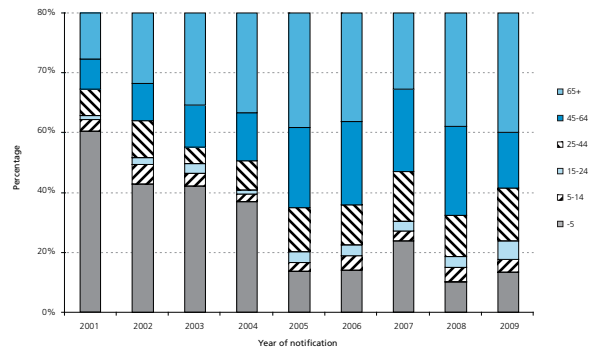


Figure 6: Notified cases of invasive pneumococcal disease in South Australia, by age-group proportions and year of notification, 1 January 2001 to 31 December 2009

Mumps

Before national vaccination, mumps was a common childhood disease in SA, with peak incidence in the 5–9 year age-group. Many young adults currently aged between 28–42 years have only received a single dose of mumps vaccine, and these individuals are encouraged to seek further vaccination. Peak infection rates have been reported in older adolescents and young adults since 2000. Cases are confirmed by detection of mumps-specific IgM antibody and a clinically compatible illness.

Two cases of mumps were notified during the last half of 2009, compared with 10 cases for the same period in 2008. The cases were males aged 43 and 80 years. One case lived in metropolitan Adelaide and one in rural South Australia. No epidemiological links were ascertained between cases.

Pertussis

More than 40 years since pertussis vaccination was introduced in SA, *Bordetella pertussis* infection (whooping cough) remains a common community infection. Pertussis demonstrates variation in time, appearing as dramatic increases in disease, roughly every 3 to 5 years.

An apparent escalation of pertussis cases since 2004, when cases peaked in October, continued until late in 2006. Some of this increase is now thought to reflect changes in laboratory testing, and some reported cases may have reflected past, rather than current infection.

However, in 2008 a resurgence occurred, though the increase is in part due to the higher sensitivity of molecular tests (PCR) compared to serology and culture which were the only tests widely available several years ago.

Between July and December 2009, 3384 cases of pertussis were notified, compared to 1058 in the same period of 2008 (Figure 7). It is likely that there was increased presentation and testing associated with concern about pandemic influenza. Cases comprised 1418 males and 1966 females with an age range of <1–95 years. Cases were geographically dispersed throughout SA. Thirty five cases were reported in Indigenous Australians.

In contrast to recent years, only 64% of cases were more than 20 years of age at diagnosis, compared to 81% for the same period in 2008. Two hundred and forty-five cases were aged less than 5 years; of these, 83 cases were aged less than 12 months of age at diagnosis. Of the 245 cases, 142 were fully or partially vaccinated; 58 were not vaccinated (usually as they were too young for vaccination) and in 45 cases, the vaccination status could not be determined. There have been no deaths in the under 5-year age group in SA since 1995 when a death was notified in a one month old male. This is reflective of the effectiveness of vaccination in reducing deaths and severe complications.

All cases in children aged less than 5 years receive urgent public health follow-up. Approximately 40 cases of pertussis occurred in children aged less than 5 years who attended childcare centres, and antibiotic chemoprophylaxis was recommended in five instances where there were susceptible contacts. Information and advice was provided to the childcare centres as per *The Australian Immunisation Handbook* (9th edition) and *You've Got What?* Some childcare workers and children were recommended to seek vaccination.

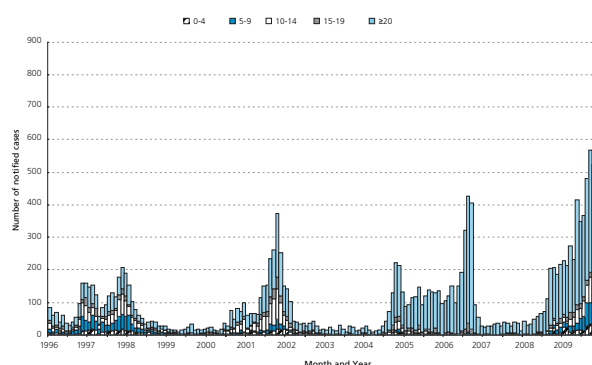


Figure 7: Notified cases of Pertussis, by month of notification and age group, 1 January 1996 to 31 December 2009

This figure demonstrates the impact of vaccination on the temporal frequency of pertussis cases; first in the 5–9 then 10–14 and, latterly, 0–4 year age-groups. However, in 2008 resurgence has occurred, in part due to the sensitivity of molecular tests (PCR).

Rotavirus

Gastrointestinal illness due to rotavirus became notifiable in SA in May 2008.

In the second half of 2009, 147 cases were notified. Cases comprised 73 males and 74 females aged from <1–93 years; 93 cases were less than 5 years of age.

Of the 22 cases aged less than 1 year, 17 had been fully or partially vaccinated. Five babies had not been vaccinated as they were less than 2 months of age.

One reported outbreak of Rotavirus was associated with an aged care facility. Ten of 91 residents were reported with illness; of these, 2 cases were laboratory confirmed.

Varicella

Among 970 cases of varicella infection reported during the second half of 2009 were 456 males and 514 females with ages ranging from <1–96 years.

Medical notification characterised 269 infections as chickenpox. These had an age range of <1–80 years, but 90% of cases were aged less than 30 years. A further 533 cases were characterised as shingles; these ranged in age from <1–91 years; approximately 88% were 20 years of age or more. As yet, 168 varicella infections have not been further classified.

Gastrointestinal diseases

The 1413 reported cases of gastrointestinal diseases in the second half of 2009 were consistent with expected seasonal notifications. In contrast to recent years, gastrointestinal illnesses were responsible for 9% of all notifications during this half year, compared to 34% for the corresponding period of 2008. The difference is attributable to the continued increase in respiratory disease notifications, especially pandemic influenza.

There were 8 outbreaks of gastrointestinal illness requiring investigation during the period.

A total of 54 outbreaks of gastrointestinal illness were reported from aged care facilities with norovirus being identified as the causative agent in 43 of these and rotavirus responsible for one outbreak.

Five clusters of Salmonellosis were investigated; four were community outbreaks and one was associated with a function in a private residence.

Campylobacteriosis

Campylobacter infection was the most commonly reported gastrointestinal disease in SA during the second half of 2009 and accounted for 62% of these diseases.

In the second half of 2009, 872 Campylobacteriosis notifications were received for cases resident in SA, both metropolitan and rural, compared to 945 cases during the same period in 2008. Cases comprised 490 males and 382 females, with an age range of <1–96 years; 18% of cases were aged less than 10 years at diagnosis.

No clusters of Campylobacteriosis were detected in the period under review.

Cryptosporidiosis

Cryptosporidiosis is a parasitic infection of the bowel and *Cryptosporidium* parasites can be found in a range of animals as well as humans. The parasite is spread by the faecal-oral route and commonly occurs by drinking contaminated water; accidental ingestion can occur whilst swimming. Those diagnosed with cryptosporidiosis should be excluded from swimming for 14 days after symptoms disappear.

Thirty-three cases were reported in the second half of 2009 compared to 23 for the same period in 2008. Cases comprised 18 males and 15 females, with an age range of 1–84 years. Residents from both metropolitan

and rural areas of SA were among the cases.

Cryptosporidiosis cases with reported risks potentially requiring public health action are referred to local government EHOs, as well as the Water Quality Section of SA Health's Scientific Services Branch.

Hepatitis A

Hepatitis A virus causes acute infection by the faecal-oral route in humans, varying in clinical severity. Most cases in SA are imported from countries where hepatitis A is endemic. Symptoms, which typically occur 15 to 50 days after infection, can include obvious jaundice. Exposure can be difficult to pinpoint because of the extended incubation period. Outbreaks due to contaminated food or water have been reported in Australia.

Seventeen cases of hepatitis A were reported during the second half of 2009, compared to six cases at the same time in 2008 (Figure 8). Cases comprised 14 males and 3 females aged 6–87 years. Four cases reported recent overseas travel to countries where hepatitis A infection is endemic; of these two were siblings who recently arrived in Australia. Seven infections were acquired locally. Three cases reported travel interstate to Melbourne; of these, two reported consumption of semi-dried tomatoes. Two cases reported travel to Fiji. Contact tracing identifies close contacts of hepatitis A cases and vaccine or immunoglobulin, as appropriate, is recommended in accordance with surveillance guidelines.

Three clusters of hepatitis A were investigated for the period.

Continuing environmental and laboratory investigations into a hepatitis A outbreak investigated in the first half of 2009 detected hepatitis A nucleic acid in samples of semi-dried tomato collected early in the outbreak. However, genotyping was not available to enable a conclusive match with the strain of virus from cases.

Public health responses to the outbreak included vaccination of high risk contacts of cases; recall of product at both distributor and manufacturer level; a communiqué to staff at an affected venue; media releases that recommended cooking semi-dried tomatoes, first in SA, and later in other states; a Public Health Alert in SA; a multi-jurisdictional investigation coordinated by OzFoodNet Australia; and an Emergency Order in Victoria requiring treatment and improved

S. Virchow phage type 8

A cluster of 13 cases of *Salmonella* Virchow phage type 8 is currently still under investigation. Hypothesis generating interviews have been completed for nine cases, all of whom reported consuming chicken. Trace-back revealed that chicken consumed by eight of the nine cases was sourced from one poultry supplier. Routine testing of poultry from this company has not identified *Salmonella* Virchow.

S. Typhimurium phage type 44

An outbreak of gastroenteritis in 16 of 27 attendees at a Christmas Eve function held at a private residence was investigated. Six cases were confirmed to be caused by *Salmonella* Typhimurium phage type 44. A cohort study of all 27 attendees found an association with eating tiramisu containing raw eggs from the property owners' backyard chickens. Environmental investigation found the chicken coop was not regularly cleaned and eggs were not washed prior to use; chicken faeces tested positive for *S. Typhimurium* phage type 44. No tiramisu was available for testing but samples of leftover Pavlova and cream tested positive for *S. Typhimurium* phage type 44. The Pavlova shell was store-bought and dressed with cream by the same person that made the tiramisu.

Shiga toxin producing *Escherichia coli* (STEC)

Among the enterohaemorrhagic *Escherichia coli* (EHEC) bacterial strains is Shiga-toxin producing *E. coli* (STEC). Some of these infections cause bloody diarrhoea, and a small proportion of cases progress to Shiga toxin-mediated haemolytic uraemic syndrome (HUS). This syndrome can cause severe, chronic disease. In SA faecal specimens from patients with bloody diarrhoea are screened in a central SA pathology laboratory for genes encoding the STEC toxins, enabling prompt notification of such infections.

Between 1 July and 31 December 2009, 30 cases of STEC infection were reported, compared to 12 between April and June 2009. All cases were interviewed with a standard risk questionnaire to collect comprehensive food and environmental data. No links were found between sporadic cases. The age range of cases (16 males, 14 females) was <1–81 years. Cases resided in a range of rural and metropolitan locations.

One outbreak of STEC was investigated during the period; gastrointestinal illness occurred in 31 members who attended a four-day church camp in a rural SA

location. No environmental source was identified but a cohort study revealed members of the camp who ate potato or pasta salad had an increased risk of illness. The six people confirmed with STEC infection had eaten potato or pasta salad.

Two cases of HUS were reported for the period; of these, one case also had STEC infection, the other was reported to be non food-related.

Shigellosis

Shigella bacteria cause a gastrointestinal infection with typical symptoms including fever, diarrhoea, vomiting and stomach cramps. *Shigella* bacteria are generally spread by person-to-person contact when contaminated objects or food are put in the mouth. The infectious dose is low; few *Shigella* bacteria are needed to cause an infection. These bacteria do not infect animals, nor do they not survive very long outside the body. Appropriate antibiotic treatment shortens illness and reduces the risk of spread to others.

Twenty-four shigellosis cases were reported in the second half of 2009, compared to 52 in the same period of 2008. Cases comprised 14 males and 10 females with an age range of 1–67 years. Of these, two cases reported no travel history or source; one case identified male to male sex as being high risk activity; three cases were associated with Aboriginal communities and of these, two were identified as being Indigenous; seven cases reported overseas travel and six cases were notified in recent arrivals from Africa. Six cases had no exposure or travel data obtainable at the time of report.

The most common isolates causing shigellosis were *Shigella sonnei* biotype g (13 cases), *S. flexneri* 2a (3 cases), *S. flexneri* 3a (3 cases), other *S. flexneri* biotypes (2 cases). *S. boydii* 13, *S. boydii* 2 and *S. dysenteriae* 3 caused one case each.

Typhoid fever

Most infections of *Salmonella* Typhi detected in SA are acquired overseas, and untreated typhoid fever has significant mortality. Typhoid is transmitted by consumption of food or water contaminated with *S. Typhi*. Unlike other *Salmonella* infections, up to 10% of those infected can become asymptomatic carriers of the infection.

One case of *S. Typhi* infection was notified in a 62 year-old male who had recently arrived from SE Asia.

He was a chronic carrier and the infection was detected on routine screening. All household members were tested, and none had become infected.

Yersiniosis

Twelve cases of *Yersinia enterocolitica* infection were notified between July and December 2009, consistent with 11 cases in the same period of 2008. Cases comprised six males and six females, aged >1–69 years.

Other diseases

Invasive meningococcal disease

In Australia past notifications of invasive meningococcal disease caused by *Neisseria meningitidis* included a proportion of cases attributed to *N. meningitidis* serogroup C and were associated with a particularly poor prognosis. Routine meningococcal C vaccination, implemented in 2003, offers vaccine to children and adolescents in the high risk age-groups of 0–4 and 15–24 years, and the program has resulted in a significant decrease in cases associated with serogroup C. The predominant serogroup of *N. meningitidis* responsible for disease remains serogroup B, for which no vaccine is available.

Eight cases of invasive meningococcal disease were reported in the second half of 2009, compared to 13 for the same period in 2008. Cases comprised three males and five females, with an age range of <1–53 years. In accordance with national guidelines, immediate contact tracing occurs with all cases; chemoprophylaxis is provided for close contacts as well as vaccination, where appropriate.

Seven infections were due to *N. meningitidis* serogroup B, and one to *N. meningitidis* serogroup Y (Figure 9).

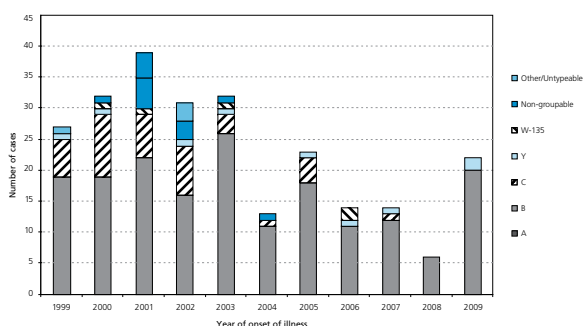


Figure 9: Notified cases of invasive meningococcal disease, by date of onset and serogroup, 1 January 1999 to 31 December 2009

Legionellosis

Twenty four sporadic cases of Legionellosis were reported during the last half of 2009, from both metropolitan and rural SA. Laboratory tests attributed 10 cases to *Legionella pneumophila* and 14 cases to *Legionella longbeachae* (Figure 10).

Ten cases caused by *L. pneumophila* Serogroup 1 were reported in six males and four females aged 22–77 years, from both metropolitan and rural SA. All were interviewed and environmental investigations by the Applied Environmental Health Branch did not elicit any common source. One case had both *L. pneumophila* and *L. longbeachae* isolated in a sputum culture. This 65-year-old female was one of two deaths resulting from the disease during this period; the other death was in a 77-year-old male.

Fourteen cases due to *L. longbeachae* infection were reported in seven males and seven females aged 41–94 years; from both metropolitan and rural SA. Of the 14 cases, only four cases reported gardening exposure, which has been regarded as a high risk for this infection.

A small cluster of five cases of *Legionella pneumophila* serogroup 1 infection were investigated in November in collaboration with the Applied Environmental Health Branch and local council EHOs. No common source of infection was identified following extensive environmental investigation. Environmental samples of a private residence of one of the cases identified *L. pneumophila* in the water system. Further laboratory sequencing revealed differences in isolates from three cases. One case died from the infection.

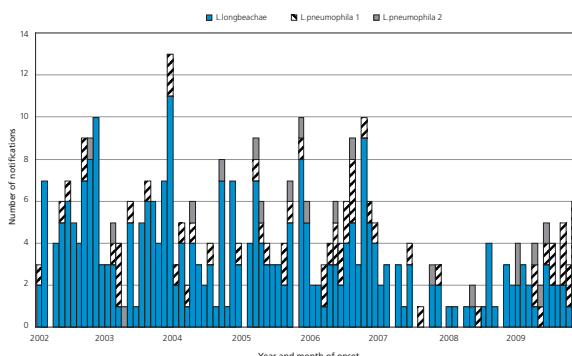


Figure 10: Notified cases of Legionella infection by year and month of onset, 1 January 2002 to 31 December 2009

These data are provisional and subject to further revision.

Communicable Disease Control Branch

Table 1: Notifiable diseases in South Australia: 1 July to 31 December 2009 and annual comparisons 2005–2009

Disease	2005		2006		2007		2008		2009	
	Jul-Dec	Total	Jul-Dec	Total	Jul-Dec	Total	Jul-Dec	Total	Jul-Dec	Total
Anthrax	0	0	0	0	0	0	0	0	0	0
Barmah Forest virus infection	15	27	1	2	4	6	15	27	16	37
Botulism	0	0	0	0	0	0	0	0	0	0
Brucellosis	0	0	0	0	0	0	0	0	0	2
Campylobacteriosis	1238	2113	1115	2661	1079	1959	1238	2113	872	1779
Chikungunya ³	-	-	-	-	-	-	-	-	0	0
Chlamydia (genital) ¹	1301	2706	965	1993	1172	2427	1301	2706	1754	3736
Cholera	1	2	2	2	0	0	1	2	0	0
Creutzfeldt-Jakob disease	0	0	0	0	1	1	0	0	0	2
Crimean-Congo Haemorrhagic Fever	0	0	0	0	0	0	0	0	0	0
Cryptosporidiosis	63	160	34	81	51	76	63	160	33	105
Dengue Fever	3	5	4	10	1	4	3	5	7	18
Diphtheria	0	0	0	0	0	0	0	0	0	0
Donovanosis ¹	0	0	0	0	0	0	0	0	0	0
Ebola Fever	0	0	0	0	0	0	0	0	0	0
Gonorrhoea ¹	161	401	116	297	162	371	161	401	129	367
<i>Haemophilus influenzae</i> infection	8	13	6	11	9	17	8	13	6	12
Hepatitis A	7	9	6	13	5	12	7	9	17	61
Hepatitis B ¹	120	276	112	205	130	223	120	276	191	444
Hepatitis C ¹	358	721	422	824	351	777	358	721	310	580
Hepatitis D	3	7	4	6	6	12	4	14	5	15
HIV ¹	20	50	29	45	29	55	20	50	34	69
Hydatid disease	2	2	5	9	3	5	2	2	3	4
Influenza ³	215	273	291	311	47	72	215	273	9545	10722
Lassa Fever	0	0	0	0	0	0	0	0	0	0
Legionellosis	30	57	45	66	27	48	30	57	24	44
Leprosy	0	0	0	0	0	0	0	0	0	0
Leptospirosis	2	3	2	2	1	1	2	3	0	0
Listeriosis	5	6	0	1	2	3	5	6	0	0
Lyssavirus infection	0	0	0	0	0	0	0	0	0	0
Malaria	19	43	15	28	11	20	19	43	19	32
Marburg Disease	0	0	0	0	0	0	0	0	0	0
Measles	0	0	21	25	4	6	0	0	0	3
Meningococcal disease	21	23	22	32	4	13	21	23	8	22
Mumps	5	8		12		3	5	8	2	12
Mycobacterial Disease (non-Tuberculous) ²	36	69	24	48	37	68	36	69	45	83
Ornithosis	1	1	1	1	2	5	1	1	2	3
Paratyphoid Fever	2	6	0	1	2	6	2	6	0	2
Pertussis	757	1409	114	233	813	926	757	1409	3393	5108
Plague	0	0	0	0	0	0	0	0	0	0
Pneumococcal disease	76	134	98	170	101	204	76	134	93	146
Poliomyelitis	0	0	0	0	0	0	0	0	0	0
Q Fever	6	20	4	13	26	36	6	20	8	9
Ross River virus infection	64	92	10	24	17	57	64	92	200	332
Rotavirus infection ³	-	-	-	-	-	-		132	148	433
Rubella	0	0	0	1	2	2	0	0	0	3
Salmonellosis	294	576	177	441	227	525	294	576	301	683
Severe Acute Respiratory Syndrome (SARS)	0	0	0	0	0	0	0	0	0	0
Shigellosis	30	47	15	30	11	57	30	47	24	52
Smallpox	0	0	0	0	0	0	0	0	0	0
Shiga toxin producing <i>E. coli</i> / HUS / TTP	13	38	15	41	23	33	13	38	30	68
Suspected Food Poisoning	49	66	19	20	57	76	49	66	3	9
Syphilis ¹	8	13	9	21	6	14	8	13	14	37
Tetanus	0	0	0	0		2	0	0	0	0
Tuberculosis ²	25	46	24	47	34	60	25	46	28	58
Typhoid Fever	1	2	1	2	1	3	1	2	1	2
Varicella infection	1080	1741	782	1231	759	1585	1080	1741	972	1827
Yellow Fever	0	0	0	0	0	0	0	0	0	0
Yersiniosis	2	7	13	18	5	6	2	7	12	17

¹ Data collected by Sexually Transmitted Diseases Services ² Data collected by SA Tuberculosis Services ³ notifiable since 1 May 2008

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