A POTENT MIX: cautionary tales of chemical mixtures

By Dr Judy Ford

Acute poisoning by synthetic or natural chemicals is well-recognised by medical clinicians. Carbon monoxide and snake or spider venoms are classic examples. Each Australian state has a major Poison Centre, usually located in a hospital focusing on children's care – children are more likely than adults to be poisoned, and the poison is more likely to be life-threatening because of their small size. Toxic chemical emergencies affecting adults most often occur because of fire or road accidents, usually involving vehicles carrying chemicals, or from major spills. These emergencies – sometimes involving the temporary evacuation of local residents – are generally well-managed.

Problems leading to toxic torts, however, are usually far more subtle. Cases frequently involve isolated incidents with a single person or a small group, or chronic exposures over extended periods. The average medical practitioner is far less well-versed in such cases and is often reluctant to believe in the patient's illness.

MULTIPLE CHEMICAL SENSITIVITY

Multiple chemical sensitivity (MCS) is possibly the most common presenting complaint in people who claim to be sick from chemical exposure. Chronic fatigue is often one of its symptoms. People with MCS have usually been exposed to one or more of a range of organic chemicals that includes pesticides and many solvents. All of the nominated chemicals have been shown to inhibit acetylcholinesterase (AchE). This enzyme normally breaks down the neurotransmitter acetylcholine at the synaptic cleft (the space between two nerve cells) so that the next nerve impulse can be transmitted across the synaptic gap. Pesticides of the organo-phosphate and carbamate types act to paralyse and kill insects by inhibiting their acetylcholinesterase. In humans, the AchE neurotransmitter system normally stimulates the brain and the nerves that relax inner organs. Poisoning of the AchE system could account for the diverse range of physical and psychological symptoms seen in MCS. >>

A common problem is that the history of each person's illness is usually one of gradual emergence. People such as photographers, radiographers, laboratory workers, tradesmen and factory workers, who have been occupationally exposed to low levels of chemicals over many years, are commonly affected. Currently, there are no identified objective measures to distinguish people with and without the condition, and many people with apparently similar exposures do not develop symptoms. However, many who report a common or similar exposure, report common or similar subsequent symptoms of debilitating disease that affect several body systems simultaneously.

Patients, as well as some physicians and researchers, are firmly convinced that the condition is organic. Other physicians and researchers believe the origin to be psychological. Since patients exhibit both physical and psychological symptoms, it is easy to see why there is some cynicism about the condition.

An example of medical cynicism is seen in the following abstract:[1]

> 'Multiple chemical sensitivity (MCS) is a syndrome in which multiple symptoms reportedly occur with low-level chemical exposure. Several theories have been advanced to explain the cause of MCS, including allergy, toxic effects and neurobiologic sensitisation. There is insufficient scientific evidence to confirm a relationship between any of these possible causes and symptoms. Patients with MCS have high rates of depression, anxiety and somatoform disorders, but it is unclear if a causal relationship or merely an association exists between MCS and psychiatric problems. Physicians should compassionately evaluate and care for patients who have this distressing condition, while avoiding the use of unproven, expensive or potentially harmful tests and treatments. The first goal of management is to establish an effective physician-patient relationship. The patient's efforts to return to work and to a normal social life should be encouraged and supported.'

Chromosomal damage

In my former laboratory, we attempted to find objective evidence for chemical exposure. Since most of the purported exposures involved chemicals that could break chromosomes, we looked for evidence of chromosomal damage in the patients' blood cells. The damage was certainly not in the majority of cells. However, most patients with MCS had elevated rates of chromosomal damage in their blood chromosomes.[2] Those with chronic fatigue without chemical exposure or MCS had the same rates as controls. I believe that this was convincing evidence that these MCS patients had had significant chemical exposure. Repeat studies on the one person showed consistent results. Nevertheless, this test is laborious, expensive and subjective, and has no chemical specificity. It is not suitable for proof of specific exposures.

Chemical mixtures

A major problem underlying the question of MCS and chemically induced illness in general is that there is little known about the effects of exposures to chemical mixtures.

PETROL: A COMMON EXPOSURE

All city-dwellers are currently exposed to high levels of petrol fumes, especially when we fill our tanks at the bowser. Petrol is a mixture in which the constituents vary between types and between batches of the same type. Petrol contains benzene, which is a known carcinogen, but also cyclohexane, ethylbenzene, xylene and toluene. There are also other solvents that vary between brands. Each component is given its threshold limit value (TLV), which is the maximal concentration of exposure to a substance over a given time, usually eight hours over an assumed lifetime. These range between 10 parts per million (ppm) for benzene and 300ppm for cyclohexane.

Activity and internal exposure

A recent study[3] used modelling to evaluate the potential toxicity from co-exposure to three central nervous system depressants (namely, toluene, ethylbenzene and xylene) under resting and working conditions. These just happen to be three components that together make up about 20-25% of petrol. The research found that, at rest, a 'modest over-exposure' occurs due to interactions between the chemicals within the body but that, when exercising, 'internal exposure was 87% more than provided by the TLV'. People exercising in streets with heavy traffic could become seriously over-exposed.

In the past, most people would have assumed that a person might inhale more of a substance during exercise. Such a dramatic increase in exposure would generally not have been suspected. Always consider the activity being performed at the time of exposure.

Local conditions

The information on protection in Caltex's material safety data sheets (MSDS – see Appendix) warns of the need for respirators when ventilation is inadequate or when vapour mists are generated. However, petrol outlets do not warn us to take particular care on days when the air is still or when there is heavier than usual traffic. Moreover, there is no guidance on how far away we should be from our tank when we open it and when we fill it. Our local Caltex station now supplies gloves. Respirators are yet to appear.

This warning about vapours has general implications for problems that are the crux of many exposures. The vapour density of volatile chemicals varies greatly with different conditions. Weather conditions clearly affect outside exposures just as ventilation affects indoor exposures. These conditions always need to be considered when evaluating exposures.

EXPOSURE TO DEFINABLE TWO-CHEMICAL MIXTURES

In a toxic tort case, the explanation is often hidden in the details of the story. The final assault that causes illness or disability is frequently due to the exposure to a mixture, rather than to a single suspect chemical. As the plaintiff is unlikely to realise this, it is critical to pay attention to the details of the story. Two recent cases well illustrate this point.

Case 1

At the end of each day, a man ('AB') who had been digging his land was covered in red dust. The digging had been going on for some months and sometimes he and his partner would swim in their dam to wash off the dust before showering. On other occasions they would just shower.

At the time of purchasing the land, AB and his partner were unaware that the land had previously been the site of a cattle tick dip. They discovered this history later when a social contact told them that their land had been decontaminated.

On the evening in question, AB went straight into the shower after working. Not long afterwards, he was staggering and disoriented. He then suffered the first of several convulsions. He remained in a demented condition for several years after the event.

Blood studies taken some months after his convulsive episodes showed that AB had extremely high blood levels of chlordane. Chlordane, now banned, was a highly toxic chemical that had been used in the old dips to eradicate termites. Residues of chlordane can remain in soil for up to 112 years.

Acute chlordane toxicity reactions occur one-half to three hours following exposure. They include central nervous system effects including convulsions and death. AB showed symptoms that were typical of having an acute exposure to chlordane at or about the time of his shower.

Chlordane poisoning usually occurs after ingestion by mouth. It is not easy to inhale large amounts because chlordane does not dissolve in water. Indeed, when chlordane was sprayed on wood or termites, it was put into an emulsion so it became soluble and more easily absorbed by the target organism.

By showering and using soap before washing off the dust, AB had inadvertently created the perfect conditions for the chlordane in the dust to become an emulsion. It was possible, in the confines of a shower, to inhale an exceptionally high and near-fatal dose. Had AB washed off the dust with water, without using soap, he would have been unlikely to have inhaled such a significant dose.

Case 2

Subject 'XY' was inadvertently sprayed with a chemical dust, polyram, that is used as a dust spray. Its active ingredient is metiram, a chemical that is moderately irritating to the respiratory mucous membranes. There is no neurotoxicity from the chemical itself. However, metiram can be metabolised to carbon sulfide, a neurotoxin that is capable of damaging nerve tissue.

Like many industrial chemicals, toxicity data refer to animal experiments that are performed on the single chemical. But, in reality, the chemical is never or rarely used alone. In this case, the polyram was sprayed in conjunction with Spraymate bond adjuvant. The details given on Spraymate are:

'*Overview*: Bond adjuvant is a high-quality sticker, deposition and retention agent that minimises chemical losses following spray applications.

Advantages: Sticks spray droplets firmly to target surfaces.

Benefits: Enables maximum chemical activity over leaf area. Provides considerable improvement over standard wetting agents.'

Immediately after his exposure to the overhead spray, XY suffered from respiratory symptoms typical of mild metiram toxicity. However, over the next 24 hours he became much sicker with headaches, muscle aches and pains, and chest pains. His symptoms were typical of exposure to a neurotoxin rather than just metiram.

The most logical explanation for the neurotoxicity was the effectiveness of the Spraymate. Presumably it held the droplets of metiram in XY's lungs long enough for it to be converted into the neurotoxin, carbon sulfide. XY then developed typical neurotoxicity symptoms.

THE CAUTIONARY TALE

In each of these cases, the exposed man would have escaped severe neurotoxicity had his exposure been to a single >>

chemical. In neither case, however, could the illness be explained without discovering the extra chemical and understanding its role in the development of the toxicity. Investigations into toxicity cases often stop before all the relevant information is recorded. Experts are called in to comment on a plaintiff's reaction to a single chemical when that single chemical could not have by itself caused the illness. Detailed investigation and history taking needs to occur at the beginning of the investigation.

Unfortunately, safety data are also usually based on experiments of exposures to single chemicals; something that rarely occurs in real situations. Often the nature of the extra chemicals is unknown. Certainly they are usually ignored unless there is rigorous questioning and discovery. Therefore, it is certainly worthwhile to listen carefully to the plaintiff's story so that any hidden elements can eventually be revealed. It is well worthwhile employing someone who can take an excellent history.

SUMMARY

Chemical toxicity is a growing problem because of the ever-increasing use of chemicals. Many doctors do not believe that chemically affected people are really ill and dispute the organic basis of MCS.

Little is currently known about the physiological effects of mixtures of chemicals, which are usually far greater than the sum of the parts. Recent research has shown that huge differences can occur between exposure at rest and during activity. Exposure during activity can lead to internal exposures that are much greater than predicted. Weather conditions and ventilation at the time of exposure also need to be considered. In this context, petrol is an example of a particularly ubiquitous and dangerous mixture.

The two recent cases cited above describe how men developed health symptoms that would not have occurred from either chemical exposure alone. In each case the second chemical was inert; one acted as a surfactant and the other was an adjuvant. These cases demonstrate how essential it is to pay attention to the details of stories and to look past the obvious when examining cases of chemical toxicity. ■

Notes: **1** Magill, MK, Suruda A (1998), 'Multiple Chemical Sensitivity Syndrome', *American Family Physician 58*: 721-28. **2** Ford JH, Behrens D, McCarthy C, Mills K, Thomas P, Wilkin HB (1998), 'Sporadic Chromosome Abnormalities in Human Lymphocytes and Previous Exposure to Chemicals', *Cytobios* 96 (383):179-92. **3** Dennison JE, Bigelow PL, Mumtaz MM, Anderson ME, Dobrev ID, Yang RS (2005), 'Evaluation of Potential Toxicity from Co-exposure to Three CNS Depressants (Toluene, Ethylbenzene and Xylene) under Resting and Working Conditions using PBPK Modelling', *J Occupational Environ Hyg* 2: 127-135.

Dr Judy Ford *is a geneticist who works as a health communicator and expert.* **PHONE** *(08) 8355 4187* **EMAIL** *judy@egs.com.au*

Appendix

The material safety data sheets from Caltex (Australia) for unleaded petrol give the following advice for exposure:

Acute – Swallowed May cause irritation to the gastrointestinal system. Symptoms may include abdominal pain, nausea, vomiting, diarrhoea or depression of the central nervous system including nausea, headaches, dizziness, fatigue, loss of co-ordination, unconsciousness and possibly narcosis. Small amounts of liquid aspirated into the respiratory system during ingestion or vomiting may lead to aspiration into the lungs with a possibility of chemical pneumonia or lung damage.

Acute – Eye May cause irritation in contact with the eyes, which can result in redness, stinging and lachrymation.

Acute – Skin Will cause irritation to the skin. This can result in itching and redness of the skin. Poisoning may occur from prolonged or massive skin contact.

Acute – Inhaled Vapours may cause headache, nausea with vomiting, dizziness, confusion and other effects of central nervous system depression. Loss of consciousness can occur at high concentrations followed by convulsions and death.

Chronic Exposure Prolonged and repeated exposure through inhalation or swallowing of this material can result in harmful effects, including central nervous system effects. Systemic effects of chronic exposure can also include damage to heart, kidneys and liver. Prolonged or repeated skin contact may also result in skin irritation leading to dermatitis.

May cause cancer: Benzene has been classified as a Carcinogen Category 1. Refer to toxicology information for further information.

Personal Protection Respirator Type (AS 1716). Avoid breathing of vapours/mists. Where ventilation is inadequate and vapours/mists are generated, the use of an approved respirator with filter complying with AS/NZS 1715 and AS/NZS 1716 is recommended; however, final choice of appropriate breathing protection is dependent upon actual airborne concentrations and the type of breathing protection required will vary according to individual circumstances. Expert advice may be required to make this decision. Reference should be made to Australian Standards AS/NZS 1715- Selection, Use and Maintenance of Respiratory Protective Devices; and AS/NZS 1716- Respiratory.

Protective Devices Eye protection: chemical safety glasses or face shield recommended as appropriate. Final choice of appropriate eye/face protection will vary according to individual circumstances including methods of handling or engineering controls as determined by appropriate risk assessments. Eye protection should conform to Australian/New Zealand Standard AS/NZS 1337- Eye Protectors for Industrial Applications.

Glove Type Impervious (neoprene or nitrile rubber) gloves recommended as appropriate. Final choice of appropriate glove type will vary according to individual circumstances, including methods of handling or engineering controls as determined by appropriate risk assessments. Refer to AS/NZS 2161 Occupational protective gloves- Selection, use and maintenance. The use of barrier cream is recommended.