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Special section: Editorial

What's your poison? Neurobehavioural consequences of exposure to industrial, agricultural and environmental chemicals.

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Toxicology is a multi-disciplinary science which draws on a number of disciplines to determine the adverse effects of chemicals in living organisms. There has been a huge increase in toxicological research over the last seventy years, as concerns have grown about the possible effects of exposure to the increasing number of industrial and environmental chemicals being produced every year, such as synthetic chemicals, fuels, pesticides, solvents, carbon monoxide, metals and related elements such as lead, mercury and arsenic (Klaassen, 2008). There are literally thousands of substances that possess the capacity to do harm in sufficient doses, and pollutants are now widespread in air, water, soil, food, homes, schools and workplaces. It has been estimated that there are over 100,000 toxic substances in commercial use and approximately 2,300 new chemicals developed and submitted for registration every year (Environmental Protection Agency Office of Pollution Prevention and Toxics (OPPT) 2011; European Inventory of Existing Commercial Chemical Substances, 2011). The capacity of industry to produce chemical substances outstrips research, meaning our knowledge regarding the potential health effects of many substances is limited, giving rise to differences in opinion and controversies regarding safe exposure standards for new and existing substances.

Establishing safe exposure standards is fraught with difficulty and is dependent on the outcome of interest (e.g. mortality, carcinogenicity, reproductive effects, physical ill health, neurological symptoms). In an ideal world the dose/response relationship for each potential health effect would be known, but financial constraints, concern for the welfare of animals and methodological issues mean not all of these outcomes are studied (Klaassen, 2008). To complicate matters further, there are substantial inter-individual differences in people's ability to metabolise and detoxify certain chemicals (Costa, Richter, Li, Cole, Guizzetti & Furlong,

2003), which makes it extremely difficult to establish safe exposure standards that will apply universally.

Few chemicals are subjected to behavioural and neurological analysis which means the neurotoxic potential of many substances is unknown. Neurotoxic substances interfere with nervous system function causing cognitive, emotional and behavioural change and neuroscientists have an important role to play in both clinical and research settings when it comes to detecting and evaluating the effects of industrial and environmental substances (Lezak et al, 2004; Lucchini, Albini, Benedetti & Alession, 2005). In this special section we have gathered together contributions from leading researchers across the globe to provide readers with a snapshot of the interesting and challenging world of neurobehavioural toxicology. Our aims are twofold (1) to stimulate interest and further research in this area, and (2) to increase awareness amongst neuroscientists, neurologists, psychologists and other healthcare professionals, of the aetiological role neurotoxic substances may play in many neurological and psychiatric conditions. Successful treatment of neurotoxic syndromes requires early diagnosis and cessation of exposure, but neurotoxic syndromes can be difficult to diagnose and are often confused with other conditions. Clinician's lack of familiarity with the potential toxicity of environmental and industrial chemicals can lead to misdiagnosis and mismanagement, which in turn can lead to continued exposure.

Special section

The papers in this special section illustrate how exposure to neurotoxic substances can occur at any point during our lifetime, e.g. prenatally, during childhood & adolescence, during adulthood or in old age. They also illustrate that exposure can take place in a variety of different contexts; through contact with toxic chemicals in the home (e.g. carbon monoxide and pesticides) or in the workplace (e.g. agricultural and chemical plant workers, military veterans and aviation workers); or via drinking water and food. In many cases individuals are unlikely to be aware of these exposures, let alone attribute symptoms of ill health to toxicity, unless they have been specifically advised that they are at risk. Furthermore, health care professionals are unlikely to consider a toxic cause for a patient's symptoms due to lack of awareness and training in toxicology.

Toxicity and the developing brain

The first three papers in this section discuss the implications of exposure to neurotoxic

substances on the developing brain. Debes, Weihe & Grandjean (this issue) present the results of a prospective study looking at the impact of prenatal exposure to methylmercury (via seafood consumption) on cognitive development. They followed a cohort of 1022 children over 22 years and found children's scores on tests of crystallized and general intelligence were lower at increased exposures and these deficits persisted over time.

Rodriguez-Barranco, Gil, Hernandez, et al (this issue) present the results of a cross-sectional study of 261 children looking at the impact of postnatal exposure to arsenic (via drinking water) on neurobehavioural function. They found a dose-response relationship between urinary arsenic levels and attentional problems in children even at levels of exposure considered to be within safe exposure standards.

Rohlman, Ismail, Rasoul, Bonner, Hendy, Mara, Wang & Olson (this issue) undertook a 10 month prospective study of 89 adolescents involved in the application of pesticides to cotton crops in Egypt. Over the course of an application season, they found that participants with high pesticide exposure (indexed by urinary levels of a pesticide metabolite) performed significantly worse than those in the low exposure group on a number of neurobehavioral measures (including psychomotor speed, executive function and attention); a pattern that worsened as cumulative pesticide exposure increased over time. These deficits persisted for several months after the application season ended, even when biomarkers of exposure had decreased.

Clearly the results of these studies are alarming, as they suggest exposure to neurotoxic substances during early development can cause permanent neuropsychological damage. In February 2014 a review article appeared in *The Lancet* attributing the increasing rates of neurodevelopmental disorders (e.g. autism, attention-deficit hyperactivity disorder and dyslexia) to exposure to industrial chemicals such as lead, methylmercury, arsenic, polychlorinated biphenyls, toluene, carbon monoxide, manganese, organophosphate pesticides and phthalates. The authors, Grandjean and Landrigan, argue genetic factors alone are unable to account for this increase in prevalence and conclude that strong evidence exists to suggest exposure to environmental and industrial chemicals at critical stages of development are to blame. This is particularly concerning because exposure to neurotoxic substances is not rare; almost half of the 201 known human neurotoxicants are 'high production volume chemicals', of which organophosphate pesticides are the largest group.

Organophosphate pesticides, cognitive impairment and neurodegenerative diseases

The next three papers in this section focus on the potential impact of organophosphate pesticides on psychiatric and neuropsychological function in adults. For example, Zhang, Wu, Yao, et al (this issue) explored the impact of recent pesticide poisoning on neurobehavioural functioning using a case-control study of farm workers in China who had been poisoned by pesticides in the previous 12 months. They found that farm workers who reported pesticide poisoning in the previous 12 months showed evidence of reduced neurobehavioral function (psychomotor speed, visual & auditory memory) and increased psychiatric morbidity, but the authors were unable to determine whether this was a result of acute poisoning episodes, or cumulative, low level exposure. The findings from this paper are important, as it is one of the first to investigate the impact of pesticides on a Chinese cohort. Chinese farmers rely on pesticides to maintain high crop yields as they have the burden of feeding 20% of the world's population on only 7% of the world's arable land. Government figures suggest between 53,000 and 123,000 people are poisoned each year, suggesting that workers from developing countries are at increased risk of occupational exposure because economic factors and limited education often mean they do not receive adequate health and safety training or invest in personal protective clothing. This is particularly concerning given that chemical manufacturing is expected to grow fastest in developing countries in the next five years (International Federation of Gynaecology & Obstetrics (FIGO), 2015).

This paper highlights a number of issues which are apparent throughout the toxicology literature. Firstly, the issue of dose-response relationships and whether the impact of high level exposure is equivalent or different from cumulative low level exposure. For many chemicals the toxic effects of a single, acute, high level exposure are known from animal testing or case studies involving incidents of severe poisoning, whereas less is usually known about the health outcomes of repeated, low level exposure, which may produce quite different effects (Klaassen 2008). Secondly, establishing a causal link between neuropsychological impairment and exposure to neurotoxic substances is not easy. Patients frequently present long after exposure has ceased and the toxic substance has been eliminated from the body which means objective evidence of exposure (i.e. a biomarker) is seldom available (Hartman, 1995). Researchers often rely on the patient's self-report to determine whether they have been exposed to a neurotoxic substance, the likely amount they have been exposed to (dose), how often (frequency) and over what time period (duration). Unfortunately patient's testimony can be unreliable because of the

limits of human memory, and processes such as recall bias and attribution error. Often the most that can be achieved is to document the opportunity for exposure and evidence suggestive of a causal relationship (Berent & Albers, 2005).

The articles by Stallones and Beseler and Sanchez-Santed, Colomina and Hernandez (this issue) explore the potential biological mechanisms by which organophosphate pesticides may cause neuropsychological and psychiatric symptoms and link those mechanisms with what is known about the biological basis of depression and neurodegenerative conditions. They explain that the way OPs cause chronic and long-term effects may be different from the commercially exploited mechanism of action. Sanchez-Santed et al go on to review the evidence concerning the relationship between pesticide exposure and the later development of neurodegenerative conditions such as Alzheimer's, Parkinsons Disease and Amyotrophic Lateral Sclerosis (ALS). They discuss common targets and pathways which underlie both pesticide exposure and neurodegeneration and conclude that the association between pesticide exposure and Parkinson's disease is compelling, but the link between pesticide exposure and Alzheimer's disease and ALS is less convincing.

Diagnosing neurotoxic injury

The articles by Mackenzie Ross; Sykes and Walker (this issue) illustrate the potential for misdiagnosis and mismanagement of neurotoxic syndromes because healthcare professionals receive little training in toxicology and may harbour misconceptions regarding the toxicity of various chemicals and likely health outcomes. Mackenzie Ross describes two patients who were exposed to toxic substances in the workplace, but for whom diagnosis proved difficult. These cases illustrate how routine medical evaluations (including CT brain, EEG, Evoked Potential studies, EMG and nerve conduction studies) often fail to reveal any abnormalities in patients who have been exposed to toxic substances which can result in neurotoxic syndromes being misclassified as psychiatric disease. Mackenzie Ross highlights the importance of taking a detailed occupational history in patients who present with atypical neurological symptoms and the crucial role neuropsychology has to play in diagnosing neurotoxic injury.

Sykes and Walker review the literature on carbon monoxide poisoning and highlight how it can be difficult to diagnose and is frequently missed by healthcare professionals. The authors explain how many individuals who survive carbon monoxide poisoning report

neurobehavioural problems, but this may not be due to carbon monoxide's affinity for haemoglobin. Instead, they present various other potential mechanisms of action which illustrates how our understanding of the way in which carbon monoxide affects nervous system function is constantly evolving.

The article by White et al focuses on military veterans and reviews the literature regarding the likely cause of Gulf War Illness (GWI). This paper illustrates how difficult it can be to determine the cause of ill health in populations where multiple risk factors and potentially confounding variables co-exist. The authors conclude that exposure to pesticides and prophylaxis medication (pyridostigmine bromide) are the most likely culprits and that psychiatric aetiologies can be ruled out. However, other researchers have reached very different opinions over the years with some attributing GWI to stress and anxiety about chemical weapons and vaccines (Kings Centre for Military Health Research, 2010) and others attributing it to chemical weapon exposure (Tuite & Haley, 2013; Haley & Tuite, 2013).

Finally, Harrison and Mackenzie Ross highlight an emerging concern in toxicology, *the potential risk to health of toxic fumes in airplane cabins*, and explore the challenges and methodological issues encountered by previous researchers who have tried to look at this issue.

Concluding comments and future directions

Neuroscientists, neurologists and neuropsychologists have an important role to play in both clinical and research settings when it comes to detecting and evaluating the effects of toxic substances (Lezak et al, 2004; Lucchini, Albini, Benedetti & Alession, 2005). Clearly there is an urgent need for clinical services and further research as an unknown number of us will be exposed to neurotoxic substances throughout our lifespan. We may be unaware of these exposures and unlikely to attribute symptoms of ill health to toxic exposure and the same may be true of the doctors we consult who receive little training in toxicology. The aim of this special section is to provide readers with a snapshot of the interesting and challenging world of neurobehavioural toxicology in the hope of stimulating interest and further research in this area. Each paper highlights challenges facing researchers such as: (1) Difficulty establishing causal links between exposure and ill health, due to uncertainty about the exact dose, frequency, duration and nature of exposure; the inability to rule out competing causes and potentially confounding factors; the ever-evolving state of knowledge regarding the biological mechanism of action of toxic substances which might cause ill health (2) Difficulty obtaining corroborating medical evidence (3) The possibility that subgroups of people exist who are particularly

susceptible to the toxic effects of substances because of biological factors (e.g. immaturity, ill health, genetic differences in the capacity to detoxify certain substances) , or economic factors (e.g. individuals from developing nations are at increased risk because of limited health and safety training). We hope this special section will stimulate discussion amongst academics and clinicians which will lead to the identification of potential solutions to some of the methodological issues described. We also hope consideration will be given to the development of clinical services, assessment/diagnostic protocols and treatment options for individuals who have developed ill health following exposure to toxic substances.

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