NZIC Chemistry IN NEW ZEALAND

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New Zealand Institute of Chemistry

supporting chemical sciences

October News

Comment from the President

One of the interesting initiatives of the present government has been the appointment of a Chief Science Advisor (CSA) to the Prime Minister, Professor Sir Peter Gluckman who, formerly, headed the Liggins Institute in Auckland. As his role is independent of the other groups that advise government policy, *e.g.* the Ministry of Research Science and Technology and the Royal Society of NZ, he is likely to be influential in the way cabinet views science in the future. In establishing the position, John Key is following well-accepted practice in other countries.

Sir Peter gave his first speech[1] as CSA at Massey University in July and defined his role under five headings:

- To advise the Prime Minister of science policy as requested
- To advise, via reports, on specific scientific issues
- To improve the public understanding of, and engagement with, science
- To build international relationships in science
- To alert the Government to opportunities and threats that science may reveal.

Later in the speech he identified two big issues. The first he posed as a question namely, *what is the purpose of public investment in NZ science, or what should NZ expect from its investment in science?* In answering this he revealed his belief that *science will be the mainstay of the transformation of NZ* – without being too specific about what New Zealand would transform into, other than to refer to productivity and the many challenges we face. He also emphasised that the value of science goes beyond the immediate project to which it is directed, and scientific understanding enriches many aspects of society. As an example, he referred to a recent report by the Royal Society (London) on the impact of science, technology, engineering and mathematics on the service sector of the British economy.[2] However, he also challenged the science community to find compelling answers to the question that will satisfy a sceptical political and public audience.

The second major issue that he raised was that of the fragmentation of scientific endeavour in NZ. Put another way: *Is it an efficient use of resources for a country of 4 million to have 20 government-funded scientific research organizations and very little industrial investment in R&D?* This was not so much an argument for the centralisation of resources as a plea for better utilization of resources through greater collaboration between the various parties with a stake in scientific research. Sir Peter held up the Centres of Research Excellence as an example of good practice in this respect – not surprising as he headed one of the CoREs until his recent appointment as CSA. Both of these big issues have been raised before by other commentators, but that should not detract from the importance of the message. As members of the NZ science community, we should support Sir Peter's efforts to improve the public and political perception of the value of science, and chemistry in particular, to NZ society. Of course, several of Sir Peter's objectives have been implicit objectives of the NZIC for many years.

In 2011 the NZIC has a great opportunity to highlight the importance of chemistry to New Zealand when we celebrate the International Year of Chemistry. Sir Peter refers to a view held in some quarters that NZ does not require much in the way of scientific research and development, and that we should import ideas and technologies from abroad. The foolishness of this approach was amply demonstrated in *New Zealand is Different* that was published by the NZIC in 1999 and which was highlighted again this year by a Brian Easton article in *The Listener*.[3] *New Zealand is Different* illustrated the importance of an indigenous research and development culture through many examples that have shaped present day New Zealand. Our plan for a follow-up edition will provide us with an opportunity to shout the importance of chemistry in NZ loudly and clearly.

References

1. P. Gluckman, *Speech notes – Massey University*, 17 July, 2009, http://www.pmcsa.org.nz/news-and-events
2. *Hidden wealth: The contribution of science to service sector innovation*, Royal Society London, 2009, http://royalsociety.org/document.asp?id=1170
3. B. Easton, *My Chemical Romance*, The Listener, 2009, http://www.eastonbh.ac.nz/?cat=2

John Spencer

President

NEWS

NZIC MEMBERSHIP MATTERS

We congratulate Drs *Gary* ***Evans*** (Industrial research Ltd., Lower Hutt) and *Peter* ***Hodder*** (Victoria University, Wellington) on their election to Fellowship of the Institute at the August Council Meeting.

We welcome to the Institute the following as new members:

MNZIC

Katerine ***Hebditch***, Baldwins, Auckland

Nicholas L ***Hyde-Sergejew***, Kelston Boys' High School

Dr *Geoff* ***Waterhouse***, University of Auckland

Dr *David Roger* ***Harding***, Massey University

Dr *Vyacheslav* ***Fifichev***, Massey University

Mrs *Heather* ***Velvin***, Freyberg High School

Mr *Mark* ***Reynolds***, Fonterra, Palmerston North

Dr *Alistair Ian* ***Longshaw***, Industrial Research Ltd.

Student Members

Miss *Yiwen* (*Angela*) ***Pei***, University of Auckland

Ms *Ashna* ***Khan***, Victoria University

Mr *Nicholas* ***Monahan***,Victoria University

Mr *Juan Olguin* ***Talavera***, University of Otago

Prizes

The Council of the Institute is please to announce the recipients of the ***2009 Awards and Prizes***.

The NZIC-RSC Easterfield Medal has been awarded to Dr *Richard* ***Tilley*** (School of Chemical & Physical Sciences of Victoria University) for his outstanding contributions to the area of nanotechnology and the development of quantum dot synthesis.

The Fontera Prize for Industrial and Applied Chemistry has been awarded to Dr *Owen* ***Catchpole*** (Industrial Research Ltd., Lower Hutt) for his seminal contributions to the development of supercritical fluid processing and extraction technologies.

The Maurice Wilkins Centre Prize for Chemical Science has been awarded to Prof *Sally* ***Brooker*** (Chemistry Department, Otago University) for her work involving macrocyclic- and heterocyclic-containing ligands and cages across a range of chemical, biochemical and technological interfaces.

The ABA Books Denis Hogan Prize for Chemical Education has been awarded to Mr *Ian* ***Torrie*** (St. Cuthbert's College, Auckland) who has given especially generously of his time to advance the teaching of chemistry in New Zealand by interaction with the teaching fraternity over many years.

New Zealand is Different

NZIC is to produce Vol. 2 of *NZ is Different* to mark the International Year of Chemistry 2011. A number of potential articles have been sourced. Anyone with suggestions for articles should contact NZIC Administration.

Reciprocal Agreement with RACI

NZIC has formalized a reciprocal agreement with the Royal Australian Chemical Institute. The principal advantage to members is to attendance at RACI events at RACI member rates (and *vice-versa* for RACI members attending NZIC events). This formalizes a long standing practise.

BRANCH NEWS

AUCKLAND

Massey University – Albany

PhD student *Andreas* ***Hermann*** graduated in June with a thesis described as a tour de force of advanced theoretical methods by one of his examiners; it was included in the Dean's List of Exceptional Theses. He was supervised by Prof *Peter* ***Schwerdtfeger*** and A/Prof *Joachim* ***Brand*** and studied the structural and cohesive properties of ice.

The proposed Bachelor and Master of Natural Sciences have received CUAP approval and are to proceed as planned. The new BNatSci degree will be offered conjointly with the established BSc programmes as an integrative, inter-disciplinary programme with a strong commitment to modern approaches to enquiry-based science learning. It will offer a broad-based, flexible course structure spanning the physical and biological sciences in order to foster interdisciplinary thinking.

Recent visitors have included Prof *Gernot* ***Frenking*** (Philipps University, Marburg) who gave two lectures in July on *Molecules with Unusual Chemical Bonding Situations – A Challenge for Theory and Experiment* and *The Nature of the Chemical Bond: Old Question, New Answers*. He showed how energy decomposition analysis (EDA) can be used to characterise the strength of chemical bonds quantitatively.

University of Auckland

The Auckland Cancer Society Research Centre (ACSRC) continues to expand its chemistry facilities with the latest renovations increasing the Medicinal Chemistry capacity to 26 full-time positions. The ACSRC was successful in receiving two three-year Project Grants in the 2009 HRC funding round. A/Prof *Bob* ***Anderson*** and Dr *Jeff* ***Smaill*** received $719,625 to investigate *Prodrug release of kinase inhibitors in cancer therapy* while A/Prof *Gordon* ***Rewcastle*** (Principal Investigator) and co-investigators (including chemists Prof *Bill* ***Denny*** and Dr *Jackie* ***Kendall***) received $1,498,525 to investigate *Strategies for developing PI3K p110 isoform specific anticancer drugs*. Additional funding for the PI3K (phosphatidylinositol 3-kinase) project has also come from a successful renewal of the contract with Pathway Therapeutics Ltd.

A very successful one-day *Winter School in Anticancer Drug Development* was held at the Medical School in July with both biologists and chemists from the ACSRC participat-

ing. The main organiser was ACSRC molecular modeller Dr *Jack* ***Flanagan***. It is hoped to make this Winter School an annual event.

In October, the Chemistry Department was in the middle of a University review process. In June news came through that *Penny* ***Brothers*** had been promoted to Professor (see last issue), a fine recognition of her contribution to inorganic chemistry and her service to the University.

On 10 June the Department hosted its inaugural Research Showcase (see elsewhere in this issue). In addition to the featured speakers, over 60 posters were entered and the prize winners from the 2nd-year PhD poster competition were *Tsz Ying* ***Yuen*** (1st), *Akihiro* ***Shimamura***, an exchange student from the University of Tokushima, Japan (2nd) and *Karthik* ***Kannappan*** (3rd). Chemistry again featured in the University's *Incredible Science* day in July, with Magic Show, Glassblowers, slime, smashing smarties and lectures - all of which were in extremely high demand.

In August, Distinguished Prof *Ted* ***Baker*** stepped aside as the director of the Maurice Wilkins Centre for Molecular Biodiscovery, which he had established and involves many chemists among the 200 researchers involved from across the country. Prof Baker has had a long research career at Massey and Auckland universities examining the physical structure of proteins - the building blocks of life. The leadership of the centre has been handed over to Associate Prof *Rod* ***Dunbar***.

Two new facilities within the Chemistry Department were featured in recent Branch meetings. At the June meeting, Dr *Cather* ***Simpson*** spoke on the *Photon Factory*, the new state-of-the-art Laser Facility, which is a joint development between the Chemistry and Physics Departments. Cather's talk on the development of the photon factory offered some insight into the capabilities of this facility, including directions which will involve microfabrication possibilities. In July, Dr *Bryon* ***Wright*** introduced the new Microfabrication Facility housed within the Chemistry Department. It has input from the Mechatronics Engineering Group and the Polymer Electronics Research Centre. Bryon outlined the capabilities of the equipment that has been assembled to date and how the facility is running projects ranging from conducting polymer-driven microfluidics to AFM investigations of nanowires.

Prof *Jonathan* ***Sessler*** visited the Department in August as a Fulbright Senior Specialist and University Distinguished Visitor hosted by Prof *Penny* ***Brothers***. Prof Sessler taught a module on supramolecular chemistry to the postgraduates, gave a seminar on *Oligopyrroles: Receptors for Potentially Hazardous Materials*, and a public NZIC-supported lecture on 20 August entitled *The impact of molecular engineering: designer molecules for health and the environment*. In the last Prof Sessler told the story of the development of motexafin gadolinium (MGd) as an agent for cancer therapy, along with a perspective on the process of drug design and development and the interplay between academic research and venture-funded commercial development.

Further recent Departmental seminars have included Prof *Abhik* ***Ghosh*** from Tromsø on *Metallocorroles as Models of High-Valent Heme Protein Intermediates*, which combined experimental and theoretical work on corroles – ligands closely related to the biologically relevant porphyin ligands; and A/Prof *Kate* ***McGrath*** (Victoria University) on *Biomineralization: from proteins to model systems to mimics*.

CANTERBURY

On 29 July a small group of NZIC members enjoyed a wine tasting run by CPIT wine appreciation tutor, *Susan* ***Taylor***. A range of exceptional NZ wines were tasted and the comments were so good that the Canterbury Chair, who himself does not drink, purchased bottles of three of the wines for future entertaining. The wines that were sampled and highly recommended by the attendees were St Claire Marlborough Sauvignon Blanc 2008, Peregrine Central Otago Pinot Gris 2008, Craggy Range Single Gimblett Gravels Vineyard Chardonnay 2007, Petter Evans Waipara Pinot Noir 2004, Aurora Bendigo Syrah 2006, and Trinity Hill *The Gimblett* 2006

In mid-August members enjoyed a fascinating talk by Prof *Mark* ***Pollard*** on *Archaeological Chemistry: A Scientific Career in Ruins*. Prof Pollard is from the Research Laboratory for Archaeology and the History of Art at the University of Oxford.

The Branch Dinner was held for members (and partners) on September 4th at Visions restaurant on the CPIT campus. The degustation menu proved to be of real interest and taste to those who attended.

CPIT

The CPIT Year 11 Chemistry Competition is scheduled to take place on Thursday 24 September, when this issue is in production. It is hoped that the maximum of 24 teams will be competing. CPIT is also looking at running a Year 10 science competition in Timaru later in the year, probably in November.

ESR

The ESR Christchurch Food Chemistry Laboratory has received approval from the ESR Board to purchase a new LC/MS/MS/MS. The laboratory looks forward to this extension of its instrumental capability that will enable it to improve the specificity and rapidity of many current analyses and develop new methods such as quantification of amino acids and anti-oxidants.

University of Canterbury

Prof *Ian* ***Shaw*** has been admitted to Fellowship of the Royal College of Pathologists (FRCPath). Toxicology is regarded as a branch of pathology and the College is an accreditation body for toxicologists world-wide with many toxicologists aspiring to Fellowship. The Royal College of Pathologists is the only royal medical college that will consider non-medically qualified members … but they don't make it easy!

Dr *Vladimir* ***Golovko*** has been successful in gaining Principal Investigator (PI) status with the MacDiarmid Institute. There was fierce competition for PI positions in the recent

round with only six new PIs appointed from 22 applications. The PIs are required to lead a research objective and to contribute to the broader objectives of the Institute by participating in education and outreach activities. PI status comes with funding for a component of salary, a research and travel allowance, and funding for a PhD student to work on Institute-related research. All existing PIs were reviewed at the same time and Prof *Alison* ***Downard*** will continue in her role.

The Minister for Tertiary Education, the Hon. *Anne* ***Tolley***, has just announced that Dr *Marie* ***Squire*** will be one of the 2009-2010 recipients of the Queen Elizabeth II Technicians' Study awards. The recipients will receive grants to enable them to undertake study and training in Commonwealth countries during the next 12 months. Marie is off to Australia, the UK, and Ireland towards the end of this year to undertake studies related to training in Mass Spectrometry and Proteomic techniques.

The Department congratulates *Sarah* ***Wilson-Coutts*** on the successful completion of her MSc(Hons) with a thesis entitled *The Synthesis and Configuration of Some Polydentate Amino Acid Complexes of Cobalt(III)*. She was supervised by A/Prof *Richard* ***Hartshorn***.

Mark ***Pollard***, Edward Hall Professor of Archaeological Science and Director of the Research Laboratory for Archaeology and the History of Art at the University of Oxford, was with us for a month from mid-July. Mark is NZ born, but has lived all his life in England. His research focuses on the chemical analysis of archaeological materials (metals, ceramics, glass, pigments, etc.), and the isotopic analysis of human bone. The former is used for interpreting patterns of trade and exchange in the ancient world, but more recently has concentrated on understanding the history of technology and the anthropology of technological development and transfer. The latter looks at the lives of individuals, from diet and health status through to mobility.

The new Compliance and Instrument Technician is Dr *Matt* ***Polson***. Matt is a former postdoctoral fellow with Prof *Peter* ***Steel***.

MANAWATU

A small quality field contested the Manawatu NZIC Quiz Night on 11 August run by quizmasters *Geoff* ***Jameson*** and *Ghislaine* ***Cousins***. Some tough questions challenged the contestants, *e.g. Who won the Chemistry Nobel Prize the year after Rutherford (1909)?* and *Who is the current President of the NZIC?* A consistent effort rewarded Jamie and the Holograms (*Jamie* ***Withers***, *Jeremy* ***Hall*** and *Mark* ***Waterland***) with a well deserved victory. Generous sponsorship was provided by Merck and Shimadzu Scientific.

On June 29 we had a visit from Dr *Mary* ***Kirchhoff***, Director of the ACS Education Division. She gave a talk titled *Shades of Green*, which considered the tools and trends in green chemistry education, and focused on initiatives with the potential to impact large numbers of students. Also, on the same day, we had *Jennifer* ***Kirchhoff*** (Florida State University) give a talk about *Utilizing Dopants to Study Complex Liquid Crystal Phases*. In July, Dr *Matthias* ***Schwalbe*** (MIT) gave a talk titled *Light-Driven Activation of Small Molecules at Metal Complexes*, Dr *Ute* ***Marx*** (Bruker BioSpin GmbH) spoke on *NMR-Based Multi Parametric Analysis of Complex Mixtures such as Blood and Urine*, and Dr *Guy* ***Jameson*** (Otago) addressed us on *Iron's Role in the Enzyme Cysteine Dioxygenase*. August saw Dr *Sharon* ***Strawbridge*** (Center for Graphene Service, Exeter) speak about *graphene physics and some of graphene's possible future applications in nanoscale devices* and Prof *Jonathan* ***Sessler*** (Texas at Austin) gave a talk titled *Oligopyrroles: Receptors for potentially hazardous materials*.

Mid-August saw a joint meeting of the Manawatu RSNZ and NZIC Branches at which Dr *Gareth* ***Rowlands*** gave a talk titled *Chemistry through the Looking Glass*. He provided a layman's introduction to molecular chirality and, with the aid of real examples, showed that it is an everyday occurrence. Some of the biological and chemical uses of chirality, ranging form single-handed pharmaceuticals to current research into chiral catalysis at Massey University, were discussed. Also discussed were some current research that is employing chirality to begin to make single molecule motors and nanoscale machines.

Our very own A/Prof *Ashton* ***Partridge*** from Massey University's IFS, has been the recipient of $5.76 M from Government Science Funding for High Efficiency Organic Photovoltaics. The project aims to produce an all-plastic, recyclable, high efficiency photovoltaic cell that can be incorporated into a roofing product by 2016. It is also to be capable of providing the total average energy requirements for a household.

Tracey ***McLean*** recently returned from the July Sapporo (Hokkaido) where she attended the 18th International Symposium of Photochemistry and Photophysics of Coordination Compounds (ISPPCC). She presented a poster titled *Exciton Interactions in Metallodipyrrins* during the student poster session. The meeting was small and specialized with *ca*. 230 scientists, including seven from NZ. Many of the presentations focused on solar energy conversion and electroluminescent devices. Two notable speakers were *Thomas* ***Meyer*** and *Daniel* ***Nocera***. Meyer discussed the ultimate goal of water splitting including how hydrogen and oxygen could be produced photochemically and then recombined in high efficiency fuel cells for the production of electricity. Nocera discussed the artificial photosynthetic device aimed at collecting and converting solar energy to current by splitting water to produce oxygen and hydrogen. Specifically, he discussed the aqueous cobalt and phosphate catalyst being employed in the oxygen-evolving complex of the device.

The Plieger group has been somewhat depleted of late with numerous overseas trips by various group members. Dr *Marco* ***Wenzel*** attended the 4th International Symposium on Macrocyclic & Supramolecular Chemistry (Maastricht, Nederlands), Dr *Paul* ***Plieger*** attended the coordination chemistry discussion group in Leeds and then made a quick trip to

Prof *Peter* ***Tasker***'s retirement symposium in Edinburgh. He spoke at the latter which provided a number of excellent talks that made it quite apparent how many chemical researchers (academic and industrial) Peter had influenced over his career. *Karl* ***Shaffer*** is currently the last group member still on secondment. He is exploring the beryllium chemistry of some of his PhD ligands at LANL.

Steve ***Kirk*** has started working on polyphosphazene/epoxy resins, a project funded from the Center of Excellence for Research in Engineering Materials at King Saud University. A/Prof *Eric* ***Ainscough*** and Prof *Andrew* ***Brodie*** are the project advisors.

OTAGO

According to a long-standing tradition, the Branch again sponsored prizes for chemistry-related projects at the Aurora Otago Science and Technology Fair at which the following prizes of $40 each were awarded:

Rust More? Rust Less? – Lisa Song (Year 11)

The Rain Effect – Nicola Crawford (Year 13)

Frozen Puddles – Jemma Fielding (Year 8)

Effective Photocatalysis – Shanna Verhoef (Year 8)

Clean ?????? – Guanyun Qi and Abigail Burgess (Year 13).

In June, the Branch organized a field trip to the Emerson's Brewery in Dunedin. By all accounts, the event was extremely successful and many were inspired by Richard Emerson's enthusiasm for beer and beer-making. Incidentally, Richard's father, George Emerson, was an academic in the Otago Biochemistry Department for thirty years, retiring in the late 1990's.

University of Otago

Dave ***Warren*** has recently returned from the UK where he visited the Universities of Bristol and Southampton to discuss and observe outreach activities. As part of the visit to Bristol, he gave a lecture to summer school students on conducting polymers. Dave also attended the 42nd IUPAC Congress in Glasgow, where he presented a paper on the recent developments in the 1st-year laboratory course at Otago. The trip was funded by the Chemistry Department and a travel scholarship from the Royal Society of Chemistry.

WAIKATO

Analytical Chemistry Competition 2009

This annual event was held in mid-June after invitations were sent to schools in the Waikato/Bay of Plenty region for teams of four students to spend the day at the University carrying out analysis. There was a total of 20 teams from all around the wider Waikato and Bay of Plenty regions. The analysis was of nickel sulfate gravimetrically (for Ni^{2+}) and volumetrically (for SO_4^{2-}) with the requirement to deduce '*n*' in the formula $NiSO_4.nH_2O$. This was a demanding task in the time available but all teams completed the exercise and some excellent results were achieved.

1st Prize: ***Katikati College*** (Pippa Grierson, Ethan Meder, Sven Knottenbelt, Michael Lancaster).

2nd Prize: ***Pukekohe High School*** (Rebecca Grass, James McIntosh, Charlotte Vandermeer, Danny Su).

3rd Prize: ***Otorohanga College*** (Cayley Ingham, Tania Fowke, Jonathan Norsoller, Megan Wylie).

4th Prize: ***Hillcrest High School*** (Kejia Wang, Shiang Ye, Casey Lin, George Yao).

5th Prize: ***Fairfield College*** (Paul Johnson, Annelise Rogerson, Kelly Taylor, Eleanor Rowan).

The day involved many Chemistry Department staff setting up the competition and supervising the labs. Special thanks go to *Brian* ***Nicholson*** for the overall organisation and coordination of the event. *Tui* ***Doak*** of Bryant Hall provided excellent lunches (sponsored by the NZIC) and Hill Laboratories donated the prizes, presented on the day by Dr *Graeme* ***Corban***. Overall the competition allowed keen Year 13 chemistry students to spend a day in the University laboratories working on an experiment that would be beyond the resources of their schools.

University of Waikato

The Departmental Chemistry prizes were presented recently as follows:

Orica Chemnet Prize (best student in 1st year chemistry advancing in Chemistry): Charlotte Bradley and Ivan Schroder

JE Allan Prize (for best second year student): Sam Pachal

Dow Agrosciences Prize (for best third year student): Megan Grainger

The Department has welcomed two new academic staff members, *Graham* ***Saunders*** and *Joseph* (*Jo*) ***Lane***. Graham, a native of Sussex, gained his first degree from Oxford University, where he also graduated DPhil under the supervision of Prof Malcolm Green. He then spent a year with Prof *Warren* ***Roper*** in Auckland as a RSNZ postdoctoral fellow. After a period as a postdoctoral researcher in fluorine chemistry with Profs *John* ***Holloway*** and *Eric* ***Hope*** at the University of Leicester, he was appointed as a lecturer at The Queen's University of Belfast. Graham's research interests include fluorine-containing ligands in organometallic chemistry, C-F bond fission, fluorinated surfaces and the floc treatment of wastewater. He has a passion for cricket (supporting Sussex and playing as long as his body permits) and nature (especially birds), and enjoys trying to play the guitar. Jo Lane was born and raised in Auckland before moving to Dunedin to undertake his tertiary studies at the University of Otago. He was awarded a BSc (Hons.) in 2005 and a PhD in 2008 after which he undertook a one year Marsden funded postdoctoral position with Prof *Henrik* ***Kjaergaard*** at Otago. His research interests include the application of high level quantum chemical calculations to predict and interpret the reaction kinetics and spectroscopy of atmospherically relevant molecules. Jo is a keen DIYer and when he isn't renovating his home you will find him riding single-track mountain bike trails.

Michèle ***Prinsep*** attended the American Society of Pharmacognosy's

50th Anniversary meeting in Honolulu giving a presentation entitled *MALDI-TOF Mass Spectrometry for Structural Determination of Bioactive Metabolites from Cyanobacteria*. Masters student *Ben* ***Deadman*** recently attended the 59th Meeting of Nobel Laureates in Lindau, Germany. This chemistry meeting provides a week of inspirational lectures by some of the most distinguished scientists of our time. The forum also gave young researchers the opportunity to engage in small group discussions with the Nobel Laureates on topics as diverse as climate change and photos of Prof *Peter* ***Agre***'s holiday in the Arctic.

In August, the annual University Chemistry social *Chemfest* was held. The students organizers put in a lot of effort and the event ran very smoothly. There was a good turn out of students, staff and friends who came along in theme - anything starting with ***P***, with some amazing costumes including a parrot, a pumpkin, a few pink ladies and Peter Andre! A good night was had by all.

Recent seminars from visitors to the Department include *Chitosan Based Gels for Wound Healing* from Prof *Lyall* ***Hanton*** (Otago), *Green Chemistry and Sustainability* by *Mary* ***Kirchoff***, (Director of the Education Division, ACS), *NMR-based Multi Parametric Analysis of Complex Mixtures such as Blood and Urine* from Dr *Ute* ***Marx*** (Bruker Biospin) and *Oligopyrroles: Receptors for Potentially Hazardous Materials* from Prof *Jonathan* ***Sessler*** (University of Texas).

Antony Parnell has started an MSc with *Bill* ***Henderson*** on forensic application of lanthanide complexes. *Kelly* ***Kilpin*** recently completed her doctorate with *Bill* ***Henderson*** with a thesis entitled *The chemistry of cycloaurated complexes*. She is now at the University of Otago, undertaking postdoctoral work with *James* ***Crowley*** and *Allan* ***Blackman***.

NIWA

In June, *Bob* ***Wilcock*** attended the joint USA-NZ symposium *Wetland Ecosystem Services in Agricultural Landscapes*, the Wetland Scientists Society's 30th annual meeting held in Madison WI). Bob spoke about geochemical processing within a wetland used for attenuating dairy farm runoff in the Waikato. He also visited Prof *Steve* ***Chapra*** (Tufts University, Boston) to discuss geochemical modelling for the Great Lakes.

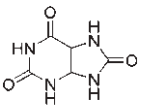
After ten or so years Bob has relinquished the reins of group manager of the Chemistry and Ecotoxicology group to *Craig* ***Depree***. Craig has hit the ground running and has already brought his own inimitable style to the position. He has had a busy last few months and was an invited speaker at a symposium in Prague in May on photocatalytic nanotechnologies (standardisation and new applications) where he gave a presentation *Photocatalytic nanosurfaces to control marine biofouling*, outlining progress in NIWA's FRST programme with IRL and James Cook University. The antifouling theme has seen a new collaboration forged between NIWA (*Michael* ***Stewart*** and *Craig* ***Depree***) with Prof *William* ***Miles*** (Chemistry, Lafayette College, US) looking at utilising synthetic methodologies to enhance the antifouling activities of previously discovered natural antifouling metabolites. Another collaborative research effort involving *Greg* ***Olsen*** has been gaining success with *Peter* ***Haglund*** (Umea University, Sweden) looking for emerging contaminants from extracts of fish and shellfish sourced from NZ harbours. Polybrominated dibenzodioxins (PBDDs), polybrominated diphenyl ethers (PBDEs) and PBDE hydroxylated metabolites were found in high levels in some shellfish.

Chris ***Hickey*** and *Max* ***Gibbs*** have produced a publication on risk assessment and decision making for lake sediment capping agents, which has been accepted for a special issue on restoration in the *NZ Journal of Marine and Freshwater Research*.

WELLINGTON

The annual Branch mid-winter dinner was held at the Red Tomatoes Pizzeria in Kelburn in mid-June. The benefit of the separate dining room was appreciated and the group of about twenty had a very enjoyable evening with good food provided. On 1 July, Dr *Mary* ***Kirchoff*** (Director, ACS Education Division) spoke to a large audience of *Green Chemistry and Sustainability*. Brought to NZ as a plenary lecturer for the biennial chemical education conference in Christchurch, she visited Wellington among a number of other centres and recorded an interview with Radio NZ whilst here. Her lecture was a showcase of improvements in the chemicals industry, not simply in a words and music way, but with some detailed chemistry to illustrate the improvements in synthesis, solvent and power usage and simplification. One example showed that the use of HF actually added benefit to the overall process despite its toxicity.

The August meeting featured Dr *Jaquie* ***Harper*** of the Malaghan Institute of Medical Research. She spoke to the 35 attendees about *Gouty Inflammation - Bringing clinical, basic and drug development research together*. She detailed the classical feature of infiltration of large numbers of neutrophils into the affected joint causing the severe inflammation of acute gouty arthritis. One of the primary functions of activated neutrophils is the production of superoxide, O_2^-, which drives the generation of highly destructive reactive oxygen species capable of damaging cells and tissues in the joint. As such, targeting neutrophil superoxide production provides potential for anti-inflammatory drug development. Recent clinical findings were linking to elevated superoxide production in the clinical disease with production of gout-causing monosodium urate crystals. Jacquie is an Otago Chemistry PhD graduate and the current Head of the Arthritis and Inflammation Group at the Malaghan Institue.


uric acid

Victoria University

The major news in the School of Chemical & Physical Sciences as we go to press is the award of MacDiarmid Young Scientist of the Year to *John* ***Watt***. John, working under the supervision of Dr *Richard* ***Tilley***, has been trying to control and limit the size and shape of palladium nanopar-

ticles with a view to their use in the removal of toxic pollutants from vehicle emissions. With the award of the Easterfield Medal to his supervisor (see above) the group is all abuzz with excitement.

Prof *Jim* ***Johnston*** was one of five 2009 Bayer Innovators Awardees for developing a world-first process in which nanoparticles of pure gold and silver are embedded in NZ merino wool to create a luxury fibre that can be used in high-end fashion garments, textiles and carpets. One of his PhD students, *Kirstin* ***Burridge***, has developed textiles that combine wool with gold to create textiles ranging in colour from light pink, through to purple, grey and gold. This led to her runner-up status in the *Adding Value to Nature* category of the Young Scientis of the year Awards. *Fern* ***Kelly***, another of Jim's students, was also a finalist.

Dr *Justin* ***Hodgkiss*** has joined the School of Chemical and Physical Sciences as a lecturer in Physical Chemistry. Born and raised in NZ, Justin gained his PhD as a Fulbright Scholar at MIT under the supervision of Prof *Dan* ***Nocera***. His work involved time-resolved laser spectroscopy to probe proton-coupled electron transfer mechanisms and multi-electron transfer reactions in supramolecular systems. After a brief period on biochemical research in India, Justin moved to Cambridge as a postdoctoral researcher in physics in the laboratory of Prof Sir *Richard* ***Friend***, again using time-resolved laser spectroscopy, there investigating photocurrent generation and loss in polymer solar cells. His VUW research programme focuses on the optical and electronic properties of semiconducting organic nanoparticles for efficient solar cells that can be printed at low cost. As announced in the last issue Dr *Rob* ***Keyzers*** returned to VUW in early June to the lectureship in organic chemistry left vacant by our author of ChemScrapes Brendan Burkett. Rob completed his PhD in marine natural products chemistry with A/Prof *Peter* ***Northcote*** in 2003, then undertook postdoctoral work at Rhodes University in Grahamstown, South Africa, with work with Prof *Mike* ***Davies-Coleman*** and Vancouver in Prof *Raymond* ***Andersen***'s group at UBC. In the 18 months prior to appointment at VUW, Rob worked in Adelaide at CSIRO-Plant Industry exploring the links between grape secondary metabolism and wine flavour and aroma. At VUW, Rob will be re-establishing his interest in bioassay-guided natural products isolation and also studying grape-derived flavour and aroma volatiles relevant to the NZ wine industry.

Dr *D.A.* ***Jefferson*** (Cambridge University) visited the materials scientists in the School and MacDiarmid Institute in early June. His lecture on *Nanoparticles: crystalline or molecular* was particularly lucid and attracted a large audience. In late July, Dr *Guy* ***Jameson*** (Otago) spoke on *Iron's role in the enzyme cysteine dioxygenase*. The lecture provided the latest insights into the way that the bound iron of the dioxygenase provides its catalytic function. Mid-August saw the visit of Fulbright Fellow Prof *Jonathon* ***Sessler*** (University of Texas at Austin) in NZ as an environmentalist. He gave a lecture to a good mix of graduate and undergraduates on *Oligopyrroles: Receptors for potentially hazardous materials*. The presentation was not only elegantly casual but also filled with fascinating polycyclic chemistry.

In June, Prof. *Ken* ***Mackenzie*** presented an invited lecture on new developments in the chemistry of inorganic polymers to the 8th Pacific Rim Conference on Ceramic and Glass Technology in Vancouver. In the previous month he visited Iran as a plenary guest speaker at the Annual meeting of the Iranian Ceramic Society in Shiraz, and gave lectures at the Iran University of Science and Technology. This happened just ahead of the ill-fated Iranian elections and considerable excitement and anticipation was evident on all the University Campuses and in the cities.

Nanotechnology: An Answer to the World's Water Crisis?

Alan Smith

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As the world's population rises from 6.5 billion today to 9 billion by 2050, access to fresh water will become even more important in the near future. Unfortunately, 97% of the world's water is salt water; of the remaining 3%, two-thirds are frozen.[1] As well as being scarce, the remaining 1% of the world's water supply is not evenly distributed, and this shortage is clearly a serious problem for developing countries.

The World Health Organization (WHO) has estimated[2] that 80% of illnesses in the developing world are water related, resulting from poor water quality and a lack of sanitation. There are 3.3 million deaths each year from diarrheal diseases caused by *E. coli*, salmonella and cholera bacterial infections, and parasites and viral pathogens. In the 1990s, the number of children who died of diarrhoea was greater than the sum of people killed in conflicts since World War II.

Water Facts

- 215 tonnes of H_20 to produce 1 tonne of steel
- 300 tonnes of H_20 to produce 1 tonne of paper
- 1,000 tonnes of H_20 to produce 1 tonne of grain
- 15,000 tonnes of H_20 to produce 1 tonne of beef

In 2004, IUPAC held a conference in Paris on *Chemistry in Water* intended to address some of the WHO statistics relating to water supplies. At that conference, the use of nanotechnology was only mentioned briefly, but, in recent years, interest has escalated. In a report,[3] the Organization for Economic Co-operation and Development and Allianz highlighted how nanotechnologies for water treatment are expected to impact upon the developing world. PLoS Medicine, an open access journal and policy forum for improving healthcare in society, has also identified[4] the importance of improved water treatment as one of the top ten ways nanotechnology will change lives. A third, more recent, paper also considered the top ten ways nanotechnologies will affect us, and clean water is listed among them.[5] Clearly, nanotechnologies are set to make a considerable impact on the water sector, most likely through three main areas: purification and wastewater treatment, monitoring, and desalination.

Purification and Wastewater Treatment

Water for People: Water for Life, a UNESCO study,[6] reports that disinfection of water at the point of use has consistently proved to be the most cost-effective treatment method, putting the onus on the poor to ensure their drinking water is clean. In the developed world, what is being described as nanofiltration is receiving a lot of attention from water-treatment companies. Nanofiltration purifies water not by forcing it through tiny holes but by using a positive charge to attract negatively charged viruses and bacteria. TriSep Corporation, based in the USA, offers two nanofiltration membranes developed by DuPont; one removes colour, iron, and hardness, and the other removes divalent ions and low molecular weight compounds, such as sugars. Argonide Corporation, also in the USA, has developed a highly electropositive filter, NanoCeram, which rapidly absorbs particles, no matter how small. The company is also promoting a new virus- and protein-separation process with a nanoalumina fibre that they claim removes 99.9999% of bacteria, viruses, and protozoan cysts. FilmTec Corporation, a subsidiary of Dow Chemical Company, makes high-quality reverse osmosis and nanofiltration elements for a wide variety of industrial, municipal, commercial, and home drinking-water applications. A number of other US companies, such as EMembrane, Inc., KX Industries, Taasi, and so forth, have also developed nanofiltration systems.

The suitability of the above examples for remote locations is not clear, but nanofiltration membranes have been used in a rural village in South Africa[7] for providing drinking water where the community water was contaminated with nitrates, chlorides, phosphates, and sulfate pollutants. The process uses four flat-sheet nanofiltration membranes and a reverse osmosis membrane.

Other techniques use the high surface area of nanoparticles or nanoclays to absorb pollutants, while an additional method uses nanoparticulate catalysts to break down contaminants. A promising development from the University of South Australia[8] is the use of pure silica, coated with an active material to remove toxic chemicals, bacteria, viruses, and other hazardous materials from water. The claims are that these particles, coated with a nanometre thin film of active material, are more effective and cost less than conventional water-purification methods and could be used for small and large quantities of water.

Anatal Ligeti, - Oasis in the Desert (1862); taken from http://commons.wikimedia.org/wiki/File:Ligeti,_Antal_-_Oasis_in_the_Desert_(1862).jpg

A further development is the use of carbon nanotubes, hollow carbon fibres only one nanometre in diameter. Seldon Laboratories of Vermont has developed a nanomesh fabric made of fused carbon nanotubes that it says can filter out all bacteria, viruses, and other waterborne pathogens to US Environmental Protection Agency potable water standards. The company claims that the mesh also removes lead, arsenic, and uranium. Researchers at Rensselaer Polytechnic Institute in the USA and Banaras Hindu University in India claim to have devised a simple method of producing carbon nanotube filters that remove microscale to nanoscale contaminants, such as nanometre-size polio viruses from water, as well as larger pathogens, such as *E. coli* and *Staphylococcus aureus* bacteria.

The University of Aberdeen is working with partners to develop a new technology that uses sunlight to treat dirty water and generate electricity at the same time.[9] Proof of concept has been demonstrated, and now they are scaling up to verify earlier indications that the process is more cost effective and environmentally friendly than existing technology, and that it can treat chemical and biological contaminants. A photoelectrocatalyst is mounted into an electrochemical cell; when it reacts with light, the catalyst interacts with any organic matter in the water, oxidizing them across the catalyst's surface.

Monitoring

The developed world is looking at the analysis of a wide variety of contaminants in water.[10] Nanotechnology offers the potential for faster and more sensitive measurements, *e.g.* in the health-care sector, the goal being to detect diseases before they have taken hold on the body. Promising nanotechnology applications for monitoring water already exist, but they tend to be specific to industrial applications where ultrapure water is being used. An exciting development on the detection front comes from NanoSight in the UK,[11] which has a system that can detect waterborne nanoparticles and viruses in real time.

Target Analytes—Australia

Metals: Cd, Cu, Pb, Hg, Ni, Zn, As, Cr, Al, Be, Ag

Nutrients: PO_4^{3-}, NH_3, NO_3^-, total P, total N

Algae: cyanobacterial toxins

Biological: biological agents for terrorism, *E. coli*, viruses, bacteria, parasites

Other: cyanide, organics, antiobiotics, chloroacetic acid, PBDEs

Desalination

As noted before, 97% of the world's water is salt water, and, despite technologies having been around for many years now, desalination is a very energy-intensive procedure with costly infrastructure and it tends to be expensive. The conventional process uses reverse osmosis, where extremely high pressure forces saline or polluted waters through the pores of a semi-permeable membrane. Water molecules under pressure pass through these pores, but salt ions and other impurities cannot, resulting in highly purified water. However, nanotechnology solutions can greatly reduce the costs of desalination and are actually being used in such places as Israel and US municipalities, *e.g.* Long Beach, California. Researchers at UCLA have developed a new reverse osmosis membrane that promises to reduce the cost of seawater desalination and wastewater reclamation. The new membrane uses a uniquely cross-linked matrix of polymers and engineered nanoparticles designed to draw in water ions but repel nearly all contaminants. These new membranes are structured at the nanoscale to create molecular tunnels through which water flows more easily than contaminants.

Children hauling water in Malawi, 2005; taken from http://upload.wikimedia.org/wikipedia/commons/e/ec/Hauling_water_in_Malawi.jpg

The nanocoated silica system from Australia, mentioned above, has been suggested as a very attractive alternative for desalination.

Conclusions

The Meridian Institute in the USA has focused on how nanotechnologies can help the poor and has produced a report[7] with case studies entitled *Nanotechnology, Water Development*. The main issues that need to be resolved include the following:

- accessibility to technologies
- affordability
- ease of operation
- fair distribution

A number of conferences have addressed the need for improved water-treatment methods, but it is unclear what action or progress has been taken, and they are more focused on improving the situation in developed countries. With thousands of children dying each day, the issues for developing countries need to be addressed very rapidly by some of the leading organizations that should be helping solve the problems. At the earliest opportunity, an assessment comparing the costs of currently accessible technologies that generate clean water with those in development is needed. This would provide a better view of the target technologies that governments should be chasing. Developments in nanotechnology for water treatment are merely drops in the ocean; a great deal of progress has been made in the last five years, but more is needed—quickly.

Mother and child hauling water near Chipata, Zambia, 1995; taken from http://upload.wikimedia.org/wikipedia/commons/e/e1/Hauling_water_%28Chipata%29.jpg

A current IUPAC project entitled *Analysis of the Usage of Nanoscience and Technology in Chemistry* will map and critically study the use of the prefix *nano* in various fields of chemistry. The last few years have shown a wide proliferation of the terminology related to nanotechnology and nanoscience in chemistry. Today, all high-impact chemistry journals contain a large number of papers devoted to this growing area, and many conferences include specific sessions on nanotechnology. This project is the first step toward recommendations on the use of chemistry terminology related to nanoscience and nanotechnology, in order to avoid confusion; for more information, see: www.iupac.org/web/ins/2007-040-2-200

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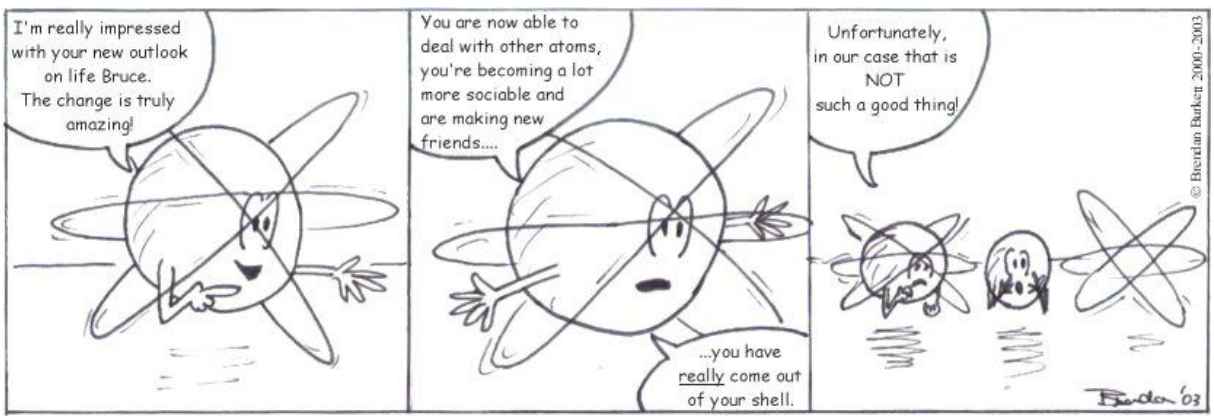
About the Author

Alan Smith <SmithAZT@aol.com> is the founder of AZ-TECH Consulting Services <www.az-technology.org> and has significant experience in nanotechnology. He is the author of numerous articles on different aspects of nanotechnology, several of which have appeared in these pages, and he has lectured worldwide on the topic. Until recently, he was an associate director of the UK's Micro Nano Technology Network and a member of the Nanotechnology Industry Association. He is a member of the IUPAC Bureau and a member of the Committee on Chemistry and Industry.

ChemScrapes



Brendan Burkett

Article

The Taming of the Flu? Influenza and Oseltamivir Phosphate

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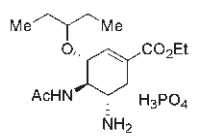
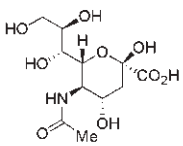
Introduction

Each year new strains of the influenza virus evolve and spread globally, typically infecting around 20% of the world population and killing several hundreds of thousands of people. Most affected are the very young, the elderly and those with chronic medical conditions. Occasionally an influenza strain will arise that is so virulent, the death toll climbs into the millions. Examples of such pandemics include the Spanish Flu (1918-1920), which is estimated to have killed between 20 to 100 million people, the Asian Flu (1958-1959) with a death toll of around 1 million, and the Hong Kong Flu (1968-1969) which killed around ¾ of a million people.[1]

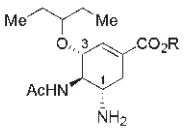
Vaccines provide some protection against influenza, although the efficacy can vary from year to year. Their effectiveness can be as high as 85% when new strains of the virus are similar to the strains used to prepare the vaccine. If new strains differ significantly from those of the vaccine, vaccine effectiveness is reduced.[2] Antiviral drugs, the ***neuraminidase inhibitors***, provide another line of defence against influenza by slowing the spread of the virus within the body.[3] Tamiflu (oseltamivir phosphate; **1**) is currently the only such orally active inhibitor available and therefore is the best known of these inhibitors. This article describes the design, synthesis and the use of Tamiflu in the treatment of influenza.



1, oseltamivir phosphate (Tamiflu)



2, sialic acid



3, R = Et, oseltamivir
4, R = H, GS-4071

Disabling a Master of Disguise

The influenza virus is able to *reshuffle* its genetic material over time.[4] This can occur through mutation or through the reassortment of viral RNA when two different viruses occupy the same cell. Reassortment can involve viruses from different species. A genetic analysis of the 2009 H1N1 *swine* flu virus has detected the presence of swine, avian and human influenza genes.[5] The reshuffling of viral genes can result in new surface antigens, which allow the virus to re-infect organisms that are immune to earlier strains of the virus. The influenza virus has two main types of glycoprotein antigens on its surface; hemagglutinin (H), which is involved in binding of the virus to target cells, and neuraminidase (N) that is involved in the release of viral progeny from the infected cell. There are nine known subtypes of N and sixteen of H, and they are referred to in the official naming of influenza viruses. For example, the current swine flu is an H1N1 influenza virus, whereas the Hong Kong flu of 1968-69 was an H3N2 virus.[1]

The structure and function of neuraminidase was elucidated early in the 1990's and provided a viable target for drug design.[3] Neuraminidase cleaves sialic acid (**2**) residues that bind new viruses to the host cell, releasing them to infect new cells. Inhibitors based on the structure of substrate **2** of neuraminidase were explored and eventually resulted in the synthesis of the analogue oseltamivir (**3**).

Tamiflu Development

Oseltamivir (**3**), developed at Gilead Sciences in the 1990's, was brought to market by Roche in 1999 as the corresponding phosphate **1** and named Tamiflu.[6,7] It is considered to be the only effective treatment for avian flu and has been used more recently to treat those infected with the 2009 H1N1 swine flu.

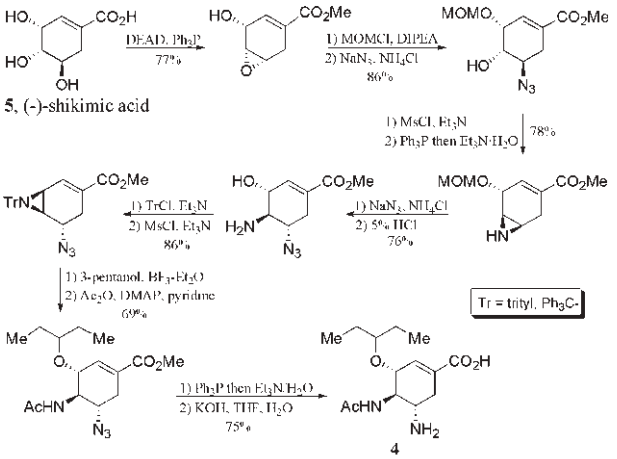
The development of **3** followed structure-based drug design using sialic acid (**2**) as a template.[3] The replacement of the sugar-like core of **2** with a cyclohexene ring introduces greater metabolic stability. The 3-oxypentyl side chain of **2** was identified as providing the optimum fit into the active site of neuraminidase. In itself, **3** is actually a pro-drug as the C5 ester has a much higher oral bioavailability than carboxylic acid moiety of **4** (GS-4071), which is the active component once inside the body.

Syntheses of Oseltamivir (3)

Many syntheses of **3** have been developed since the 1990's,[3,6-15] too many to fully describe in this article. While all of the syntheses contain fascinating chemistry, only a few are presented and discussed in detail below.

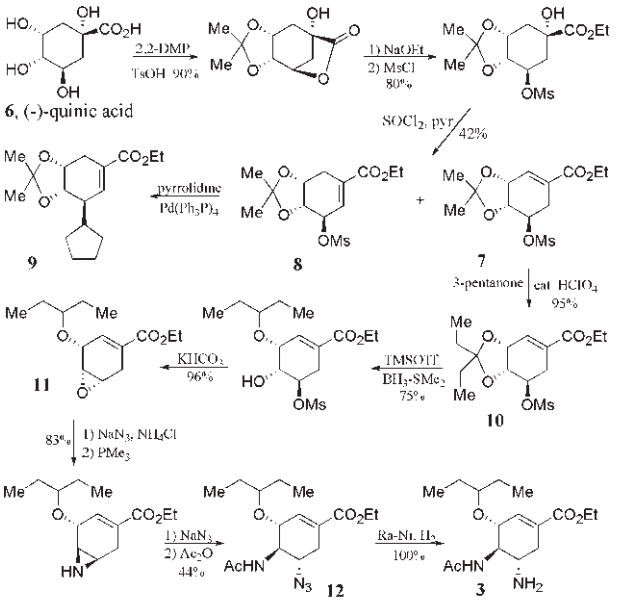
Choice of Starting Material

A number of starting materials have been used in the synthesis of **3** based upon their structural similarity to the drug, their availability and, of course, their cost. The first synthesis of **3**, used (-)-shikimic acid (**5**) (Scheme 1) as the starting material[6] due to the similarity of its structure to the target, its useful functionality, its ready availability and its low cost. Initially, acid **5** was obtained by extraction of the Chinese star anise, but when large scale syntheses were developed there was concern that the supply of star anise might be limiting. Other sources of **5** were sought and the extraction of ginkgo leaves was investigated. Additionally, other starting materials were also explored as shown in Schemes 2-4. Eventually, a bacterial fermentation, using a genetically engineered strain of *E. coli*, was developed and it now provides the majority of **5** required for the synthesis of **3** by drug companies such as Roche.[16]



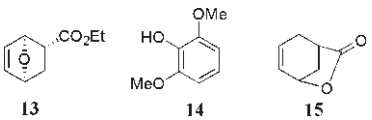
Scheme 1. The first synthesis of oseltamivir; see refs. 3 and 6.

(-)-Quinic acid (**6**) (Scheme 2) is similar in structure to **5** but initially was more abundant and much cheaper. However, its conversion into **3** involves a greater number of steps. Gilead used **6** in the first process route to **3** as shown in Scheme 2, although Roche subsequently reverted to the use of **5** in their first process route.[3]

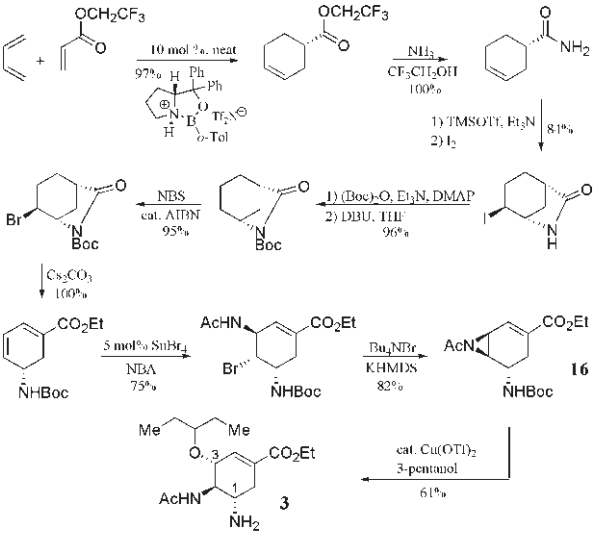


Scheme 2. The first process route to oseltamivir (3); see ref. 6.

Oseltamivir has also been synthesised from other starting materials, *e.g.* **13-15**, partially driven by early predictions of shortages of acid **5**. Abrecht *et al*. have described two novel approaches.[8] The first utilised a Diels-Alder cycloaddition followed by enzymatic resolution to provide the oxabicycloheptene **13** for further elaboration into **3**. The second approach involved selective functionalization, reductive dearomatization and desymmetrization of phenolic diether **14**. This starting material was also used by Zutter *et al*. to synthesise **3**.[9]



In 2006, Corey *et al*. also used a Diels-Alder approach (Scheme 3) to develop a relatively short synthesis of **3** with good yield (~30%) over 12 steps.[10] The use of inexpensive and abundant starting materials, complete enantio-, regio- and diasterocontrol, plus the avoidance of explosive azide intermediates make this approach elegant. Corey's group did not patent this method but left it in the open literature for anyone to use.



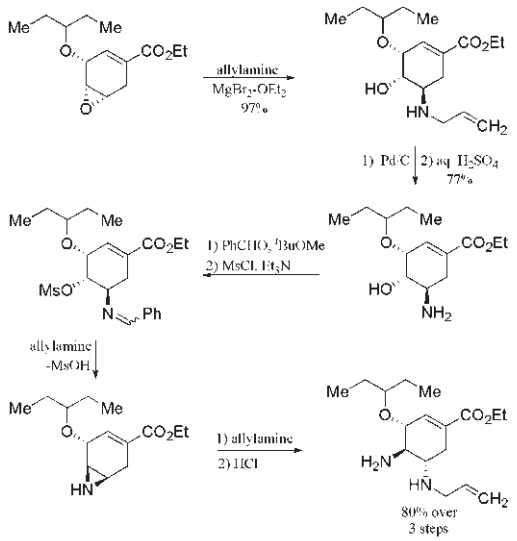
Scheme 3. The Corey approach to Oseltamivir - see ref. 10.

In 2008, Trost and Zhang published[11] what was, at the time, the shortest synthesis of **3**. It involved use of the commercially available lactone **15** and required just eight steps to give **3** in an overall yield of 30%. In 2009, Nie *et al*. also published an eight step synthesis (47% yield) using acid **5**, as the starting material.[12]

Azide-Free Approaches

The early syntheses of **3** depicted in Schemes 1 and 2 utilized azide chemistry to incorporate amine groups via the opening of aziridines and/or epoxides. The hazardous and toxic nature of azides, particularly at an industrial scale of operation, provided the opportunity for improvement through the development of alternative reagents.

The first azide-free synthesis of **3** (Scheme 4) was developed by Karpf and Trussardi[13] and used the magnesium bromide etherate-catalysed addition of allylamine, followed by Pd catalysed deallylation to provide the desired amines. *t*-Butylamine and diallylamine were used in a similar fashion by the Roche group in Colorado.[14]



Scheme 4. An azide-free approach to Oseltamivir- see ref. 13.

Syntheses from starting materials other than acids **5** or **6** provide more options for the introduction of the amine functionalities of **3**. Iodolactonization was used to introduce the first amine functionality via the Corey *et al*. methodology of Scheme 3.[10] This enabled regioselective ring opening of the *N*-acetyl aziridine **16** with 3-pentanol allowing simultaneous placement of the necessary amine functionality at C2 and introduction of the desired 3-oxypentanyl ether at C3. Other researchers have used a similar approach in establishing the C2 and C3 functionality.[11]

Process Route Considerations

Syntheses developed by drug companies, *e.g.* as shown in Scheme 2, favour reactions that are amenable to large scale preparations. Reactions that are strongly exothermic, produce viscous mixtures and/or suspended solids, use hazardous reagents, volatile solvents and expensive reagents have to be avoided where possible.[17] Reaction products that can be used subsequently without purification or which are readily purified by crystallisation are preferred over those requiring chromatography. Gilead's first process route (Scheme 2) used many readily available and inexpensive reagents and crystallization was used to purify compounds at key points during the synthesis, *e.g.* compounds **7**, **11** and **12**. When compound **7** proved difficult to separate from by-product **8** using fractional crystallization, **8** was removed by selective conversion to the pyrrolidinium compound **9**. Introduction of the diethyl ketal moiety of compound **10** was not made until late in the synthesis because such ketals do not readily crystallize.

How Effective is Tamiflu at Treating Influenza?

The effectiveness of Tamiflu depends on its use. Prophylactic use of Tamiflu in placebo-controlled double-blind studies has been shown to have a 74 to 82% efficacy in preventing infection.[18] No significant side effects were observed.

The use of Tamiflu to treat those infected with influenza is most effective when treatment starts within two days of the first symptoms. Treatment reduces symptoms and shortens the duration of the infection by one to two days.

Conclusion

Tamiflu provides a mildly effective treatment for influenza, but it would be overstating its usefulness to claim that it has *tamed the flu*. However, drug synthesis is as much about the journey as the destination. The new methodologies and novel approaches developed by chemists to synthesise oseltamivir (**3**) also serve to advance the field of synthetic organic chemistry, providing new tools for the synthesis of tomorrow's drug molecules. The development of anti-viral drugs has always challenged medicinal chemists, and Tamiflu is but one step in the direction of new, more effective influenza drugs.

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21st Century Chemistry and the *Promiscuity* of the Sex Hormone Receptors: An Overview

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Introduction

Modern chemistry has brought us many benefits from pharmaceuticals to advanced materials. With these advances comes a responsibility to balance the benefits against undesirable environmental effects. This balance is critical when chemicals interfere with the most fundamental biological process – reproduction. Recently, interference of this type was demonstrated when the population of fathead minnows in an isolated Canadian lake was brought to near extinction in just 7 years by exposure to parts per billion concentrations of 17α-ethynylestradiol (**6**), the synthetic estrogen used in birth control pills.[1] The reproductive capacity of both male and female fish was affected by the exposure. A similar outcome is possible for humans on exposure to hormonally active chemicals at inappropriate times.

The sex hormones, the estrogens and androgens, are chemical messengers in the human endocrine system. They are small molecules that bind to specific receptor proteins in the first step of a complex and tightly regulated sequence of events that controls growth, sexual development, and reproduction (Fig. 1). There are three endogenous or naturally occurring estrogens **1-3** (17β-estradiol, estriol and estrone) and two endogenous androgens **4** and **5** (testosterone and 5α-dihydrotestosterone). The estrogens bind to two distinct estrogen receptors, ERα and ERβ, and the androgens bind to a single androgen receptor, AR. The estrogens and androgens, and their receptors, are present in both males and females but in different amounts (Table 1). ERα is primarily responsible for the development of female sex organs and secondary feminine characteristics, such as enlarged breasts. AR is responsible for male sex organ development and secondary masculine characteristics, such as facial hair and deepening of the voice. There are very few locations in which both ERα and ERβ are expressed in significant amounts, and, at those locations, the two receptors are found in different cell types. ERα appears to be involved in activating cellular functions, including cell division, while ERβ acts in suppressing these functions. The AR is widely distributed and appears in significant amounts in nearly all tissues in which the ERs are found.[2]

Although the sex hormone receptors have evolved to be highly specific in recognizing and binding with their intended endogenous ligands, they are apparently easily fooled by 21st century chemicals. Many modern chemicals are able to bind with the sex hormone receptors and either initiate, or block, the same chain of events that endogenous hormones control. This results either in amplification or cancellation of natural hormone signals at inappropriate times. These so-called endocrine disrupting compounds

Table 1. Distribution and relative abundance of the human estrogen receptors – see ref. 2

ERα Predominant	ERβ Predominant	Both ERα and ERβ
Uterus	Prostate	Mammary gland
Vagina	Testis	Bone
Testis	Leydig cells in adult	
Leydig cells in fetus germ cells	Ovary	
Sertoli cells in adult spermatozoa	Thyroid	
Liver	Skin	
Kidney	Bladder	
	Gastrointestinal tract	
	Salivary glands	
	Heart	
	Blood vessels	
	Certain neurons in central and peripheral nervous system	
	Immune system	

(EDCs) are present as contaminants in our food and water, from pharmaceuticals (**6**, **10**) and from plastics (**7-10**) and detergents (**8**, **9**). They are used in personal care products as preservatives (**13**), as ultraviolet light stabilizers (**17-20**) and as active ingredients in sunscreens (**17-21**), and antibacterial hand soap and toothpaste (**11**). Some EDCs (**10**, **12**, **14-16**) are produced in the body by the metabolism of other chemicals, while others (**22-24**) occur naturally in foods such as soy. EDCs have many different chemical structures, but it is the combination of H-bonding functionality located at opposite ends of the molecule, *e.g.* the C3 and C17 hydroxyl groups of **1**, and the hydrophobic nature of the intervening molecular framework that is necessary for binding with the receptor.

At levels of hormonal activity, EDCs are not toxic in the classical sense in that exposure is not fatal, but they do have profound effects on both individuals and populations as shown by the declining populations of bald eagles in Florida (1952) and of seals in northern Europe (1988). In 1992, declining sperm count was the first human effect attributed to EDC exposure. These, and other observations, were finally connected and brought to the public stage in the 1996 book *Our Stolen Future*[3] that is to endocrine disrupting chemicals what Rachel Carson's *Silent Spring* was to pesticides in the 1960s.

EDCs have been implicated in a variety of medical problems in humans including uterine fibroids and ovarian

tumours,[4,5] hormone related cancers,[6] deformities of the male genitalia,[7] precocious puberty in girls,[8] declining male and female fertility,[9] obesity,[10] and developmental disabilities and changes in sexual behaviour.[11] These adverse effects arise not only from exposure as an adult but also from relatively small doses during specific windows of vulnerability.[4] One critical period appears to be during early embryonic and fetal development, when cells are rapidly differentiating and tissues are growing quickly. The fetus is protected from high levels of natural hormones by the placenta, a protection assumed to extend to foreign chemicals. However, EDCs are able to cross the placenta.[12-15] Developmental exposures are particularly difficult to monitor and quantify since the outcomes may not be observed until many years later.

Hormone Action and Interference

Two factors are important in the control of cellular response to hormones, the availability of free hormones at the sites of the hormone receptors, and the geometry of the receptor binding pocket. Interference with either of these can result in inappropriate hormone action.

Sex hormone concentrations in the blood are tightly controlled to ensure that they act only at both the desired time and place in the body. The hormones are hydrophobic and have limited solubility in blood. To fulfil their role as chemical messengers, circulating hormones are bound to plasma-steroid-binding proteins for transport from the site of production to where they are needed. The human sex-hormone-binding globulin (hSHBG) is the main specific transport system for sex hormones. Estrogens and androgens bind to different sites on hSHBG.[16] Since only free hormones are able to bind with their receptors, transport-binding proteins play an important role in controlling the concentrations of free hormones in the body. Certain EDCs, *e.g.* alkylphenols **7-9** but not phthalates **10**, are able to bind hSHBG in a reversible and competitive way and displace the endogenous hormones, resulting in an increase in blood concentrations of the free hormones.[16,17] The binding of EDCs with hSHBG is generally weak. Their affinity constants are 10^3-10^4 times lower than those of the endogenous hormones with the effect that a larger fraction of the total EDC concentration is available to interact with the receptors. There is also evidence that EDCs act additively or synergistically. Even though the concentration of an individual compound may be low, humans are exposed to a mixture of EDCs, and the sum of the individual concentrations can be high enough to induce an effect.[18,19]

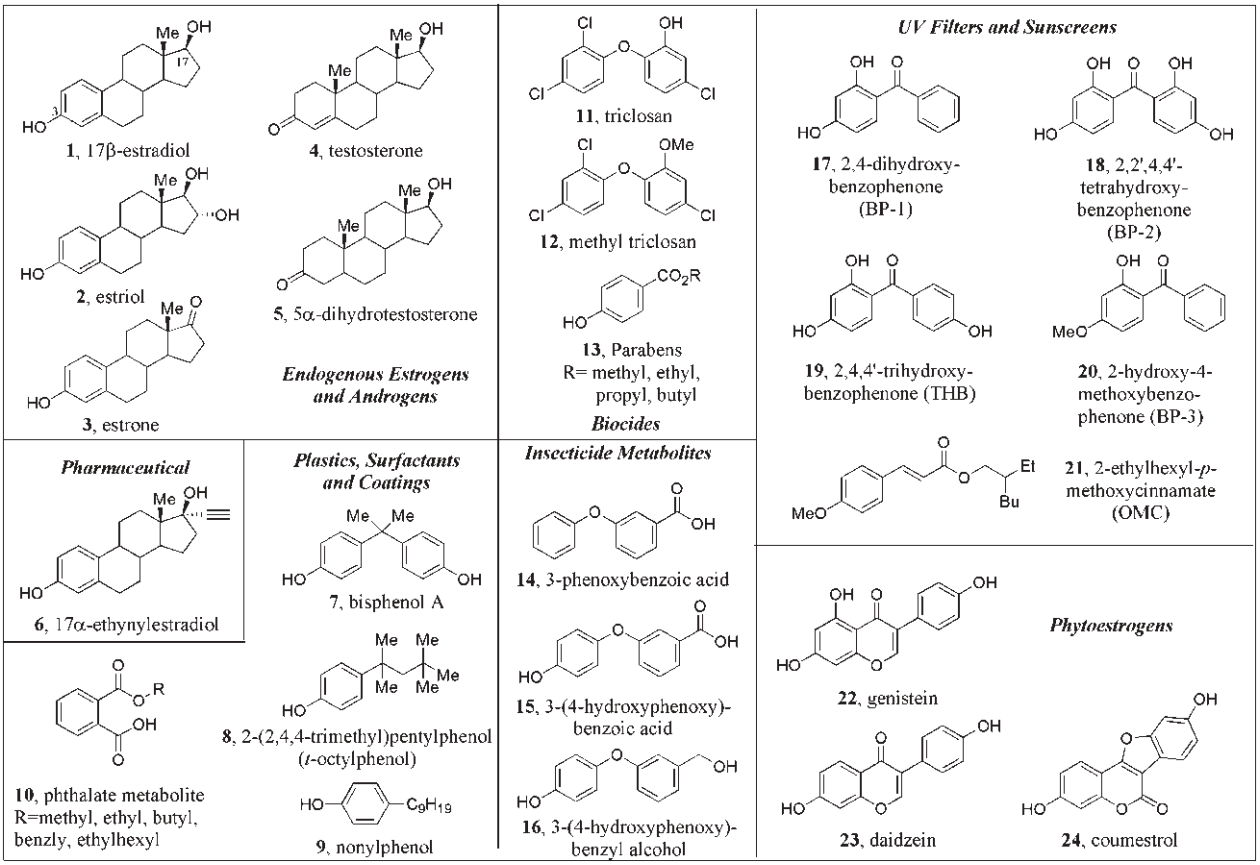
The estrogen receptor binding pocket (450 Å^3) is large in comparison to its endogenous ligand, **1** (17β-estradiol: 245 Å^3).[20] and it is very hydrophobic, as expected for the accommodation of **1**. The two main ligand-anchoring mechanisms in ER are i) a three-way H-bonding bridge between the phenolic H of estrogen and two amino acids and a water molecule at one end of the pocket, and ii) an H-bond between the 17β-OH of the estrogen and a single amino acid at the other end of the pocket. The three-way H-bonding arrangement works with hydrophobic residues in the region to form a clamp that holds the estrogen aryl ring in place so that the H-bonding at the opposite end of the ligand further secures the ligand in the pocket. The rigidity of ligand **1** requires the precise interaction of these residues for its tight binding. The aryl clamp also aids in discriminating between estrogens and androgens. The androgen receptor is similarly oversized for its endogenous ligands and a similar water-mediated H-bonding network serves to anchor the androgen ligands via the ketone group.[21]

On binding their endogenous hormone ligands, the ERs and AR undergo a conformational change that enables them to dimerize, recruit co-factor proteins, and bind to DNA to initiate transcription of their target genes. EDCs that mimic endogenous hormones in this process are called agonists and those that disrupt this process are called antagonists. A single EDC can have any combination of agonistic or antagonistic behaviour with the ERs and AR, as well as a range of efficiencies with which they are able to initiate transcription of the target genes. For example, the isoflavone genistein (**22**) has a binding affinity for ERβ *ca*. ~30-fold higher than for ERα, but only a 4- 5-fold increase in its ability to express an ERβ-selective gene over an ERα-selective one. However, it is less efficient in expressing an ERβ-selective gene over an ERα-selective one.[22] Isoflavone **22** is described as a selective ERβ modulator, a full agonist for ERα and a partial agonist for ERβ. It also illustrates the fact that strength of receptor binding does not necessarily reflect a ligand's ability to initiate gene transcription. This selective EDC modulation is a manifestation of the extent that the conformational change, which occurs in the receptors on ligand binding, influences the efficiency of receptor dimerization and continues along the transcriptional activation path. This differential receptor activation and deactivation is dependent upon both the receptor type and the specific EDC. This complex ligand-receptor interaction, coupled with the differential distribution of receptors in male and female tissue (Table 1), results in effects that are difficult to predict. This is because they can either compete or act synergistically, depending on the sex of the individual and the range and relative amounts of EDCs to which the individual is exposed.

The *promiscuity* of sex hormone receptors is manifest in their inability to distinguish between their endogenous ligands and EDCs. It is possible that the rigidity and similarity of molecular structure of the estrogen and androgens have driven the receptors to develop these highly specific H-bonding networks to discriminate between the intended hormone and other hormones and, at the same time, retain their binding pocket size. This large, somewhat plastic binding pocket, coupled with their relative flexibility, enables the EDCs to bind with the receptor, although with much lower affinity compared to the endogenous ligands. EDCs are able to adopt conformations in the binding pocket that may not necessarily be the low energy ones in free solution. The H-bonding and hydrophobic interactions with the surfaces of the pocket provide additional stability to permit EDCs to bind with differing affinities.

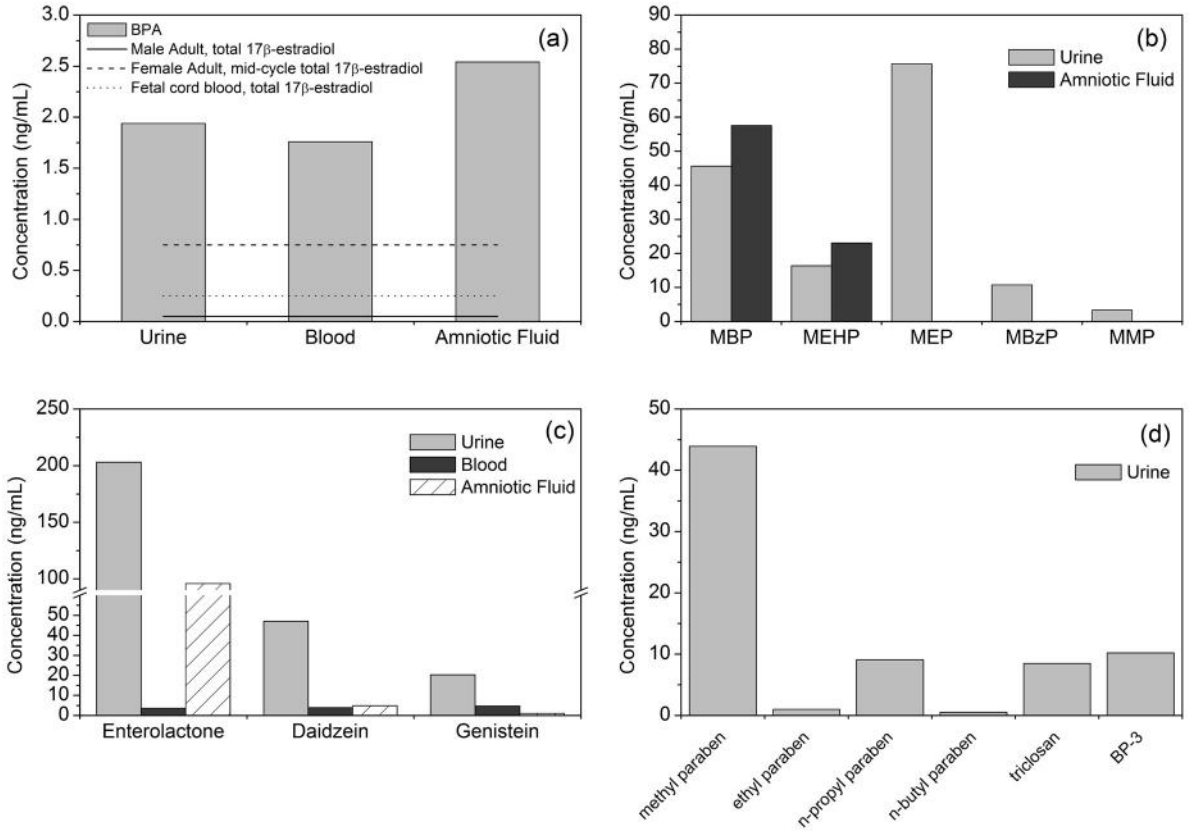
Fetal Exposure

Several EDCs have been detected in amniotic fluid[13-15,23] and in a variety of other human biological fluids and tissues that include blood (serum or plasma),[23-25] umbilical cord blood,[23,24] urine,[13,26] semen,[27] ovarian follicular fluid,[23] breast milk,[28] and placental tissue.[24] These studies have each focused on a single compound, *e.g.* bisphenol A (**7**), or a family of compounds, *e.g.* selected phthalate metabolites **10** or the parabens **13**. However, they have not looked at mixtures of EDCs arising from different sources. Selected results have been combined and are presented in Fig. 2. For reference, total serum levels of **1** (17β-estradiol) for adult males and females and for umbilical cord blood are also included. As Fig. 2 shows, the measured levels of individual EDCs are much higher than endogenous hormones in the fetus, and in adult males and females. Clearly, the mechanisms of the placenta that protect the fetus from maternal hormones are not effective with EDCs.



Compounds	Source
1-3	Endogenous estrogens
4, 5	Endogenous androgens
6	Synthetic estrogen used in oral contraceptive pill
7	In polycarbonate plastic food containers, epoxy linings of food cans, epoxy dental fillings
8, 9	Surfactants, detergents, plasticizer in some polystyrene products
10	Primary metabolite of phthalate diesters that are plasticizers in a variety of plastics, in personal care products to maintain suspensions and in making enteric coatings for medications
11, 12	Biocides. Used in various personal care products (waterless hand sanitizers, soaps, deodorants, toothpastes, shaving creams, mouth washes), medical wash products for skin infections. Infused in consumer products e.g. kitchen utensils, toys, bedding, socks, and trash bags.
13	Preservatives - bactericides and fungicides: In personal care products (shampoos, commercial moisturizers, shaving gels, personal lubricants, topical pharmaceuticals, spray tanning solution and toothpaste. Also used as food additives
14-16	Metabolites of permethrin and cypermethrin are active components in domestic aerosol insecticides
17-20	Hydroxybenzophenones: UV filters used in sunscreen products, added to personal care products and their packaging to protect the product from UV degradation
21	UV filter used in sunscreen products
22-24	Phytoestrogens: Occur naturally in nuts, oilseeds, legumes, soybeans, Brussels sprouts, alfalfa, spinach and clover

Fig. 1. Endogenous hormones, selected endocrine disrupting compounds and their sources.



a) Bisphenol A levels in urine, blood, and amniotic fluid compared with total blood levels of 17β-estradiol (**1**) in adult males, females and umbilical cord blood; b) phthalate ester metabolites in urine and amniotic fluid: MBP = monobutyl phthalate; MEHP = monoethylhexyl phthalate; MEP = monoethyl phthalate; MBzP = monobenzyl phthalate; MMP = monomethyl phthalate; c) phytoestrogens in urine, blood, and amniotic fluid; d) EDCs from personal care products in urine.

Fig. 2. Comparison of EDC levels in human biological fluids. Personal care products in urine: parabens (**13**), triclosan (**11**), BP-3 (**20**).

EDC exposure is believed to be most critical during the period of human fetal development when sexual differentiation occurs – within the first 20 weeks of gestation. Around the 11th week, the fetus begins to produce urine that enters the amniotic fluid. The amniotic fluid is swallowed by the fetus and absorbed by the gastrointestinal and respiratory tracts. EDCs in the amniotic fluid are present from maternal exposure and are ingested by the fetus, resulting in systemic exposure. Thus, amniotic fluid obtained between 16 and 20 weeks gestation is seen as a valid representation of fetal exposure during the period of sexual differentiation.[15]

Challenges in Attribution of Adverse Effects

EDCs do not behave like traditional toxic compounds and, therefore, are not amenable to the conventional environmental risk assessment framework. This framework was established by the US National Research Council in the early 1980s and has been almost universally adopted.[29] It includes the following steps i) hazard identification, ii) dose-response assessment, iii) exposure assessment, iv) risk characterization, and has several shortcomings:[30]

i) The target of the risk assessment is the adult. It does not consider effects on children or the fetus.

ii) Risk is assessed for each chemical individually and not admixed with other chemicals.

iii) The framework is designed to detect high dose effects of chemicals over short time periods.

iv) The framework does not detect the effects of long-term, low level exposure to multiple chemicals.

All of these shortcomings are critical in the risk assessment of EDCs.

In the last two decades, greater focus has been placed on vulnerable populations in risk assessments. These *vulnerable* populations have generally included children, the elderly, and other *susceptible* individuals who, by genetic predisposition or some illness or disease state, are more likely to be affected than the normal healthy individual. The fetus has yet to be included in the vulnerable population category.[31] At the same time, the importance of mixtures of chemicals in risk assessment was recognized and the conceptual challenges in dealing with combination effects have been articulated by Kortenkamp and co-workers over the last decade.[18,32]

Mixtures and synergistic effects

Characterizing how EDCs act together requires new models to quantify effectively both the relative potencies of the individual components and their relative amounts in the mixture. The concept of potency is somewhat ambiguous as it is usually defined with reference to a particular

end point or function (Table 2). Potency depends on the identity of the EDC, the receptor to which it binds, the degree to which the EDC is an agonist or antagonist for the receptor, the relative distribution of the receptors in the target tissue, and the sex of the individual. Currently, potency is operationally defined by the choice of assay (Table 2) and that choice will result in a selection of specific EDCs for ranking in different orders of relative potency.

The relative proportion of chemicals in a mixture is more straightforward to determine. However, if the observed effect is due to a metabolite of a given chemical and not to the chemical itself, then this knowledge is critical in deciding what needs to be quantified.

The degree of agonism or antagonism an EDC expresses cannot be determined solely by measuring binding affinity to the receptor, as shown by the example of **22** (genistein) given above. It can only be characterized by an assay that includes some type of transcriptional activation. In a mathematical context, agonism may be thought of as having a positive sign, antagonism having a negative sign, and selective modulator having a sign dependent on the receptor subtype. This now allows for two chemicals in a mixture, with one able to mathematically cancel the effect of the other, when present in the correct proportion. Whether this happens *in vivo* has yet to be established.

Low Dose and End Point

The definition of low-dose is challenging. For evaluating EDCs, the clinical thresholds in endocrinology can provide some guidance for evaluating toxicological thresholds. The shift in balance of estrogenic and androgenic effects may be small in a female of reproductive age who is already experiencing monthly blood free 17β-estradiol (1) concentration[33] swings of from 0.3 pg/mL to greater than 4 pg/mL and up to 1000 pg/mL during pregnancy, but in an adult male or pre-pubertal males and females (<0.9 pg/mL) the shift may be significant. This shift is also likely to be significant in a developing fetus, especially during sexual differentiation, when concentrations of free **1** are between 20 and 300 pg/mL.[34]

The application of the threshold assumption to EDCs may not be appropriate because the endocrine system, at baseline, has already achieved a physiological threshold. In some cases, adverse effects occur when hormone levels are still in the normal ranges defined for a population but are, in fact, elevated for a given individual. Thus, defining thresholds above which an effect could be expected becomes very difficult.[35]

Often, EDCs do not fit the traditional toxicological model of monotonic dose-response curves where the concept of a threshold, below which there is no effect, has meaning.[36] Low doses often produce effects of greater magnitude

Table 2. *In vitro* and *in vivo* assays for determining estrogenic and androgenic activity of chemicals.

Assay	**End point**	Comments ***- in vitro***
Binding assays (competitive, kinetic)	Measure of receptor-ligand binding affinity	Gives only measure of receptor binding affinity. No information on ligand behavior or transcriptional activation
MCF-7 human breast cancer cell	Cell proliferation	ERα specific. These cells grow and divide in a dose-dependent manner the presence of ER agonists.
Yeast Estrogen Screen (YES)	Transcriptional activation via increase in β-galactosidase activity	ERα specific. Activation of gene by ERα results in yeast producing the β-galactosidase enzyme which reacts with substrate that incorporates a chromophore which changes color.
Yeast Androgen Screen	Transcriptional activation via increase in β-galactosidase activity	Activation of gene by AR results in yeast producing the β-galactosidase enzyme which reacts with substrate that incorporates a chromophore which changes color.
Chinese Hamster Ovary Screen	Transcriptional activation via increase in firefly luciferase activity	Assay can be designed to be specific for ERα, ERβ or AR.
COS-1	Transcriptional activation via increase in chloramphenicol acetyltransferase activity	COS-1 cells transiently cotransfected with the wild-type receptor and an estrogen-responsive chloramphenicol acetyltransferase reporter gene.
Yeast 2-hybrid	Coactivator dependent transcriptional activation	Gives information on ability of a ligand to activate the receptor for binding with different coactivators to select specific genes for transcription.
Rainbow trout (or other fish, amphibians, reptiles, birds)	Vitellogenin induction	Vitellogenin is both the name of the gene responsible for production of the egg yolk protein precursor and the name of the protein produced. Both male and female fish have the gene but it is normally dormant in males. Male fish, on exposure to estrogen or estrogenic compounds produce the protein in a dose-dependent way. ERα biased because hepatocytes are used in the in vitro test.
		Comments - in vitro
Uterotrophic studies	Increase in mouse uterus weight on exposure to chemical	Biased due to ERα predominance of receptor in uterus

than do high doses. This results in an *inverted U-shaped* dose-response curve. This, in turn, leads to fundamental flaws in the traditional assumptions that high dose studies can be used to predict low dose effects, and that there is a threshold below which no adverse effect is observable.[37] Exposure to EDCs at concentrations when free hormones operate can have an entirely different suite of effects during active stages of development than they do when administered in high doses after an individual has fully developed.[36]

The definition of end point or adverse outcome in a risk assessment is critical in determining what is measured in characterizing the dose-response relationship of a chemical. For EDCs, the end point of interest may not be defined as clearly an adverse health outcome as for a suspected carcinogen. The end point of interest may be a perturbation in hormone levels, which could be a risk factor for a particular adverse health outcome. Since there cannot be a no-effect level when measuring a hormone response, the extrapolation of traditional studies to determine a no-effect level does not adequately protect future progeny from the adverse effects of EDCs.[37]

Summary

Although the sex hormone receptors are highly discriminatory towards endogenous hormones, they are quite promiscuous in the presence of 21st century chemicals. The potential for this sophisticated biological control mechanism to be hijacked so easily by foreign chemicals and so seriously impair our ability to reproduce, is alarming. Attributing adverse effects such as declining sperm count to these chemicals, and hence our ability to reduce these impacts is hampered by the conceptual and regulatory frameworks that have been adopted to deal with more *conventional* toxic chemicals.

It is now becoming clear that EDCs act along at least two different pathways. One is the direct effect on the exposed individual, which is amenable to standard risk assessment methodologies. However, the effects of EDCs occur at much lower doses and are more subtle than standard risk assessment frameworks consider. The second, and more insidious pathway, is the effect on the fetus resulting from maternal exposure during gestation. Current risk assessment methodologies do not consider the fetus as an individual and so it is disregarded in conventional assessments.

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NZIC Annual General Meeting

The NZIC AGM will take place at Victoria University in the Murphy Building, Lecture Theatre MY220, Kelburn Parade, at 5.30 for 6 pm start on Wednesday 11 November 2009. Entry to the Murphy Building is directly off Kelburn Parade (right hand side going up near the first pedestrian crossing) and the theatre is on Level 2.

AGENDA

1. Apologies
2. Minutes of 2008 AGM held at the University of Otago on Tuesday 2nd December 2008
3. Matters arising
4. Financial Report – including auditor's report
5. Election of Officers

   President

   1st Vice-President

   2nd Vice-President

   Treasurer

   Honorary General Secretary

6. Recommended change to Rule 20.8.6.

   The rule currently reads:

   20.8.6 To forward to the Council a copy of the Annual Report of the Branch, an audited copy of the Statement of Accounts and a list of papers read before the Branch during the year.

   Council recommends that this be revised to:

   20.8.6 Independent Financial Review

   The financial statements of the Branch shall be reviewed and reported on annually by a person or firm, not being an officer or member of the Branch Committee, appointed by members of the Committee. The financial reviewer shall at all reasonable times have access to the books and accounts of the Branch and shall be entitled to such information and explanations as may be necessary for the performance of the review.

   Then:

   20.8.7 To forward to the Council a copy of the Annual Report of the Branch, a reviewed copy of the Statement of Accounts and a list of papers read before the Branch during the year.

   And ***20.8.7*** becomes ***20.8.8***

7. Any other business

Nominations for the Officers of Council close with NZIC administration on 31 October 2009.

Article

Options for Assessing the Bioavailability of Metals to Soil Dwelling Organisms

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Introduction

International regulatory agencies are grappling with the appropriate way to manage contaminated land. Due to the large costs associated with remediation and disposal of soil, there is a need to find viable alternatives to *dig and dump* for managing contaminated soils that only slightly exceed soil acceptance criteria. One option is to allow marginally contaminated soil to remain in place, provided it can be demonstrated that there will be no adverse effect on terrestrial organisms or human health. Numerous studies have demonstrated that the total metal concentration(s) in soil does not always correlate with tissue metal concentrations and/or toxic effects in terrestrial organisms.[1,2] Soil acceptance criteria based on total soil metal concentrations may, for some contaminated soils, be overly conservative. Incorporating site-specific bioavailability assessments into regulatory decision making has the potential to improve the management of contaminated land. Over the last thirty years significant research effort has gone into understanding the processes that govern the bioavailability of metals in soil.[2] Herein, the processes that influence the bioavailability of metals in soils are discussed and an overview of the options currently available for assessing the bioavailability of metals in soil to terrestrial organisms is provided. A previous paper in this journal[3] outlined the options for assessing human exposure to contaminants in soil.

Defining Bioavailability

A plethora of definitions of bioavailability exist. The International Standards Organisation's (ISO) definition is: *Bioavailability is the degree to which chemicals present in the soil may be absorbed or metabolised by human or ecological receptors or are available for interaction with biological systems*.[4] The US National Research Council in their review of bioavailability, rather than defining it, referred to *bioavailability processes*. They defined these as *the individual physical, chemical and biological interactions that determine the exposure of organisms to chemicals associated with soils and sediments*.[1] The bioavailability of contaminants can vary with time as well as between species and soils. A contaminant can be considered as bioavailable when the following three criteria are met: i) a target organism is exposed to the matrix (soil) containing the contaminant, ii) a proportion of the contaminant is available for uptake, and iii) the organism is able to take up the contaminant.[5]

Effects of Metal Contamination on Ecological Receptors

Metals of concern in contaminated NZ soils include arsenic, cadmium, copper, chromium, lead, mercury, nickel and zinc.[6] Industries and activities that can be sources of these metals are listed in Table 1. Depending upon their soil concentration, metal concentrations in plant and invertebrate tissues can exceed toxicity thresholds for wildlife, and in edible crops may exceed those for food standards. Adverse effects of metal contamination in soils include reductions in crop yields, inhibited growth and reproduction in soil invertebrates, and alteration of the soil microbial community structure disrupting key soil functions, including the degradation of organic matter and nutrient cycling.[7-9]

Table 1. Metals of concern in New Zealand contaminated soils - adapted from the Hazardous Activities and Industries List, Ministry for the Environment – see ref. 6.

Activity	*As*	*Cd*	*Cu*	*Cr*	*Pb*	*Hg*	*Sn*	*Zn*
Battery recycling		x			x	x		x
Electrical transformers			x		x	x	x	
Pesticides	x	x	x		x	x		x
Fertilisers		x	x					x
Mining	x					x		
Timber treatment	x		x	x			x	
Metal works		x	x	x	x		x	
Gas works	x		x	x	x			
Firing ranges			x		x		x	x

Bioavailability of Metals in Soils

The bioavailability of metals in soils depends upon the metal species present in both the solid phase and the soil pore water, and the partitioning of the metals between these two phases. Metals interact with the soil solid phase through a variety of mechanisms including ion exchange, non specific adsorption and complexation, as well as the formation of precipitates and organometallic complexes.[2] The composition of a soil can affect the sorption and hence bioavailability of metals. Soil properties that influence metal bioavailability include cation exchange capacity, soil organic matter content, iron and aluminium oxides, clay content, moisture content, and pH.[7,9] These properties determine the soil surface charge and the number and types of sites available for sorption of metals, and hence influence the partitioning of the metals between the solid phase and the soil pore water. The composition of the soil pore water also influences partitioning as well as determining the aqueous speciation of the metals. Key soil solution properties include the ionic strength, the presence of competing ions, the concentrations of dissolved organic matter and inorganic ligands (HCO_3^-, Cl^-), and the redox conditions.[10,11]

The bioavailability of metals can decrease with time as

metals in soil undergo processes that inhibit their desorption from the soil solid phase to the soil pore water. These processes are referred to as *aging* and include sorption mechanisms that transform surface electrostatic interactions at ion exchange sites to more stable chemical bonds, surface precipitatation, occlusion by coatings of organic matter and amorphous iron oxides, and diffusion into the mineral matrix and organic matter.[1]

Remediation strategies for contaminated soils often rely on reducing the bioavailability of metals in soil by applying soil amendments that immobilise the metals. A wide variety of amendments have been tested and these include lime, phosphates (both soluble and rock) and organic materials (bio-solids, compost). These amendments immobilise the metals in the soil by altering the pH, increasing the ion exchange sites available to bind metals, or by forming insoluble precipitates that encapsulate the target metals.[12] In situations where the risk(s) associated with contaminated soil is managed by reducing bioavailability, landowners and regulatory agencies will need tools to monitor the effectiveness of the remediation strategy over the long-term.

Bioavailability also differs between species of organisms because exposure pathways and defence mechanisms can vary. Uptake from the soil pore water is the main pathway for plants and microorganisms. Soil invertebrates, including earthworms, may also be exposed to metals through ingestion of soil and food.[11,13] Terrestrial organisms themselves can alter the bioavailability of contaminants in soil.[11,14] Plant roots under nutrient deficient conditions excrete low molecular weight organic acids and protons in order to mobilise nutrients from the soil solid phase. Transpiration processes can reduce the concentration of metals in soil pore water inducing further desorption of metals from the solid phase. Plants may also decrease the bioavailability of metals by adding organic matter to soil thereby increasing the sites for metal sorption.[10] Microorganisms have been shown to both enhance and decrease the bioavailability of metals.[15] Microbial activity produces acids (organic, sulfuric and nitric) that alter the soil pore water pH, enhance dissolution of mineral phases, degrade organic matter and alter redox conditions. Microorganisms can decrease the bioavailability of metals by acting as a sorbent. Earthworms alter the bioavailability of metals in soil by stimulating microbial activity, altering pH through secretion of mucus, and altering the dissolved organic carbon concentration in soil pore water.[13] In addition, organisms can regulate uptake of essential metals, *e.g.* copper and zinc, that become toxic above physiologic threshholds.[7,16]

Measuring the Bioavailability of Metals in Soils

Bioassays

Bioassays can be used to determine toxicity and uptake of metals into tissues from contaminated soils, providing a true measure of bioavailability. For plants and invertebrates, the organism(s) of interest are exposed to the contaminated soil either under laboratory conditions or in the field for a set time period. The measured toxicity endpoints for plants and invertebrates include tissue accumulation, growth, reproduction, and mortality. Assays for effects on microorganisms include the measurement of enzyme activities, respiration rates and microbial biomass in the contaminated soil. Examples of available standardized methods for measuring toxicity and bioaccumulation of metals from soil are summarised in Table 2. ISO standard 17616:2008 provides guidance on the selection and evaluation of bioassays for ecotoxicity testing.[17] Landcare Research has developed protocols for soil toxicity testing of NZ soils and test organisms include kakabeak (*Clianthus puniceous*), lettuce (*Lactuca sativa*), millet (*Panicum milliaceum*), earthworms (*Aporrectodea caliginosa*), and woodlice (*Porcellio scaber*). These protocols were used to derive ecotoxicity thresholds for arsenic, copper and chromium in soil.[18] Drawbacks to the use of bioassays include the time needed to undertake them, the costs involved, and the selection of appropriate test organisms. As the toxicity and accumulation of metals may vary both between and within species, the selection of appropriate target organisms is clearly important.[19-21]

Chemical Extractants

A wide variety of chemical extractions have been proposed as surrogates to bioassays in order to determine the bioavailable fraction of metals in soil. The advantages of a single extractant test compared with a bioassay to determine bioavailability include the simplicity and reproducibility, reduced costs and reduced time frames.[22] These techniques use dissolution, chelation and ion-exchange/desorption processes to extract metals from soil.[10] Several studies have reported a correlation between the extracted *bioavailable* fraction and either toxic effects on, or tissue accumulation in, terrestrial organisms.[1,2,23] The extractants can be classified into the following groups: neutral salt extractions; dilute solutions of weak or strong acids, and complexing agents (Table 3).[24] Improvements in instrumentation, including the development of commercially available ICP-MS instruments, have lowered the achievable detection limits for metals. In turn, the improved limits have enabled use of milder neutral salt extractions and the direct measurement of soil pore water to estimate the bioavailability of metals in soils.[10]

The chemical extraction methods for assessing the bioavailability of metals in soil are all operationally defined.[25] Dried soil (10-20 g) is shaken with a fixed volume of extractant solution for a set time period. The solution is then filtered and acidified with nitric acid before being analysed by ICP-OES or ICP-MS.[1] For example, the German Regulatory method DIN 19730 requires 20 g dried soil and 50 mL of 1 M NH_4NO_3 to be shaken for two hours before filtering, acidifying and analysing.[26] The experimental conditions, including the composition and concentration of the extracting fluid, soil mass to extraction volume ratio, time, and shaker speed and type, can all affect the proportion of the total metal extracted.

Complexing agents such as ethylenediamine-N,N,N,N-tetraacetic acid (EDTA) and (diethylenetriamine) pentaacetic acid (DPTA) were among the first extraction solutions to be tested as surrogate measures of bioavailability.

Table 2. Examples of standardised test methods for bioassays to assess the toxicity and bioaccumulation of metals from soils.

Organism	Target endpoint	Method
Plants	Bioaccumulation Phytotoxicity	ASTM D5435 - 03(2008) Standard Test Method for Diagnostic Soil Test for Plant Growth and Food Chain Protection
Plants	Phytotoxicity	ASTM E1963 – 09 Standard Guide for Conducting Terrestrial Plant Toxicity Tests
Plants	Phytotoxicity	OECD Guidelines for the Testing of Chemicals Test No. 208: Terrestrial Plant Test: Seedling Emergence and Seedling Growth Test
Brassica rapa, Avena sativa	Seedling Emergence Growth	ISO 22030:2005 Soil quality – Biological methods – Chronic toxicity in higher plants
Earthworms: *Eisenia fetida/Eisenia andrei*	Reproduction	OECD Guidelines for the Testing of Chemicals Test No. 222: Earthworm Reproduction Test (*Eisenia fetida/Eisenia andrei*)
Earthworms: *Eisenia fetida*	Mortality Reproduction avoidance	ISO 11268 Soil quality – Effects of pollutants on earthworms (*Eisenia fetida*). Part 1: Determination of acute toxicity using artificial soil substrate. Part 2: Determination of effects on reproduction. Part 3: Guidance on the determination of effects in field situations
Juvenile snails: *Helix aspersa aspersa*	Growth	ISO 15952:2006 Soil quality – Effects of pollutants on juvenile land snails (*Helicidae*) – Determination of the effects on growth by soil contamination
Enchytraeids: *Enchytraeus albidus*	Reproduction	ISO 16387: 2004 Soil quality – Effects of pollutants on Enchytraeidae (*Enchytraeus sp*.) – Determination of effects on reproduction and survival
Microorganisms	Nitrification, N mineralisation (28 d incubation)	ISO 14238:1997 Soil quality – Biological methods – Determination of nitrogen mineralization and nitrification in soils and the influence of chemicals on these processes
Microorganisms	Respiration Biomass (fumigation-extraction)	ISO 14240-1:1997 Soil quality – Determination of soil microbial biomass – Part 1: Substrate-induced respiration method – Part 2: Fumigation-extraction method
Microorganisms	Substrate induced respiration	ISO 17155:2002 Soil quality – Determination of abundance and activity of soil microflora using respiration curves

Table 3. Examples of extraction solutions used to estimate the bioavailability of metals in soil – see ref. 24.

Extractant Type	*Simulates*	*Example*
Water	Soil pore water concentration	Vacuum sampler Centrifugation
Neutral salt	Soil pore water concentration	0.01 M $CaCl_2$ 1 M NH_4NO_3 0.1 M $NaNO_3$
Acid extraction	Potentially soluble in water	Dilute strong acid: 0.43 M HNO_3 Weak acid: 0.43 M acetic acid
Complexing agent	Potentially soluble in water	EDTA

These extractants were originally developed for assessing nutrient levels in soil and in mimicing plant mechanisms to release essential nutrients from mineral phases in soil.[10] The complexing agents form soluble complexes with metals in solution, thus reducing their activity and causing additional metal ions to desorb from the soil. The complexing agents are aggressive and solubilize solid phase minerals giving a potential to over-estimate the bioavailable fraction of metals in soils.[27] McLaughlin *et al*.[10] suggested that complexing extractants may provide a better estimate of potential hazards from future mobilization of metals through changes to the soil, including pH and degradation of organic matter, than neutral salt extractions.

Unbuffered neutral salt solutions (0.001–1.000 M) have been used as soil extractants to predict bioavailability of metals to plants, soil invertebrates and microorganisms.[1] A wide variety of neutral salts have been trialled, with $CaCl_2$ and NH_4NO_3 being among the most commonly used.[25] These solutions target metals in soil pore water as well as metals sorbed on cation exchange sites and, depending on the salt used, they can also form complexes with metals. The overall solution pH is controlled by the soil and the extraction solution has a comparable ionic strength to the soil pore water.[1] Studies comparing results for several neutral salts indicate that, overall, these extractions provide similar information and that metals generally have the same order of extractability. Extraction with 0.01 M $CaCl_2$ is often preferred over other neutral salts because it has the lowest salt concentration, thereby reducing analytical interferences.[28] The best correlations between neutral salt extractions and organism tissue concentrations have been observed in studies where there is a wide range in soil metal concentrations.[1] A systematic review of 104 studies comparing the effectiveness of neutral salt, acid and complexing extractants found that, overall, neutral salt extractions provide the best indication of phytoavailability.[21]

Extractions with weak acids and dilute solutions of strong acids (HNO_3, HCl) target soluble and potentially soluble metals in soil.[1] Unlike total acid digests with concentrated strong acids, the metals in the mineral lattice are not removed by these less aggressive acid extractions;[29] examples of weak acid extractions include the use of acetic and citric acids.[2] Plants excrete low molecular weight

organic acids (LMWOAs) from their roots and these may then release sorbed metals from the soil matrix. Solutions of LMWOAs have been used to extract metals from soil to simulate plant uptake. For example, the *Rhizo method* uses an extraction solution containing acetic, lactic, malic and formic acids in a molar ratio of 4:2:1:1.[30]

Soil Pore Water Measurements

The advances in available analytical techniques have enabled metal concentrations to be measured directly in soil pore water. Methods for collecting soil pore water include centrifugation and the use of vacuum samplers, including rhizon samplers. After sample collection, either the free metal is measured using ion selective electrodes or anodic stripping volatammetry, or the sample is acidified and the total metal concentration is measured by ICP-MS.[1] The soil moisture content may be adjusted to a standardized water holding capacity with deionised or milli-Q water before extraction.[31] Pore water extraction methods tend to be time-consuming and the speciation can change during extraction.[10,29]

DGT Devices

Diffusive gradients in thin films (DGT) is a kinetic-based technique that simulates metal uptake by plant roots. These devices measure the soil pore water metal concentration as well as the ability of the soil solid phase to re-supply the soil pore water with metal ions. The device consists of a small round plastic deployment moulding that contains an ion exchange resin (Chelex 100) embedded in a hydro gel and covered by a protective filter. Cations in the soil pore water diffuse across the hydro gel and accumulate in the resin. The resin depletes metals from the soil pore water inducing further metal ions to desorb from the solid phase. The DGT device is deployed for a set amount of time by placing it in contact with soil. The metals are extracted from the gel by nitric acid and measured by ICP-MS and the effective concentration, C_E, calculated. It is a measure of the concentration of the metal in the soil pore water plus the metal ions re-supplied by the soil solid phase, and is determined by the physico-chemical characteristics of the soil.[2,32]

A variety of other techniques are being tested for their suitability as surrogate measures of bioavailability. These include isotope dilution techniques, ion exchange membranes, sequential extraction procedures, extraction solutions that mimic the digestive processes in earthworms, and solid and solution phase speciation models.[2,33,34]

Limitations of Available Methods

A key limitation to the widespread adoption of chemical extractions as surrogate measures of bioavailability is that there has only been limited validation of the available methods. Few studies have validated the results of chemical extractions with the results from bioassays over different soil types, contamination levels and organisms. There are also only a limited number of certified reference soils available to enable laboratories to validate their analytical methodologies and ensure consistency between laboratories. To date, no one extraction method has been shown to satisfactorily perform under all conditions for all organisms and/or metals.[1,25,34] The currently available extraction methods do not have a mechanistic basis and instead rely on empirical relationships. The NRC, in their review of available tools to assess bioavailability, recommended that mechanistic tools needed to be developed and that the mechanistic basis of bioavailability required further investigation.[1]

Current use of Bioavailability Testing in New Zealand

Bioavailability testing is already used in the NZ agricultural sector for assessing the nutrient status of pasture soils and essential metals (Cu, Zn). Soil tests using EDTA and Mehlich3 solutions (0.200 M CH_3CO_2H + 0.250 M NH_4NO_3 + 0.013 M HNO_3 + 0.015 M NH_4F + 0.001 M EDTA) are available through commercial analytical laboratories.[35] Extractions with neutral salt and complexing solutions have been used as research tools in studies investigating plant uptake of metals from NZ soils.[19,31,36]

Regulatory Acceptance of Bioavailability Testing

Currently bioavailability testing is not used in NZ to assess contaminated land. Only a limited number of countries

Table 4. Examples of soil acceptance criteria based on neutral salt extractable metal concentration. Units are mg/kg – see refs. 37 and 38

	1 M NH_4NO_3					0.1 M $NaNO_3$
Country	**Germany**		**Austria**		**Slovakia**	**Switzerland**
	Plant growth	***Plant quality***	***Plant growth***	***Plant quality***	***Plant quality***	***Soluble content***
As	0.4		0.6	0.1	0.4	
Cd		0.04/0.1		0.04	0.1	0.03
Cr				0.1		
Cu	1		1.5	0.8	1	0.7
Hg				0.005		
Ni	1.5		1.0		1.5	
Pb		0.1		0.3	0.1	1.0
Th		0.1				
Zn	2		4		2	0.5

currently incorporate bioavailability testing into regulatory decision-making for management of contaminated land. Countries with soil acceptance criteria for neutral salt extractions of metals include Switzerland, Germany, Austria, and Slovakia (Table 4).[37,38] The Dutch National Institute for Public Health and the Environment (RIVM) has recently selected methods for a pilot study investigating the feasibility of incorporating bioavailability tests into policy for risk evaluation for contaminated soils. The two methods selected for metals (Cu, Pb, As) are extraction with 0.01 M $CaCl_2$ to estimate actual (bioavailable) concentrations and a weak acid extraction with 0.43 M HNO_3 to estimate potential (bioavailable) concentrations.[29]

Incorporation of Bioavailability Testing into the Regulatory Framework of NZ

Before bioavailability testing can be incorporated into the NZ framework for the management of contaminated land, appropriate methods would need to be selected and validated for use in our soils. NZ soils *are* sufficiently different from many of the soils used in studies overseas, making it inadvisable to adopt bioavailability testing methodologies from overseas without appropriate validation. Overall, NZ soils tend to have a higher organic content and lower pH levels than soils in other regions of the world.[39]

The ISO has recently published a standard on method selection for assessing the bioavailability of contaminants in soils, namely *ISO 17402:2008 Soil quality -- Requirements and guidance for the selection and application of methods for the assessment of bioavailability of contaminants in soil and soil materials*.[40] This standard could be used to select appropriate methods for validation under NZ conditions. The recommended selection criteria include a method that does not alter the soil's physical properties, has a mechanistic/physiologic basis; has a correlation with biologically measured effects and has been validated by inter-laboratory trials.[24] RIVM also considered the acceptability of the method to policy makers, and the cost of the method, when selecting appropriate methods for their pilot study.[28]

Summary

It is now widely accepted that measuring the soil total metal concentration may not accurately predict the risks associated with soil contamination. Over the last three decades extensive research has focussed on understanding the processes that determine the bioavailability of metals in soil. Efforts to develop tools to predict bioavailability have only had limited success. Further work will be required to develop and validate tools that enable bioavailability assessments to be incorporated into regulatory decisions for management of contaminated land.

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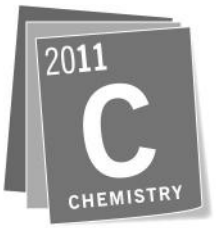

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Article

More Bang for your Buck: An Introduction to CHNO Explosives

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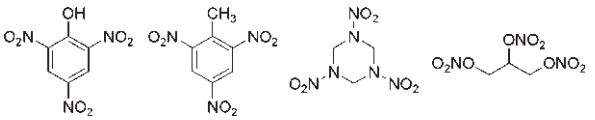
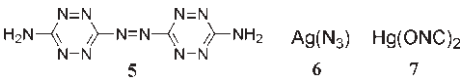
Introduction

Explosives, explosions and violent reactions have fascinated chemists for centuries. The current development of explosives is the culmination of extensive efforts to understand the chemistry of energetic molecules and the reactions that they undergo. There are various types of explosives with CHNO molecules, the most abundant class, *e.g.* **1-4**. These structurally related compounds all have an oxygen-containing group and release their energy through the violent combustion of the carbon and hydrogen atoms of the skeleton.



1, picric acid **2**, TNT **3**, RDX **4**, nitroglycerine

Many other molecules react sufficiently violently to cause explosions, although they are much less commonly used on a large scale. Important classes of such explosive compounds include organic molecules almost exclusively carrying nitrogen, *e.g.* tetrazine **5**.[1] Such molecules have extremely high energies of formation and this is released when they react. Inorganic complexes with energetic counter ions, such as silver azide (**6**) and mercury fulminate (**7**) are also commonly used as explosives, particularly in detonators due to their sensitivity.



5 **6** **7**

Explosives can be roughly divided into three classes:[2]

1. *Propellants* are materials with a slow rate of reaction that is not dependent on atmospheric oxygen for combustion. Such mixtures are used in rockets and fireworks.
2. *High explosives*, which make up the bulk of common explosives. They react energetically, but are relatively insensitive to detonation.
3. *Initiators* are unstable and easily detonated. In common explosives small amounts are used to instigate a primary shockwave to start the explosive reaction.

The combustion reactions of explosives fall into two types dependent on the speed of reaction each giving different effects. *Deflagration* is a process analogous to burning, in which energy is released relatively slowly by thermal conduction and radiation. Deflagration occurs in propellants where the explosive is consumed over a comparatively long period of time. *Detonation* processes have an associated shock wave which travels above the sonic velocity of the material. High temperatures and pressures exist within this shock wave, giving rise to faster and more vigorous reactions than are possible in deflagrating explosives.

Explosive detonations have various properties that differentiate them from chemical reactions that occur in a less violent manner. The energy of an explosion is released in an extremely short period of time. In detonation, a shockwave passes through the explosive extremely quickly;[3] typical detonation velocities vary from 6000–8500 ms^{-1}. The travelling shockwave represents a huge step jump in temperature and pressure, an increase so large that the material behind the advancing detonation front reacts, immediately propelling it forward. Under these conditions, the explosive material is almost exclusively transformed into hot and voluminous gases. Orthogonal to the direction of the detonation front, a rarefaction wave is released as a shock front, removing energy from the detonation wave, releasing pressure and removing the detonation products. The combination of the large amounts of gas released, the high temperatures, and the shockwave causes much of the damage associated with an explosion.

Reactions in explosives under detonation occur faster than diffusion of external reactants into the detonating material. Therefore, for the reaction to be complete, sufficient reactants must be available within the explosive mixture. In CHNO explosives, the combustion of the carbon and hydrogen is the main reaction and it requires oxygen. If there is sufficient oxygen to react with the combustible material within the explosive, it is said to be *oxygen balanced*. If the explosive is deficient in oxygen, the products will contain unreacted or partially reacted carbon and hydrogen. An explosive with an excess of oxygen will be able to oxidize material other than carbon and hydrogen, leading to the formation of toxic side products, typically nitrogen oxides. The oxygen balance of a particular explosive can be expressed as the weight percent of oxygen released after all combustible material is consumed. Ammonium nitrate releases about 20% of its weight as free oxygen and can be combined with a fuel source, such as diesel oil to give the oxygen balanced binary explosive ANFO (ammonium nitrate fuel oil). The goal of modern high explosives research is to attain oxygen balance at the molecular level. Industrial explosives are designed to have slightly more oxygen than necessary in order to reduce emissions.

It can be shown, using fluid dynamics, that the change in pressure in an explosion is proportional to the density of the explosive, multiplied by the detonation velocity and the velocity of the products of the detonation.[4] The detonation velocity is the sum of the velocity of the products of detonation and the speed of sound in the explosive, which is higher in more dense materials. Therefore, charges of higher density will have a greater effect per unit volume due to faster detonation velocity and higher final pressures. Brisance is the destructive fragmentation effect of an explosion on material in its immediate

vicinity. Brisance is increased by the speed of the detonation wave and the pressure of the explosive products; as shown above, both are dependant on the density of the explosive.[5] The relative effectiveness of an explosive is often measured in comparison to **2** (TNT) as a moderately powerful explosive of moderate brisance (ρ 1.65 g/cm^3).

History of Explosives

The early history of explosives almost exclusively involves the development of gunpowder. This consists of a mixture of saltpetre (potassium or sodium nitrate) as the oxidising agent, with carbon and sulfur as fuels. Saltpetre is formed by the decay of proteins and can be recovered from ores. Sulfur is found in high concentrations at sites of volcanic activity, and the heating of wood in an oxygen-free environment forms charcoal. Explosive mixtures were often formed by accident. A notable example occurred *ca*. 220 BC when a group of Chinese chemists mixed saltpetre, charcoal and sulfur together in an attempt to extract gold from an ore – it caused a large explosion.[6]

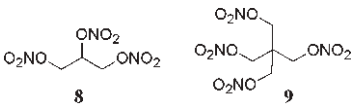
Initial gunpowder formulations were of limited effectiveness due to impurities in the available saltpetre. However, in the 13th century, Roger Bacon successfully purified saltpetre by recrystallizing it from water.[7] From then on the strength of gunpowder grew with the increasing purity of the components until the late 18th century when it reached its peak. In order to attain peak effectiveness, the components of gunpowder need to be mixed adequately to ensure intimate contact between the oxidising agent and the fuel. At the molecular level this is done by increasing the number of oxygen atoms per molecule and it is most easily achieved by the attachment of nitro groups to organic molecules. One of the earliest organics to be treated in this way was glycerine, first nitrated by the Italian chemist Sobrero who halted his efforts upon discovery of its explosive nature. Alfred Nobel, a student contemporary of Sobrero, and his father Immanual developed the industrial nitration of glycerine by using a mixture of concentrated nitric and sulfuric acids. However, numerous early industrial accidents occurred due to explosions and, in 1864, one such detonation destroyed the first Nobel factory and killed Alfred's brother.[8] The use of nitroglycerine was greatly improved from Nobel's discovery that mixing it with filler mitigates accidental detonation, and then with the development by Alfred Nobel of a reliable mercury fulminate detonator.[3]

The CHNO explosives attain their oxygen balance on the molecular scale from the addition of nitro groups. They can be broadly divided into three different classes, dependent on the site of attachment. The strength of the bond to the nitro group determines the ease of detonation. The weaker the bond, the easier it is to initiate the detonation process. Bond strengths decrease from nitrated carbon (**C**-NO_2) > nitramine (C**N**-NO_2) > nitrate ester (C-**O**NO_2) with bond strengths of ~300, ~200 and ~170 kJ/mol, respectively.[9] When a CHNO explosive detonates, the weakest bond is broken and this must release enough energy to break the next weakest, and so on until all are consumed by combustion and the energy released in the form of hot gases.

Nitrate Esters

Nitrate esters were the first synthetic explosives to be produced on a large scale, with the nitroglycerine of Alfred Nobel. They are formed by the reaction of a nitronium ion (NO_2^+) with a pendant alcohol group to give a nitrate ester (–ONO_2). As a general rule, the more nitrate ester groups that an explosive contains, the more powerful the detonation will be, and the more sensitive the explosive. Nitroglycerine (**8**), the prototypical nitrate ester explosive, is produced by mixing concentrated nitric acid and fuming sulfuric acid with glycerine. Generally, the method can be used to produce nitrate esters from alcohols. They are powerful, but sensitive to detonation and often chemically unstable. Nitrate **8** is particularly prone to accidental detonation when solid (m.p. 12.5 ºC),[3] or impure. Dynamite is a mixture of nitroglycerine with diatomaceous earth, which reduces the shock sensitivity and provides for safe transport.

Nitrate esters are no longer used on a large scale either in civilian or military applications, but they are occasionally added to other explosives as sensitizers. It is interesting to note that nitrated compounds often have medicinal properties, for instance nitroglycerine has been used as a treatment for angina. In the body, nitrate esters are broken down by enzymatic reduction to nitric oxide (NO), a biochemical signalling molecule.[10]

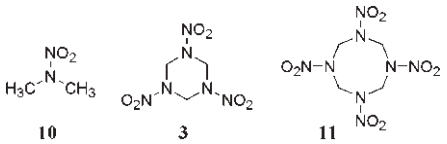


8 **9**

Pentaerythritol tetranitrate (PETN, **9**) is the most common of the nitrate ester explosives still in use. It has an intermediate sensitivity that places it between initiating explosives, such as azides and fulminates, and bulk explosives. It is commonly mixed with other secondary explosives to sensitize them to ignition, and it is the base material of primacord® fuses, surrounded by a protective polymer layer. PETN (**9**) is produced by nitration using the ICI method that has removed the need for sulfuric acid in the synthesis.[6] It has considerable strength as an explosive, due to its high detonation velocity (8274 m/s) and high density (1.77 g/cm^3). PETN (**9**) has a slight negative oxygen balance (-10%) upon detonation and leaves behind a little detonation residue, giving mostly CO_2, N_2, H_2O and CO.[11]

Nitramine Explosives

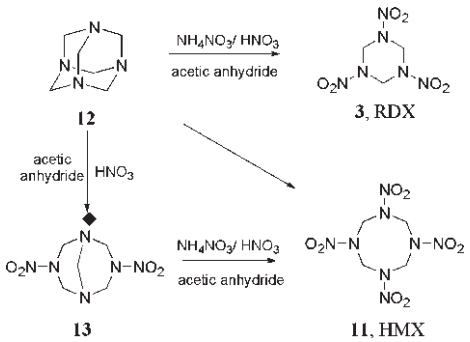
The first nitramine to be synthesised at the turn of the 20th century was RDX (**3**), but for use as a medicine. Development of nitramines proceeded in the 1920's with various derivatives being produced. Nitramines are some of the most powerful explosives in use today, while also being stable and insensitive to accidental detonation.[12] The nitramine group (N-NO_2) is formed by nitration of an amine with the nitronium ion. Non-cyclic nitramines, such as dimethylnitramine (**10**), are only weak explosives while cyclic nitramines, such as RDX (**3**) and HMX (**11**), are more powerful. RDX has a specific energy of ~1400 kJ/kg, which corresponds to 1.5 that of TNT.[3]



10 **3** **11**

Nitramine explosives are insensitive to accidental detonation. Indeed **3** and **11** can be heated safely to their melting point. They are insensitive to impact with **3** (RDX) being about half as sensitive as PETN (**9**) that has comparable explosive strength. Cyclic nitramines are dense solids (1.82 g/cm^3), giving them fast detonation speeds; RDX has a detonation velocity of about 8400 m/s, compared with 6900 m/s for TNT.[3] Nitramines are mixed with polymers to form plastic explosives, with the widely known military explosive Composition-4 (C-4; **12**) being a mixture of RDX and polyisobutylene.

The commercial scale synthesis of **3** is shown in Scheme 1. It is performed over a single step by mixing hexamethylenetetramine (**12**) with ammonium nitrate and nitric acid in acetic anhydride. When originally undertaken, some HMX (**3**) was isolated as a minor product. The nitration of the bicyclononane **13**, under conditions similar to the production of **3**, gives HMX (**11**) exclusively. This precursor was formed from **12** with nitric acid and acetic anhydride.



Scheme 1. Industrial synthesis of **3** and **11**.

Given the relationship between density and explosive power, it is important to fully characterise all the possible polymorphs of an explosive to ensure that the highest possible density is reached. Nitrate **3** (HMX) has four polymorphs that are formed by heating below the melting point followed by slow cooling.[13] Two of these are shown in Fig. 1, and differ in the conformation of the eight-membered ring and the orientation of the nitro groups. The β-polymorph of **3** is formed by heating to 116 ºC; it is the most stable polymorph and, paradoxically, the most powerful having with the highest density (ρ 1.90 g/cm^3). The δ-polymorph of **3**, formed by heating to 193 ºC, is the least dense (ρ 1.58 g/cm^3) and most sensitive, being about seven times more sensitive to detonation than the β analogue.

Studies of the reaction products of explosions are important in the design of new explosives.[12] However, they suffer from the significant problem of needing analysis of product distributions over the course of extremely fast and violent reactions. This can be simplified by focusing upon the products of the initiation process. In these initial stages of an explosion, sufficient heat must be generated to begin detonation. Studies of the thermolysis of explosives

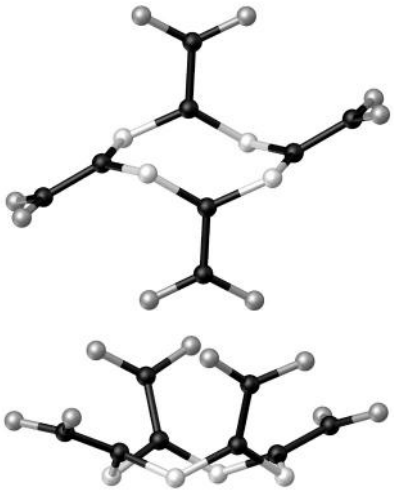
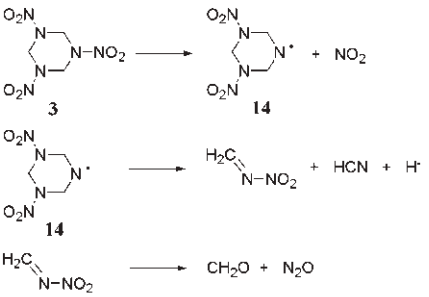


Fig. 1. The structures of the β- (upper) and δ-polymorph (lower) of HMX (**3**); hydrogen atoms are omitted for clarity.

simply involve heating an explosive at various temperatures and following this by analysis of the product distribution. Studies on **3** (RDX) have shown that it requires approximately 160–200 kJ/mol to detonate. This is consistent with the initial reaction being the homolysis of the N-N nitramine (N-NO$_2$) bond.[14] These bonds in **3** and **11** are much weaker than those in non-cyclic nitramines such as dimethylnitramine (**10**), possibly explaining why these molecules are more explosive. The detonation chemistry of nitramines is shown in Scheme 2 and begins with homolysis of the N-NO$_2$ bond to produce amine radical **14** and nitrogen dioxide. Radical **14** then induces ring fragmentation to form (eventually) nitrous oxide and formaldehyde. All the fragments react further in the extreme conditions to give the overall product distribution, which consists mainly of nitrous oxide and molecular nitrogen with some carbon dioxide, carbon monoxide, residual solid and water.[15]

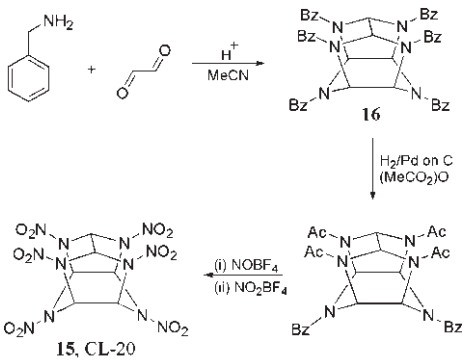


Scheme 2. Initial reactions in the detonation of RDX (**3**).

One of the most powerful military explosives currently being trialled is the caged nitramine – hexanitro-**15** (CL-20) (Scheme 3).[16] Caged molecules have high energies of formation that are released during detonation, and high densities, leading to violent explosions. CL-20 is less sensitive to heat than either **3** or **11**, and, like the latter, it can exist in various polymorphic forms, the most stable having a density[17] of 2.04 g/cm^3.

The synthesis of **15** is remarkably simple and high-yielding. Benzylamine reacts with glyoxal (ethane-1,2-dione) under acid catalysis and in acetonitrile to produce the hexabenzyl analogue **16** of CL-20 (**15**). Reductive acylation replaces four of the benzyl groups of **16** with acetates

(Scheme 3). This is then sequentially reacted with the strong nitrating agents nitrosotetrafluoroborate and nitrotetrafluoroborate to give **15** in ~40% yield.[16]

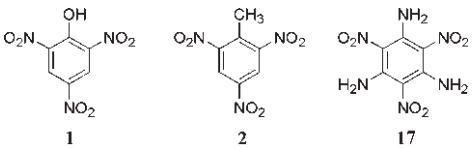


Scheme 3.

Studies on the initiation of CL-20 (**15**) show that, as for **3**, the first reaction is the homolysis of the nitramine bond. However, once this has occurred, the amine radical is stabilized by intermolecular reactions with other caged molecules, accounting for the stability of **15**. In an explosion, nitrogen dioxide is released before intramolecular reactions occur, thereby producing different products to RDX (**3**) or HMX (**11**). Despite having a slightly deficient oxygen balance, this gives reaction products higher in NO_2 and NO than from **3** or **11**.[13,19]

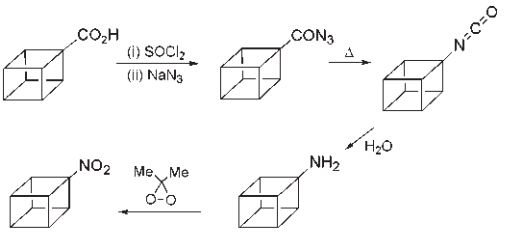
C-Nitro Explosives

The most well known class of explosives is the nitrated aromatics, with the most widely recognized being 2,4,6-trinitrotoluene (TNT, **2**). TNT was developed as an explosive in the late 19th century[3] as a safe alternative to picric acid (**1**), a common early propellant and explosive. Wet picric acid is less sensitive to detonation, but is extremely corrosive towards metals and the metal salts formed are dangerously sensitive to accidental detonation. Until the development of the petroleum industry in the early 20th century, TNT could not be made in large quantities due to a lack of toluene. It is a popular explosive, easy to mix with other explosives, and insensitive to accidental detonation, while being quite powerful.



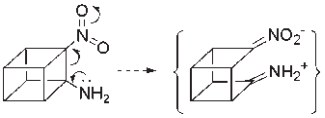
Nitrated aromatics are quite easy to synthesize and nitration is a common reaction in undergraduate laboratories. The sensitivity to detonation for these explosives is due to the high strength of the C-NO_2 bond (*ca*. 300 kJ/mol). As noted above, **2** has a relatively slow detonation speed compared to more modern explosives. Its relative strength is also slightly lower due to a negative oxygen balance (-73%) that leaves reaction products not been fully oxidised. These include a large amount of CO and even some H_2.[20] Further developments of nitrated aromatics have included the use of other nitrogen functional groups. A modern explosive used for its extreme insensitivity to accidental detonation is 1,3,5-triamino-2,4,6-trinitrotoluene (TATB, **17**). This has been used in specialist applications where early detonation can prove disastrous, such as in the trigger of nuclear weapons. This robust solid has a melting point above 600 ºC, and is one of the densest nitrated aromatics known (ρ 1.94 g/cm^3), which makes it one of the more powerful. With more nitrogen per molecule than TNT it also produces more complex nitrogen, containing residues (such as HCN and HNCO) when it explodes.[21]

The search for denser and even more powerful explosives has followed development of other explosives, *e.g.* **15**, into the use of caged molecules. Cubane is extremely energetic, having an enthalpy of formation of *ca*. 630 kJ/mol and, while being kinetically stable, its decomposition occurs only above 220 ºC. Cubane is also one of the densest hydrocarbons known[22] with a density of 1.29 g/cm^3, making nitrated cubanes a goal for new explosives research. Octanitrocubane is predicted to be even denser (ρ_{calc} 2.1 g/cm^3) and this would make it one of the densest CHNO explosives known. It is predicted to release 20–30% more energy than CL-20 (**15**) in an explosion. Octanitrocubane has a zero oxygen balance and, in an explosion, should give only molecular nitrogen and carbon dioxide, depending upon the mechanism of fragmentation on explosion. Simple nitrocubanes can be synthesized from the corresponding carboxylic acids using standard procedures,[23] as shown in Scheme 4 for the mono-nitro derivative. A cubane-1-carboxylic acid is converted to its azide, which upon heating undergoes a Curtius rearrangement to give the corresponding isocyanide. This, in turn, is then hydrolysed to an amine and oxidation with dimethyldioxirane generates the nitro moiety.[24]



Scheme 4. Synthesis of nitrocubane.

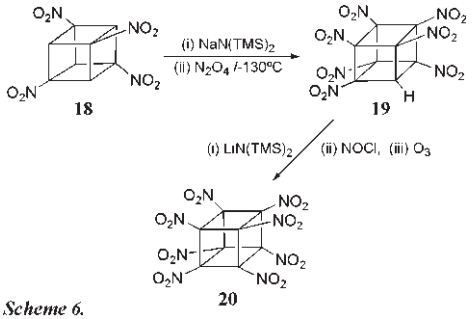
Attempts to synthesise cubanes with adjacent nitro groups using these methods have failed because the products fragment as illustrated in Scheme 5. When an electron-donating amine group is adjacent to an electron-withdrawing nitro group the strain of the cubane skeleton causes the molecule to fragment.[25] This seemed to put the synthesis of more nitrated cubanes in doubt, until it was recognised that the protons of 1,3,5,7-tetranitrocubane are acidic, with a pK_a equivalent to the α-proton of a carbonyl group.[26]



Scheme 5.

Treatment of tetranitrocubane **18** with a strong base, such as tetramethylsylamide, can form the sodium salt that can then be nitrated with dinitrogen tetroxide at the interface of a melting tetrahydrofuran solution of the salt. Indeed, if this is done with four molar equivalents of base, heptanitrocubane **19** is produced (Scheme 6), but this does

not react further to give octanitrocubane (**20**) under these conditions. However, if the lithium or sodium salt of **19** is treated with nitrosyl chloride, followed by oxidation using ozone in cold dichloromethane, **20** is formed, probably by way of (nitroso)heptanitrocubane.



Scheme 6.

Although produced only on a small scale, a single suitable crystal of **20** was grown and the X-ray structure is shown in Fig. 2,[27] but the density was lower than expected (ρ 1.98 g/cm^3). Since calculations of the densities of these compounds have been found accurate in the past, it is possible that, as for with HMX (**11**) and CL-20 (**15**), other polymorphs of **20** may exist. Currently, heptanitrocubane is of most interest as it is significantly easier to synthesize, and the isolated polymorph more dense (ρ 2.028 g/cm^3).[9]

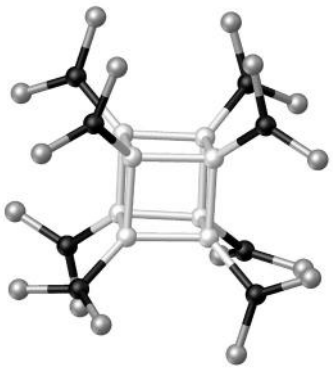


Fig. 2. The structure of octanitrocubane (**20**).

Conclusion

Explosives have been an important part of the development of society over the last two centuries. The CHNO explosives are the most common class of explosive molecules, with the desire to combine high explosive force with low sensitivity to accidental detonation driving future development. The power of explosives is dependant on attaining the highest density through choice of compound and polymorph. Investigations of the detonation chemistry are also crucial to gaining a complete understanding of the properties of an explosive. Caged molecules, such as CL-20 (**15**) and octanitrocubane (**20**), with their high densities and large energies of formation are at the forefront of current explosives research.

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Showcasing Research at YOUR University – An International Trend

Cather Simpson

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The Chemistry Department at Auckland University (UoA) hosted the ***Inaugural Chemistry Research Showcase*** last June, with great fanfare. In so doing, the Department joins a new international trend to highlight the breadth and depth of research at a single institution, often within a single discipline. Google *research showcase* or *research spotlight* or similar phrases and you will get a dizzying number of hits from institutions of all sizes and prestige levels. It seems like everyone's got some sort of ***look at us!*** research celebration.

The origin of these events can be traced to the recent evolution of universities away from the aloof ivory tower, a bastion of scholarly endeavour that *[advances] society-at-large through knowledge distribution*,[1] towards the fully engaged, approachable leader of socioeconomic transformation. Universities still focus upon generating new knowledge and educating future graduates. However, in the 21st century they lead in other spheres as well, from government and the economy to energy and the environment.[2] Corporate attitudes that have infused higher education, motivated to meet these goals,[3] endorse self-promoting events that laud excellence from within. It should come as no surprise that *look at us!* research events are often driven by research offices, public affairs divisions, alumni outreach organizations, and other branches of the upper administration, to encourage scientists to network with potential funding agencies and/or research partners, actively raise research funds, and participate in collaborative initiatives.

Fortunately, these added motives do not detract one little bit from the time-honoured benefits of such research meetings. As with the more traditional cross-institutional conferences, like the local meetings the ACS has sponsored for decades,[4] and like the recent MacDiarmid Institute Student and Postdoctoral Symposium,[5] young scientists are the focus. *It is a great opportunity for students at all levels to practice their presentation skills and compete for prizes*, said Prof Mary Barkley, Chair of Chemistry (Case Western Reserve) where a very successful, university-wide *Research ShowCASE* is held annually.[6] Ancillary events include workshops on research topics, entrepreneurship, and other areas that provide critical training for modern academic scientists on the verge of their professional careers.

In addition to celebrating – and advertising – young scientists and their research, bringing together industry representatives, students, research staff, and university administrators at *look at us!* occasions may catalyze innovative solutions to critical problems. Prof Dan Nocera, (Energy Professor, MIT, Cambridge, USA) put it this way: *One of the greatest challenges facing our societal future is energy. This problem cannot be solved by simply engineering 'off-the-shelf' science. If it could be solved this way, we would have already done it. To penetrate the market, new materials, new reactions and new processes will have to be discovered. Our existence on this planet's future rests in the hands of the research scientist.* Success in this endeavour is likely to require that research scientists communicate with engineers, industrial partners, and government and private funding officials. Research days like the one held at the UoA foster just these sorts of interactions.

Winners of the 2009 Chemistry Research Showcase abstract competition (left to right) K. Rathwell (honourable mention), T. Kjällman, D. Larsen, R. Peltier, S. Guéret, A. Dalebrook, S. Tong, Grant McIntosh (honourable mention), J. Paauwe, and C. Lam.

Enjoyment at the Poster Session

The Department established Chemistry Research Showcase to shine the spotlight on our postgraduate students and to actively strengthen our research activities with industry. The one-day event featured oral presentations by eight PhD students selected from a fiercely competitive entry of abstracts. Over fifty posters were presented and prizes were awarded by Prof Alan Lee, Dean of Science. An exciting key-note talk was delivered by Prof Bill Denny (co-Director, Auckland Cancer Society Research Centre), both a Rutherford and Adrian Albert Medalist and a co-

founding scientist at Proacta Therapeutics. His presentation highlighted his experiences in taking science from the laboratory to the clinic. Generous sponsorship was provided by Fonterra, Fisher & Paykel Healthcare, Sigma-Aldrich, New Zealand Scientific Ltd, New Zealand King Salmon, Coherent Scientific, UoA Wine Science, ECP, and the Auckland Branch of the NZIC. The day finished with a mixer particularly designed so that students and industry representatives could network. Over 200 people attended and it was pronounced a success widely – from the viewpoint of the ivory tower and all of the other perspectives of the 21st century university.

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3. Perhaps this is most evident in the relatively recent explosion of university, faculty, and department strategic plans: see: Fain, P. *Chron. Higher Ed*. **2007**, *54*(6), A.26.
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When is Medicinal Chemistry Patently Obvious?

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In order to be granted a valid patent, an invention must be both novel and non-obvious (*i.e*. inventive) in light of what was public knowledge at the time. In a recent decision from the United States District Court of New Jersey[1] and later the US Court of Appeals for the Federal Circuit [2] (CAFC), the issue of whether it is obvious to modify a pharmaceutical compound by substituting a methoxy group for a methyl group has been considered.

Background

Altana Pharma holds, and exclusively licences to Wyeth, the patent for the compound pantoprazole, which is the active ingredient in Protonix®, a prodrug treatment for stomach ulcers. This compound is one of a family of compounds known as proton pump inhibitors (PPIs), one of the original and most famous of which is the blockbuster drug omeprazole (Fig. 1), the active ingredient in Losec® and Prilosec®.

In April 2004, Teva Pharmaceuticals and later in March 2005 Sun Pharmaceuticals (collectively "Teva") both filed applications to the FDA for approval to sell a generic version of Protonix®. Following these submissions, Altana Pharma and Wyeth (collectively "Altana") filed suit against Teva for patent infringement. In response, Teva conceded infringement of the Altana patent but argued that the patent was invalid because the invention was obvious in light of what was known at the time of filing. Altana then sought an interim injunction to prevent sales of the generic drugs while the case for patent invalidity makes its way through the courts.

This decision relates to the interim injunction, which means that at this stage it is not the validity of the patent *per se* which is at question. However, it can give an indication of strength of the case against the validity of a patent.

What was the basis of the argument that the invention was obvious?

To establish that an invention concerning the modification of a chemical compound is obvious in the United States it must be shown that, based on the knowledge publicly available at the time, a chemist would:

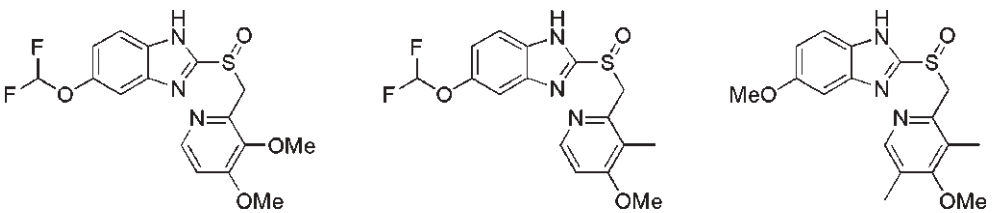
i. have some motivation for selecting a lead compound (the compound to be modified); and

ii. have some motivation for modifying the lead compound in the way that would produce the compound claimed as the invention.

With this in mind, Teva set out their argument for obviousness using four documents:

i. An earlier patent[3] owned by Altana that disclosed a number of compounds including a compound known as compound 12 as being potent PPIs (see Fig. 1).

ii. An article,[4] which Teva claimed taught that it would be desirable to lower the pKa of a PPI to 4, because it would



Pantoprazole "Compound 12" Omeprazole

Fig. 1. The proton pump inhibitors (PPIs) at issue in the US Courts

improve the stability of the compound in the body.

iii. Another article[5] that Teva claimed taught that a methoxy group at the 3-position of a pyridine ring would provide a lower pKa than a methyl group in the same position.

iv. Finally, the patent for omeprazole[6], which Teva said demonstrated the feasibility of substituting a methoxy group for a methyl group at the 3-position of the pyridine ring in a PPI.

Teva argued compound 12 would be the lead compound and the other documents would give the means and motivation for modifying it to pantoprazole.

What is the other side of the argument?

Altana argued that there was no reason to select compound 12 over the approximately 90 compounds included in their own earlier patent (even though "compound 12" was included in an experimental section which demonstrated the activity of eighteen compounds). They also suggested that for a lead compound to be obvious, the prior art should point only to a single promising compound rather than the multitude of potential leads.

What was the outcome?

It would seem that the District Court was at least in part persuaded by the argument set out by Teva and refused to grant the interim injunction. Several factors are considered when deciding whether to grant an interim injunction. In this case, regarding the question of the validity of the patent, the District Court decided Teva had demonstrated a "substantial question of invalidity". The Appeals Court then found the District Court had not applied standards which were clearly erroneous and therefore upheld the decision. However, there is a glimmer of hope for Altana, as one of the judges in the Appeals Court, while agreeing with the decision not to grant the interim injunction, stated that she did not believe the evidence established invalidity of the patent. Since this is only an interim injunction it is not necessary to establish invalidity, only a "substantial question of invalidity", therefore her comments were still in keeping with the judgement.

So it appears that Teva have won round one but, with the final decision on validity of the patent (and subsequent damages) still to come, this is a fight that has some time to run.

What does this mean for me?

Advances in medicinal chemistry are often made in increments, by making modifications to previously known pharmaceutical compounds or natural products. When engaging in this type of research (and hoping to patent the results) it is worth considering the two points set out above. Firstly, is the known pharmaceutical compound a natural choice as a lead compound? Remembering that when we say "natural choice" this should be based on public knowledge, not your own private research or gut instinct. Secondly, if it is a natural choice for further research, are the modifications based on standard chemistry with predictable beneficial results or are they based on trial and error or lead to surprising discoveries?

It is the element of unpredictability in medicinal chemistry which leads to patentable results.

For our next issue we ask you, the reader, to contact us with your burning questions regarding patents, patent ownership, or indeed any form of intellectual property:

Patent Proze

Baldwins Intellectual Property

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Email: *email@baldwins.com*

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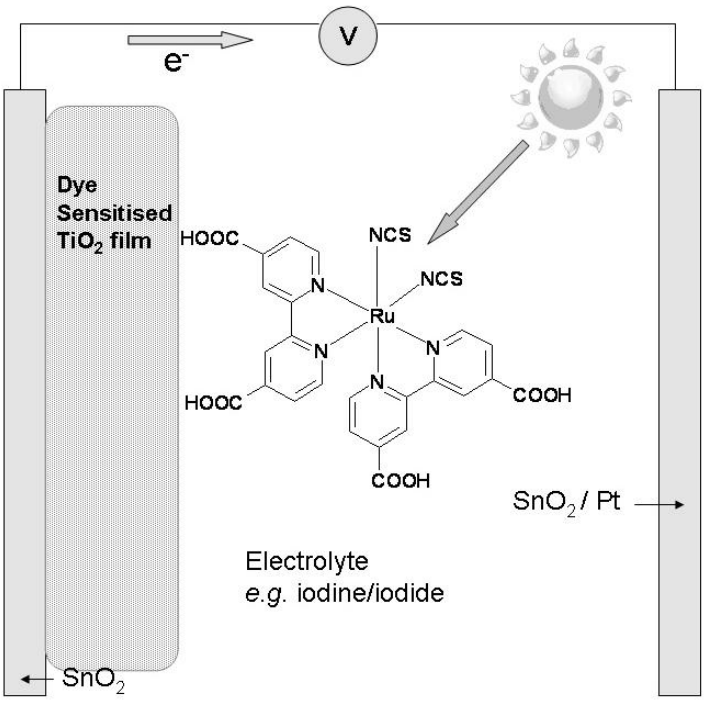
Recent Advances in Dye Sensitised Solar cells

With the ever increasing need to create new methods of electricity generation in the move away from the dependence upon fossil fuels, research into alternative energy sources including harvesting energy from the sun is escalating. A solar cell harnesses light from the sun and converts it into usable electrical energy. The solar light energy excites electrons within certain regions of the solar cell to higher energies, so that they can subsequently be withdrawn as electricity. Solar cells based on microcrystalline silicon have energy conversion efficiencies of up to 15%. However, they are very expensive to manufacture and require direct illumination by sunlight to operate efficiently.

In the search for new solar energy conversion systems, dye sensitised, wide band gap semiconductors have attracted much attention. They can be sensitised to visible light using inorganic compounds exhibiting charge-transfer excited states. Single crystal and polycrystalline films of titanium dioxide (TiO_2) were originally used in the 1970s but the surfaces were flat and after the sensitizer was absorbed onto the surface less than 1% of the incident light could be captured. Today, nanocrystalline films of TiO_2 can be used to give a higher surface area and longer path length resulting in light harvesting efficiencies of up to 99%. The nanostructured films consist of very small particles interconnected in a porous, three dimensional



Measuring photocurrent efficiency at TiO_2 surfaces

network. The interconnections between the particles allow for electric conduction throughout the network and the porous structure results in a large interface between the electrolyte and a dye sensitised semiconductor.

Dye sensitised solar cells (DSSCs) or Grätzel cells.

A DSSC is comprised of three major parts: a nano-structured semiconductor electrode, *e.g.* TiO_2, the sensitizer or dye, and an electrolyte which acts as the redox couple. (See Figure). Light absorption is performed by a monolayer of dye chemically absorbed onto the surface of the semiconductor. After excitation by a photon of light, the dye, usually a transition metal complex with ligands specifically designed for the task, is able to transfer an electron to the semiconductor (TiO_2) (the process of injection). The electric field within the bulk material allows extraction of the electron. Positive charge is transferred from the dye to a redox media (*e.g.* iodine/iodide electrolyte) present within the cell and then to the counter electrode. The redox media is a redox couple which ferries charge around the cell and must not absorb solar energy itself. The TiO_2 serves as a high surface area support for the sensitizer, a pathway for electrical current and a porous membrane for the diffusion of the redox couple.

The sensitizer, or dye, is the key element of the solar cell. It must absorb visible light, pump an electron into the semiconductor and accept an electron from the redox couple solution and repeat this cycle many times. Additionally, it has to be highly stable in the oxidised, excited and ground states, a good absorber of solar energy and be of relatively low cost to be commercially viable. Ruthenium(II) polypypridyl complexes fulfil most of these criteria and complexes incorporating 4,4'-dicarboxy-2,2'-bipyridine moieties can be attached to TiO_2 surfaces. $[Ru(bpy)_3]^{2+}$ and its derivatives have been extensively studied in solar energy applications. Ruthenium(II) complexes are stable, low spin d^6 species which can be oxidised or reduced. Ruthenium can coordinate to a wide variety of ligands forming coloured coordination complexes with metal-to-ligand-charge-transfer (MLCT) bands absorbing in the visible region of the electromagnetic spectrum. One of the most efficient Ru sensitizers is *cis*-dithiocyanobis(4,4'-dicarboxy-2,2'-bipyridine)ruthenium(II) $\{[Ru(dcbpy)_2(NCS)_2]$.

Telfer *et al*. at Massey University (*Inorg. Chem.,* **2009**, *48*, 13) are looking at mixed dipyrrin/bipyridine ruthenium(II) complexes as dyes. These metal complexes show parallels with chlorophyll in nature and therefore can capture sunlight and be used in solar cells. However, ruthenium is a rare metal and is very expensive so alternatives are currently being investigated. Gordon, Campbell, Officer *et al.* at the universities of Massey and Otago (*J. Phys. Chem. C.* **2007**, 111, 11760) reported the synthesis, electronic and photovoltaic properties of novel green porphyrin sensitizers. The dye sensitized cells used zinc tetraarylporphyrin malonic acids as the sensitizer. One of the Royal Society of Chemistry's (RSC) top accessed papers of 2008 by Constable and Grätzel (*Chem. Comm.* **2008**, *32*, 3717) reported that copper(I) complexes can interact with light in a similar way to ruthenium. The light conversion efficiencies of the copper complexes were about 4 times lower than the ruthenium complexes currently used but the cost of the copper sensitizer would be an order of magnitude lower than ruthenium. By modifying the ligands around the copper centre they hope to improve their light conversion efficiencies.

It is not only metal-based dyes that can be used as sensitizers. Indeed, a mini-review published within the *Eur. J. Org. Chem.* (**2009**, 2903) reports upon the design requirements and synthetic aspects of organic dyes for use in DSSCs. The organic dye needs an anchoring group(s) to attach to TiO_2 surfaces, must be chemically stable in the photoexcited state and dye aggregation on the TiO_2 surface must be avoided as this leads to low conversion efficiencies of the DSSC. The organic dyes investigated include; coumarines, polyenes, hemicyanines, thiophenes, indulines, heteropolycyclics, catechols, pthalocyanines *etc*. More recently the *Journal of Materials Science* (**2009**, *19*, Issue 30) published a themed issue on the topic of solar cells. It includes the most recent advances in liquid and solid state dye sensitized solar cells, bilayer cells based on small molecules, and bulk-heterojunction polymer solar cells. The feature article looks at replacing liquid electrolytes in DSSCs with polymer or gel polymer electrolytes.

No doubt as this selective overview demonstrates the future is bright in solar cell research!

Dates of Note

On Oct. 16, 1846, American dentist Dr *William Thomas Green* ***Morton*** gave the first public demonstration of ether as an anaesthetic The patient inhaled from a blown glass flask during an operation performed at the Massachusetts General Hospital in Boston.

Gustav Robert ***Kirchhoff***, who with Bunsen, established the theory of spectral analysis, died on Oct. 17, 1887, the same day as *William* ***Cookworthy*** in 1780. The latter chemist pioneered the manufacture of porcelain in Britain. Sir *William Jackson* ***Pope***, who broadened understanding of stereoisomerism, died 70 years ago this same day.

Christian Friedrich ***Schönbein***, the German-Swiss chemist who discovered and named ozone in 1840 and was the first to describe guncotton (nitrocellulose), was born on Oct. 18, 1799, the day 40 years ago that cyclamates were banned in the US. Oct. 19 marks the 5th anniversary of the death of *Lewis* ***Urry***, the Canadian-American chemical engineer who invented alkaline and lithium batteries. It is also the 72nd anniversary of Sir *Ernest* ***Rutherford***'s death.

October 20 marks 25th anniversary of the deaths of *Paul A. M.* ***Dirac*** (the English physicist and mathematician who originated quantum mechanics and the spinning electron theory) and *Carl* ***Cori***. Cori teamed with his wife and discovered in 1933 a phosphate-containing form of the simple sugar glucose and its universal importance to carbohydrate metabolism.

October 21 is the birth date of *Alfred* ***Nobel*** (1833) and the 130th anniversary of ***Edison***'s demonstration of the first durable and commercially practical electric light bulb. It marks 185 years since Portland cement was patented by Joseph Aspdin.

On Oct. 23, 1803, *John* ***Dalton*** presented an essay at the Manchester Literary and Philosophical Society on the absorption of gases by water, at the conclusion of which he gave a series of atomic weights for 21 simple and compound elements. On Oct. 27 in 1938, Du Pont announced a name for its new synthetic fibre yarn: ***nylon***.

October 28 marks the 95th anniversary of the births of *R. L. M.* ***Synge***, the British biochemist who shared the 1952 Nobel Prize for Chemistry (with Martin) for the development of partition chromatography and Dr *Jonas Edward* ***Salk***, who developed the first safe and effective vaccine for poliomyelitis.

125 years ago on Nov. 1 in 1884, Greenwich Mean Time (GMT) was adopted universally at the International Meridian Conference in Washington, DC. *Thomas* ***Anderson***, the Scottish organic chemist who discovered pyridine, died on Nov. 2 in 1874, 135 years ago. *Thomas* ***Midgley***, Jr. died 65 years ago on the same day. He was the chemist who discovered the effectiveness of tetraethyl lead as an antiknock additive for gasoline in 1921.

Born on 3 November 1749 and died 15 Nov 1819, *Daniel* ***Rutherford*** was the Scottish chemist who discovered the portion of air that does not support combustion. He let a mouse live in a confined quantity of air until it died, then burned a candle and burned phosphorus in the same air as long as they would burn. He presumed what remained was carbon dioxide, which he dissolved by passing it through a strong alkali. Yet there still remained gas and it was incapable of supporting respiration or combustion. He called it *phlogisticated air* following the phlogiston theory of Stahl. It was later properly described by Lavoisier as nitrogen. He was also the first to design a first maximum-minimum thermometer.

Ralph ***Wyckoff***, the American pioneer of X-ray methods for crystal structure determination and one of the first to apply them to biological substances, died 15 years ago on Nov. 3. November 4 marks the 140 years since the first issue *Nature* was published, while on Nov. 7, 1908, *Ernest* ***Rutherford*** announced in London that he had isolated a single atom of matter.

Born 155 years ago on Nov. 8 was *Johannes Robert* ***Rydberg***, known for the constant, which carries his name and relates the wave numbers of spectral lines of an element. The following day, Nov. 9, is 15 years since element 110 darmstadtium (Ds) was detected Darmstadt, Germany.

Joseph ***Black***, the British chemist and physicist who experimented with *fixed air* (CO_2), discovered bicarbonates and identified latent heat, was born Nov. 10, 1799. *Nicolas-Louis* ***Vauquelin***, the French chemist who discovered the elements chromium (1797) and beryllium (1798), died 180 years ago on Nov. 14, and *Alfred* ***Werner***, the French-born Swiss chemist whose founding research into the structure of coordination compounds brought him the 1913 Nobel Prize, died 90 years ago the next day.

Carl von ***Linde*** died 75 years ago on 16 Nov. He invented a continuous process of liquefying gases in large quantities that forms the basis for the modern technology of refrigeration. November 17 marks the opening of the Suez Canal in 1869, while the 18th marks 39 years since *Linus* ***Pauling*** declared that large doses of vitamin C could ward off colds.

November 20th is the 5th anniversary of *John Robert* ***Vane***'s death. He was the English biochemist, who shared the 1982 Nobel Prize for Physiology or Medicine (with Bergström and Samuelsson of Sweden) for their isolation, identification, and analysis of prostaglandins.

Johan August ***Brinell*** was born on Nov. 21 1849. This Swedish metallurgist devised the hardness test named after him for the rapid, non-destructive means of determining the hardness of metals. On the same day 5 years ago *Audley Bowdler* ***Williamson***, the British inventor and manufacturer of skincare products died; he invented Swarfega, the hand cleaner. November 22 marks 200 years since the first US patent for a writing pen was issued to *Peregrine* ***Williamson***.

The 125th anniversary of the death of *Hermann* ***Kolbe*** is on November 25. *Chaim* ***Weizmann***, the Russian-British-Israeli chemist who used bacteria for the synthesis of organic compounds was born 135 years ago on Nov. 27, the day the electric motor was invented by *Thomas* ***Davenport*** in 1834. On this same day 20 years ago the first living liver transplant was performed.

Enrico ***Fermi*** died on Nov. 28, 1954 as did *Lewis Hastings* ***Sarett*** ten years ago on Nov 29. The latter was the American

chemist who synthesized synthetic cortisone in 1944. *Andrew Jackson* ***Moyer***, who invented a method for mass producing penicillin,was born 110 years ago on Nov. 30. On the same day 10 years ago *Robert A*. ***Swanson***, the co-founder of Genentech, Inc. (1976), the company that pioneered the biotechnology industry, died.

The 50th anniversary of the first colour photograph of earth being taken from outer space is on Dec. 1, whist the 3rd marks the 25th anniversary of the Bhopal chemical leak disaster. December 7 marks 100 years since the first plastic was patented; *Leo* ***Baekeland*** received his US patents for Bakelite in 1909. The day marks 120 years since *John Boyd* ***Dunlop***, a Scottish inventor, was issued a patent for his pneumatic tyre. It is also the day 125 years ago (1884) that *Louis* ***Pasteur*** made his much-quoted remark: *In the fields of observation chance favours only the prepared mind (Dans les champs de l'observation le hasard ne favorise que les esprits préparés)*. December 7 is also the birth date of *Fritz* ***Haber***, *Claude Louis* ***Berthollet*** and *Carl Wilhelm* ***Scheele***.

Element 111 was discovered 15 years ago on Dec. 8, while Dec. 9 is the 90th birthday of *William Nunn* ***Lipscomb***, Jr who won the Nobel Prize for Chemistry in 1976 for his research on the structure of boranes.

John W. ***Macklin***, the African-American analytical chemist who refined the technique of Raman spectrometry to test very small sample sizes has his 70th birthday on Dec. 11, while *Ludwig* ***Mond***, the German-born British chemist and industrialist who perfected a method of soda manufacture by improving the Solvay alkali process, died 100 years ago on the same day. It is also the day 165 years ago that nitrous oxide was first used for a tooth extraction.

Maurice ***Wilkins***, the New Zealand-born British biophysicist was born on Dec. 15, 1916. It is also the 25th anniversary of the death of *Frank Harold* ***Spedding***, the American chemist who made the individual rare-earth elements available to industry at reasonable prices. Sir *Ernest* ***Marsden***, the British-born New Zealand nuclear physicist, died on this day in 1970. On Dec. 15 in 1939, nylon yarn was sold to hosiery mills to make women's stockings. It was the first use of commercial yarn for apparel.

Bruce Nathan ***Ames***, the American biochemist and molecular biologist who developed the test that carries his name as an indicator of the carcinogenicity of chemicals, is 80 years old on Dec. 16. *Herbert C*. ***Brown***, the English-born American chemist who developed organoboranes, died 5 years ago on Dec. 19.

Cyril ***Ponnamperuma***, the Ceylonese-American chemist and exobiologist who was a leading authority on the chemical origins of life, died on Dec. 20, 1994. On Dec. 20 130 years ago, in 1879, *Thomas A*. ***Edison*** privately demonstrated his incandescent light at Menlo Park. *Charles Benjamin* ***Dudley*** was the American chemical engineer who supported the standardization and material testing in industry; Dec. 21 marks 100 years since his death.

In 1879, the liquefaction of oxygen was announced on Dec. 22 by *Raoul Pierre* ***Pictet*** (1846-1929), by sending a telegram to the French Academy: *Oxygen liquefied today under 320-atm and 140 º of cold by combined use of sulfurous and carbonic acid*.

On Christmas day in 1914, the thyroid hormone, thyroxine, was first crystallized by biochemist *Edward C*. ***Kendall*** of the Mayo Foundation in Rochester, NY. December 26 is the 5th anniversary of the death of *James Francis* (*Frank*) ***Pantridge***, the Irish cardiologist who developed the life-saving portable defibrillator.

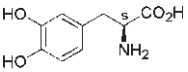
Nobel Laureate *Kary B*. ***Mullis***, the American biochemist who invented the polymerase chain reaction (PCR), is 65 years old on Dec. 28, the day 160 years ago that dry-cleaning was apparently discovered by *M*. ***Jolly-Bellin***. Apparently he upset a lamp containing turpentine oil on his tablecloth and noticed it had a cleaning effect. December 30 represents 85 years since *Edwin* ***Hubble*** announced the existence of another galactic system in addition to the Milky Way

William Merriam ***Burton***, the American chemist who devised the first thermal cracking process that more than doubled the proportion of gasoline yield from crude oil by using high heat and high pressure, died 55 years ago on Dec. 29.

Sir *Alastair* ***Pilkington***, founder of the glass industrial company that carries his name and inventor of the float glass process, died 90 years ago on Jan. 7. *Valdimir* ***Prelog*** died the same day 12 years ago. He shared the 1975 Nobel Prize for Chemistry (with Cornforth) for his work on the stereochemistry of organic molecules and reactions. January 7 also marks the 400th anniversary of Galileo dating his first letter describing the moon craters which he saw using his twenty-powered spyglass.

Fukui ***Kenichi***, the Japanese chemist who shared the 1981 Nobel Prize for Chemistry (with Hoffmann) for investigations of the mechanisms of chemical reactions, died on Jan. 8, 1998. In 1952, at Kyoto University, Fukui introduced his now famed *frontier orbital theory of reactions*. January 11, 80 years ago (1930), the element Fr (francium) was discovered whilst the 13th marks 400 years since Galileo Galilei discovered Callisto, the fourth satellite of Jupiter.

Benjamin ***Silliman***, Jr., whose reports on the potential uses of crude-oil products gave impetus to plans for drilling the first producing oil well near Titusville, PA, died 125 years ago on Jan. 14. On the same day 40 years ago in 1970, L-dopa (4-dihydroxy-L-phenylalanine) was reported to benefit about 5% of the patients in reversing the progress of Parkinson's disease.



L-dopa

William ***Prout***, the English chemist and biochemist noted for his discoveries concerning digestion, metabolic chemistry, and atomic weights, was born on Jan. 15, 1885, 125 years ago. January 17 is the 100th anniversary of *Friedrich Wilhelm Georg* ***Kohlrausch***'s death. He was the German physicist who investigated the properties of electrolytes and contributed to the understanding of their behaviour. Some of Kohlrausch's pioneering achievements include conductivity measurements on electrolytes.

Sir *Edward* ***Frankland***, the English chemist who was one of the first investigators in the field of structural chemistry, invented the chemical bond, and became known as the father of valency. He was born on Jan.18, 1825. *André-Marie* ***Ampère*** was born on Jan 22, 1775.

Conference Calendar

BIT's 7th Annual Congress of International Drug Discovery Science and Technology

Shanghai, China, 22-25 October.

Further details available at the website: *http://www.iddst.com*

22CRC 22nd Conference of Residue Chemists

Sydney, Australia, 9-12 November 2009.

Further details available at the website: *http://www.crcaustralia.com.au/*

11th Frank Warren Conference, covering all branches of organic chemistry

Pietermaritzburg, South Africa, 17-21 January, 2010.

Further details available at the website: *http://chemweb.unp.ac.za/FW2010/*

ICONN 2010, International conference on nanoscience and nanotechnology

Sydney, Australia 22-26 February 2010.

The 2010 International Conference on Nanoscience and Nanotechnology (ICONN 2010) will bring together the Australian and International community working in the field of nanoscale science and technology to discuss new and exciting advances in the field. ICONN 2010 will cover nanostructure growth, synthesis, fabrication, characterisation, device design, modelling, testing and applications.

Further details available at the website: *http://www.ausnano.net/iconn2010/*

Third International Conference on Semiconductor Photochemistry

Strathclyde, United Kingdom, Europe 12-16 April 2010,

Further details available at the website: *http://www.sp3conference.com/*

ICCC39, 39th International Conference on Coordination Chemistry

Adelaide, Australia, 25-30 July 2010.

ICCC39 will encompass all aspects of coordination chemistry through plenary, keynote and section lectures and poster presentations.

Further details available at the website: *http://iccc2010.eventplanners.com.au/*

Pacifichem 2010

Honolulu, Hawaii, 15-20 December 2010

The goal of Pacifichem 2010 is to promote collaborations among Pacific Basin chemical scientists that will improve the quality of life around the world. It is a very large chemical congress attracting ~15,000 chemists and a similar number of papers. It is organised around several hundred symposia, suggested by chemists from the region on the basis that they represent current cutting edge and 'hot' topics in chemistry.

Further details available at the website: *http://www.nzic.org.nz/pacifichem.html*

Grants and Scholarships

2010 Dumont d'Urville NZ/France S&T

Applications for the 2010 Dumont d'Urville NZ/France S&T Support Programme are now being called for to promote and support scientific and technological cooperation between New Zealand and French researchers in the public, non-government and private sectors in the fields of renewable energy, biotechnology, and nanosciences.

See: *http://www.royalsociety.org.nz/Site/International/dUrville/default.aspx*

Deadline 4pm Monday 12th October 2009.

International Science and Technologies Linkage funds.

1. To support international science and technology links between New Zealand and the world.

   The next round of applications is expected to be in October 2009.

   See: *http://www.royalsociety.org.nz/site/funding/isat/default.aspx*

2. To support international science and technology links between New Zealand and Germany.

   It is expected that applications for the 2010-11 year be open in December 2009.

   See: *http://www.royalsociety.org.nz/site/funding/germany/default.aspx*

3. To support international science and technology links between New Zealand and Spain.

   It is expected that applications will be called for in September 2009.

   See: *http://www.royalsociety.org.nz/Site/funding/spain/default.aspx*

Ramsay Memorial Fellowships for Chemical Research (Postdoctoral)

The Trustees will, in February 2010, consider applications for the award of General (British) Ramsay Memorial Fellowships.

The Fellowship(s) will normally be tenable in the United Kingdom for two years from 1 October 2010. Candidates will generally be expected to have had already some postdoctoral experience of research, although this should normally not have exceeded two years. The value of a Fellowship will be £30k per annum. Although the Fellowship may be fully funded by the Trust, the expectation is that it will normally be co-sponsored and jointly funded either by a university department, an industrial company or another body approved by the Trustees. Where this is the case, the Trust will contribute 50% towards the total salary costs of the Fellowship, up to a maximum of £15,000 per annum, with the balance of all other costs to be paid by the co-sponsor. In addition, a limited grant, usually not exceeding £1,000 per annum, may be requested for (non-travel) expenses.

Further information and application forms are available online at *http://www.ucl.ac.uk/ramsay-trust/* or from the Executive Secretary, Ramsay Memorial Fellowships Trust, c/o Academic Services, University College London, 2 Taviton Street, London WC1E 6BT, UK; telephone (0207) 679 8592; fax (0207) 679 8595; email: *h.lilley@ucl.ac.uk*

Completed application forms must be received by no later than 15 November 2009.

Wool Research Organisation of New Zealand Inc and New Zealand Wool Industry Charitable Trust Post Doctorate Fellowships

These fellowships are for holders of PhDs for study and research in topics related to wool including protein chemistry and process chemistry. Successful applicants receive a stipend of between $50,000-$65,000 per year for up to three years.

Applications close 31 October 2009.

For further details and the research topics given priority see the website: *http://www.meatandwoolnz.com/main.cfm?id=233*

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