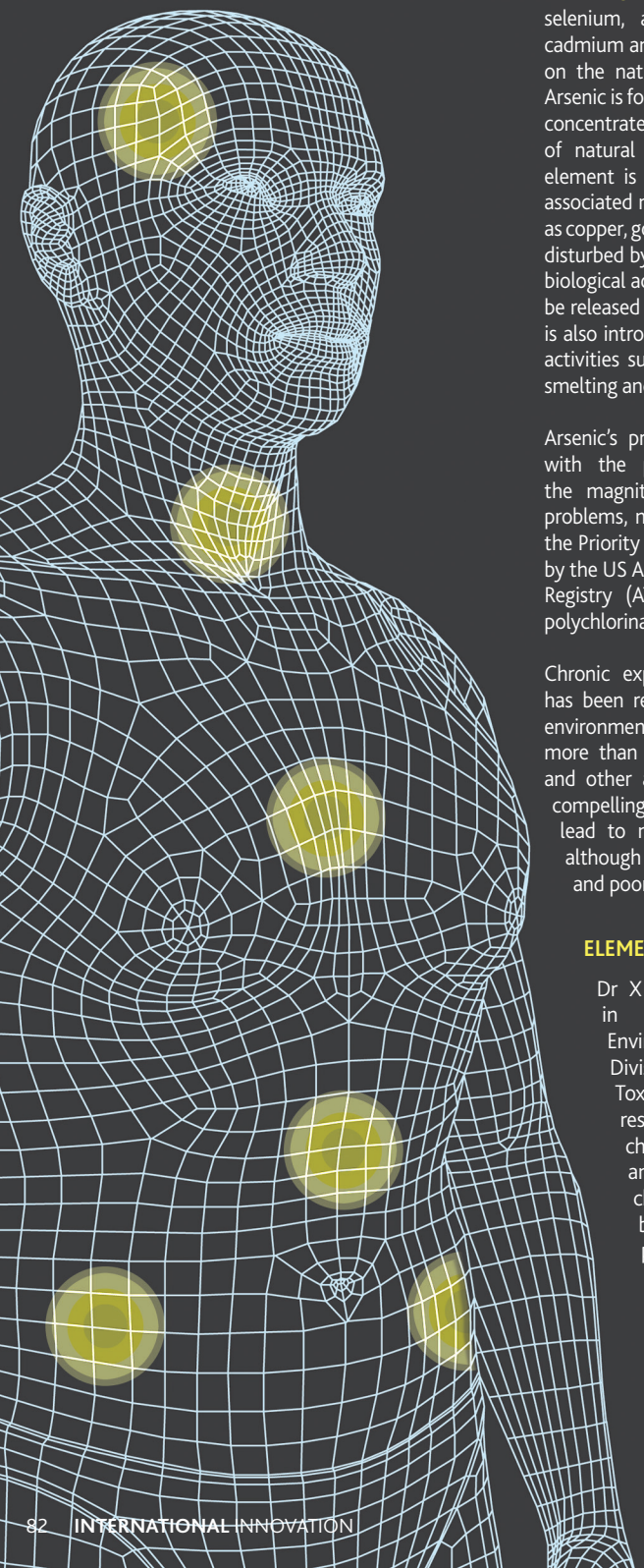
An element of **risk**

The Bio-Analytical Technology and Environmental Health programme at the **University of Alberta**, Canada, brings together researchers from various disciplines to study the implications of human exposure to arsenic and consequent effects on DNA repair



METALLOIDS SUCH AS arsenic, antimony and selenium, and metals such as mercury, lead, cadmium and vanadium have an important impact on the natural environment and human health. Arsenic is found in the Earth's crust and can become concentrated in some parts of the world because of natural mineralisation. This ubiquitous trace element is a component of 245 minerals and is associated most frequently with other metals such as copper, gold, lead and zinc in sulphidic ores. When disturbed by natural processes such as weathering, biological activity or volcanic eruption, arsenic may be released into the surrounding area. The element is also introduced into the environment by human activities such as burning fossil fuels, mining, ore smelting and well drilling.

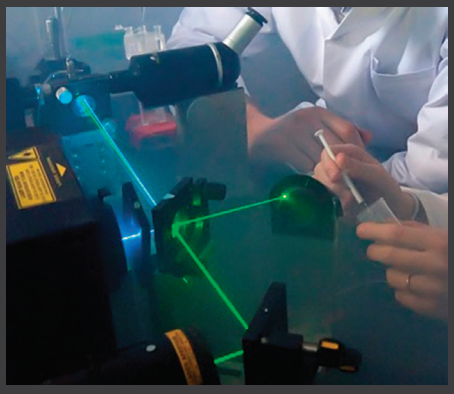
Arsenic's prevalence in the natural world, along with the potential for human exposure and the magnitude and severity of related health problems, means the element ranks at the top of the Priority List of Hazardous Substances compiled by the US Agency for Toxic Substances and Disease Registry (ATSDR), ahead of lead, mercury and polychlorinated biphenyls (PCBs).

Chronic exposure to arsenic from groundwater has been recognised as the cause of the largest environmental health disaster in the world, putting more than 100 million people at risk of cancer and other arsenic-related diseases. There is also compelling evidence that exposure to arsenic can lead to numerous other adverse side effects, although the exact mechanisms are complicated and poorly understood.

ELEMENT SPECIATION

Dr X Chris Le is Canada Research Chair in Bio-Analytical Technology and Environmental Health and Director of the Division of Analytical and Environmental Toxicology at the University of Alberta. His research programme is a collaboration of chemists, toxicologists and clinicians, and has three major themes: arsenic chemistry and toxicology; DNA damage biomarkers; and novel techniques for protein detection.

In view of the significant impact of metals and metalloids on the natural environment and human health, the chemical speciation of trace elements plays a major role in the work of Le's team, which has developed chromatography and mass spectrometry techniques to analyse trace element species in environmental, biochemical and toxicological studies. Le explains: "The toxicity of arsenic depends on its chemical forms (species). The relative toxicities of arsenicals vary by more than a million times between the most toxic arsenic species to the least toxic arsenic species." As a result, Le believes that rather than measure the total amount of arsenic, it is more toxicologically important to measure individual species of the element.



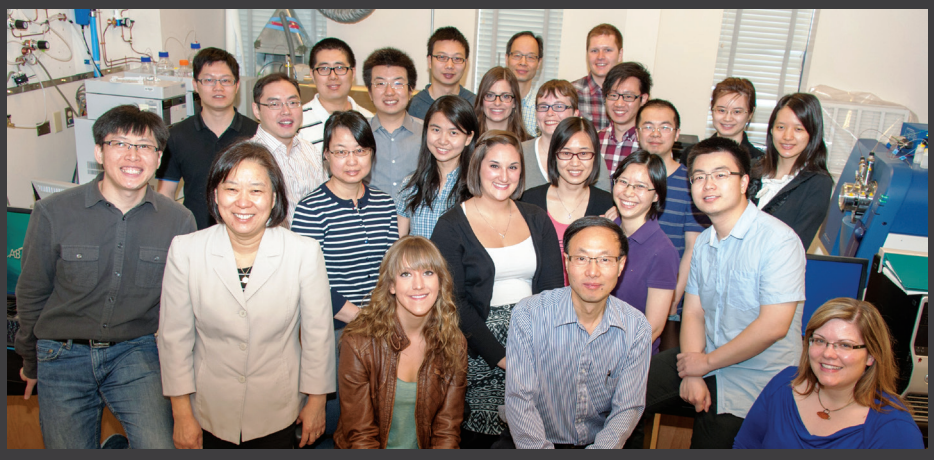
A LASER-INDUCED FLUORESCENCE POLARISATION SYSTEM BUILT IN THE LE LAB

The researchers' speciation techniques have enabled the identification of arsenic metabolites and their interaction with proteins, which is essential to the understanding of arsenic metabolic pathways and arsenic resistance mechanisms in microorganisms. According to Le, "a mechanistic understanding of arsenic's health effects is necessary for establishing scientifically sound regulatory guidelines that protect public health and also for developing arsenic-based therapeutics".

DNA DAMAGE BIOMARKERS

The second area of the group's research involves the development of highly sensitive bioanalytical techniques for studying DNA damage, which represents a common link between many environmental contaminants that may contribute to human cancer. DNA damage and cellular repair are key determinants in the early stages of carcinogenesis, ageing and cancer therapy.

Le and collaborators have developed a novel assay for measuring DNA damage, with a detection limit of 3×10^{-21} moles. This ultrasensitive assay, which has received both US and Canadian patents, allows the measurement of DNA damage caused by environmentally and clinically relevant exposures, and has paved the way for studies into DNA repair and enhanced biomarker development.



THE LE GROUP CONSISTS OF STUDENTS AND RESEARCHERS FROM DIVERSE ACADEMIC BACKGROUNDS

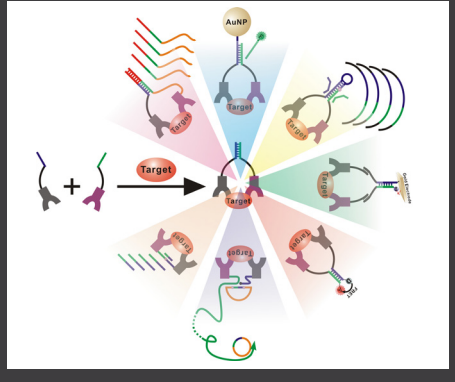
"Our research team and others have shown that trivalent arsenic species interfere with the repair of DNA damage caused by other agents, such as ultraviolet light and chemicals present in cigarette smoke," elaborates Le, who sees these findings as consistent with population surveys, which show synergies between arsenic exposure and cigarette smoking in lung cancer risk.

PROTEIN DETECTION

The third area of Le's research involves the development of novel techniques for protein detection, taking advantage of DNA-protein binding, nano-material assembly and polymerase amplification. These techniques are applied to studies of protein biomarkers, natural toxins, therapeutic drugs, environmental contaminants and DNA-protein interactions. Often, just a few protein molecules are sufficient to control biological functions, hence the importance of developing an ultrasensitive detection method for minuscule amounts of proteins.

Very small amounts of DNA can be amplified by the polymerase chain reaction (PCR), but there is no comparable technique to chemically amplify proteins. As a result, the detection of low-abundance proteins represents an enormous challenge for researchers. To resolve this issue, Le and his colleagues developed innovative techniques to detect trace levels of proteins.

First, the team binds specific DNA aptamers that have unique and high affinity binding to target proteins. The aptamer-protein complex is then separated from the unbound aptamer by using capillary electrophoresis. The fractions containing the aptamer-protein complexes are collected, the aptamer is dissociated from the complexes, and the dissociated aptamer is amplified by PCR.



SEVERAL DNA-PROTEIN BINDING ASSAYS INCORPORATING SIGNAL AMPLIFICATION STRATEGIES

The amplification of the aptamer to which the protein binds dramatically improves the sensitivity of the detection of proteins. The group is able to detect as few as 180 molecules of a viral protein. As Le describes, "this concept and approach have diverse potential applications, ranging from bio-sensing to personalised and point-of-care diagnostics to the study of molecular interactions".

ULTRASENSITIVE ASSAYS

Looking ahead, the team would like to expand their research to cover antimony and vanadium, as these chemical elements carry similar environmental and health risks to arsenic. Further research will also target a mechanistic understanding of the effect of toxic elements on the induction and repair of DNA damage caused by common carcinogens in the environment such as cigarette smoke.

Meanwhile, the progress made by the researchers in detecting remarkably low levels of proteins has opened up new horizons in biomedical and environmental health research, and Le intends to further develop ultrasensitive assays for other targets and extend the methodology to point-of-care diagnostics.

The University of Alberta group's studies into the effects of arsenic on DNA repair are improving our understanding of how arsenic causes cancer. All of the knowledge gained will also have implications for cancer research in general, as DNA repair is an essential process in protecting against cancer. In addition, fellow scientists will be able to apply Le's research approach to their own studies into other environmental carcinogens.

In advancing analytical and toxicological sciences, Le and his collaborators hope their work will help regulatory bodies to develop rational guidelines on arsenic as well as measures to prevent and reduce health problems caused by the element, as Le concludes: "We seek novel approaches to assess and prevent adverse health effects in humans and our environment".

INTELLIGENCE

CANADA RESEARCH CHAIR IN BIO-ANALYTICAL TECHNOLOGY AND ENVIRONMENTAL HEALTH

OBJECTIVES

To develop new analytical technology for the study of the impact of environmental contaminants, such as arsenic compounds, on human health. Linking chemistry, toxicology, clinical medicine and public health, the group designs ultrasensitive and highly specific techniques and assays for proteins, DNA and environmental contaminants.

KEY COLLABORATORS

USA: **Dr K Cantor**, National Cancer Institute; **Dr S Cohen**, Nebraska University School of Medicine; **Dr D Thomas**, National Health and Environmental Exposure Research Laboratory

Canada: **Dr W R Cullen**, University of British Columbia; **Dr K J Reimer**, Royal Military College; **Dr M Weinfeld**, Cross Cancer Institute

China: **Dr G B Jiang**, Chinese Academy of Sciences; **Dr M D Lai,** Zhejiang University; **Dr Q K Zhuang**, National Natural Sciences Foundation of China; **Dr H F Zou**, Chinese Academy of Sciences

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PROFESSOR X CHRIS LE holds an inaugural Canada Research Chair in Bio-Analytical Technology and Environmental Health. He is Distinguished University Professor in the Departments of Laboratory Medicine and Pathology, Chemistry, and Public Health Sciences, and is the Director of Analytical and Environmental Toxicology Division. In 2010, Le was elected Fellow of the Royal Society of Canada, Academy of Science. As well as receiving numerous awards and distinctions for his contribution to research and teaching, Le has published 190 peer-reviewed research articles, 25 book chapters and 10 patents.

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