



Toxicology Group Newsletter 2021

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Dear Readers,

Welcome to the Toxicology Group's Newsletter for 2021.

We are beginning to dip our toes back into the water of in-person scientific meetings. Please see the 'Forthcoming Meetings' section for details of the RSC Toxicology Award Seminar (in November) and the ever-popular Current Issues in Contaminated Land Risk Assessment (in December). Both will be available as either face-to-face or virtual formats to maximise accessibility and choice. There are also meeting reports from various on-line meetings that have been held.

Alan Lansdown – a member - has provided a viewpoint on the toxicology of silver and Andy Smith provides a reflection on one of John Hoskins' many contributions to toxicology, which has been acknowledged in a review article more than 30 years later. A fitting tribute to a valued colleague and long-serving RSC Toxicology committee member who sadly died earlier this year.

Enjoy the reading, be well, and stay safe.

Kate Jones
Chair, RSC Toxicology Group

Committee members

Chair: Kate Jones (HSE)

Treasurer: John MacLachlan (retired)

Secretary: Chris Waine (bibra)

Members: Lindsay Bramwell (Newcastle University), Sarah Bull (WRc plc / TARA Consulting), David Hart (retired), Mark Hosford (International Platinum Group Metals Association), Anais Kahve (Exponent), Trudy Knight (Birmingham University), George Kowalczyk (Consultant), Jo Lerner (University of Hertfordshire), Mike Quint (Consultant), Martin Rose (Consultant), Paul Russell (Unilever), Ovnair Sepai (UKHSA), Andrew Smith (MRC-Leicester),

Keep in Touch

MyRSC is the RSC's social media platform. RSC Toxicology has a group on this site, and we would encourage you all to sign up via the link below:

<http://my.rsc.org/groups/home/462>.

This is an easy way for us to share information about the group and to have discussions. Our web pages will continue to host forms and more static content.

We've now got 290 people signed up to the MyRSC group – but as we have nearly 500 Toxicology group members, there's still a way to go to get everyone on board!

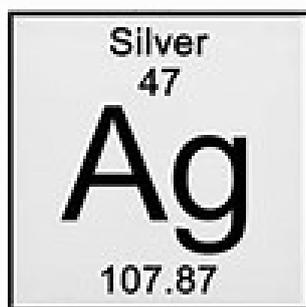
In recognition that not everyone wants to use MyRSC, we also have a **LinkedIn** group (<https://www.linkedin.com/groups/12014086>) and a **Twitter** account ([@RSCToxGroup](https://twitter.com/RSCToxGroup)). Please do join in with the conversation!



The Toxicology of Silver – a viewpoint

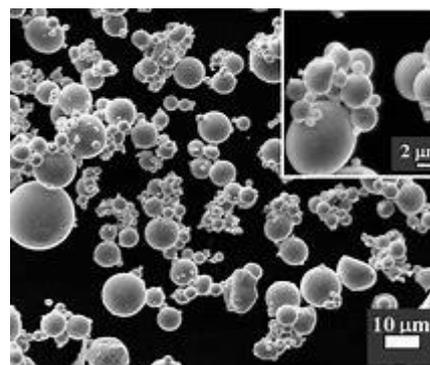
This is a personal view of one of our members, Dr Alan Lansdown FRSC (Faculty of Medicine, Imperial College, London).

FUNDAMENTAL MISCONCEPTIONS ON THE TOXICOLOGY OF SILVER



Silver has been recognised for its antimicrobial properties for more than 100 years and in that time, metallic silver, nanoparticulate silver (AgNP) and certain silver compounds have been employed in medical practice, a vast range of medical devices, and the disinfection of water. In the early days, silver nitrate was the mainstay of silver antibacterials, but more recently this has been largely superseded by less corrosive silver preparations with a lower toxic risk. In compliance with regulatory guidelines for safety, elemental silver, AgNP and other silver preparations have been extensively evaluated from clinical case studies, experimental studies in animals and in cell and tissue explants in culture. Review of major assessments recently has shown several major misconceptions in the physico-chemical properties of elemental silver and AgNP, and their interaction with and metabolism in mammalian systems. Such misconceptions have led to erroneous conclusions and predictions of human safety.

Silver is one of the least toxic of elements in the Periodic Table. It is marginally soluble in moisture, body fluids and secretions (<1 µg/mL), and is absorbed into the body following ingestion, inhalation, implantation of medical devices, or penetration through skin wounds. Fundamental studies conducted by Robert Burrell (2003) in Canada emphasised that the solubility of silver and release of the biologically active ion Ag⁺, is proportional to the surface area of particles. Nanocrystalline silver particles with a crystal size of <20 nm show a solubility in water of 70-100 µg/mL and proportionately higher antibacterial action and absorption. Birringer (1989) studied the physico-chemical form of silver particles and claimed that AgNP showed atomic changes in the 'grain boundary' region, possibly representing a new state of solid matter. In his view, "the dissolution process reaches a steady state condition dependent upon temperature when silver concentrations in solution are between 70 and 100 µg/mL.



Absorption of silver and its metabolism in the mammalian body are poorly recognised in many reviews. A proportion of elemental or AgNP ingested with the diet or administered orally is excreted but some is endocytosed by the gastrointestinal epithelium or absorbed as Ag⁺. Silver inhaled as dust or AgNP can be expected to be endocytosed by pulmonary epithelia, lymphocytes and macrophages. Metallic silver or Ag⁺ is not absorbed percutaneously through skin in view of the effective keratin barrier function. Keratinised cells of the trachea will presumably limit silver penetration by this route. Although there are numerous reports of silver related pathology in the eye (argyrosis) and functional changes, I have seen no evidence that silver is absorbed directly into the eye.

A common misconception in silver toxicology is a failure to recognise that the biologically active Ag⁺ ion induces and binds key intracellular proteins, notably the cysteine rich metallothioneins (MT), and macroglobulins and albumins. As protein complexes, silver enters the circulation to be deposited in tissues remote from the site of its absorption. A small amount is retained in an inert fashion in liver, kidney, muscle and other soft tissues. I have not studied silver precipitation or retention in bone or tooth but contrary to many opinions, there is no clinical or experimental evidence that silver or Ag⁺ pass across the blood brain barrier (Lansdown, 2008). Where silver is reported in the brain or other neurological tissues, it is confined to vascular tissues. Silver in the form of protein complexes is eliminated in bile and in urine. Occasional reports refer to pathological changes in liver and kidney but there is minimal evidence that either organ is a target site for silver toxicity. Transitory changes in metabolising enzymes are reported, but silver protein complexes in tissues are inert. (Renal pathology is seen where silver nitrate is instilled directly into the renal pelvis to treat infections.) The reader is referred to research demonstrating the cytoprotective role of metallothioneins (I and II), which act as carrier proteins for certain trace and xenobiotic metals (e.g., Cu, Zn, Cd, Hg, Pb).

The skin and eye are principal target organs for silver toxicity. Neither argyria or argyrosis characterised by precipitation of silver sulphide or silver selenide in dermal or conjunctival cells, are life threatening but the long-standing or permanent discolorations can be highly disfiguring. The two conditions are frequently seen concurrently in people exposed chronically to silver dust or emissions in industry, long term implantation of silver-containing medical devices, but rarely in the clinical application of silver as an antibacterial in wound care, catheters or textiles. A large proportion of the clinically reported cases of argyria in recent years relate to the use of the so-called "colloidal silver" products. They are sold through clandestine means and are not licenced for sale in Britain, USA and many other countries. Far reaching claims for their efficacy in treating diseases of many types are unfounded and not justified by clinical or experimental research. The silver content, chemical formulation and potential for ionisation of products like Argyrol, Protargol etc are not documented.

My final concern relates to predictions of silver toxicity based upon experimental studies in animals. There is no suitable surrogate for the human in many branches of toxicology and at best, experiments in rats, mice, dogs etc can only serve as a guideline for risk assessment in more definitive clinical studies. As illustrated by earlier work on the inhalation toxicology of titanium dioxide, animal models do not exhibit comparable respiratory patterns nor anatomical and cellular profiles in the pulmonary tract to humans. Particle deposition and toxic responses were quite different. Similar findings are seen in the very limited and widely scattered information available on the inhalation toxicology of silver dusts, sprays, vapours and airborne AgNP. At the moment, most information concerning health risks through inhalation of elemental silver and AgNP derive from occupational health reports. These are inconsistent and vary greatly in detail and circumstances of exposure. Some have concluded that “the health effects of exposure to silver nanoparticles in humans are still largely unknown”. This is a frank misconception.

References

- Burrell, R.E (2003) A scientific perspective on the use of topical silver preparations, *Ostomy Wound Management*, 49, 19-24.
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- Lansdown, A. (2007) Critical observations on the neurotoxicity of silver. *Crit Rev Toxicol.* 37 ,237-50.

Forthcoming Meetings

Please take note of the following meetings and sign up early to avoid disappointment. Bursaries are available to any RSC Toxicology member for attendance at our meetings, subject to the usual [conditions](#).

Toxicology Award Seminar

10 November 2021, London, United Kingdom

Professor Kelly received the 2019 RSC Toxicology Award for researching free radical/antioxidant toxicological mechanisms relevant to pulmonary toxicity, monitoring and modelling of chemicals in city air pollution and effects on human health, and leadership in the risks from compromised air quality. This seminar will feature Professor Kelly and several of his colleagues.

Prof Frank Kelly - Air Pollution and Health: oxidant/antioxidant wars in the respiratory tract

Dr Ian Mudway - Air Pollution Metalomics

Dr Stephanie Wright - Characterising microplastic exposure and effects

Dr Leon Barron - Rapid risk assessment approaches for emerging chemical contaminants in the environment

This is a free to attend event supported by the RSC Toxicology group but we would like to ask for donations to [Pancreatic Cancer UK](#) in recognition of one of our long-standing committee members, [Dr John Hoskins](#), who died earlier this year.

2021 Current Issues in Contaminated Land Risk Assessment

8 December 2021, London, United Kingdom

An annual meeting to update those in the field on new and emerging topics in contaminated land risk assessment.

Posters are welcome - contact info@sobra.org.uk.

[Toxic Tort in the UK: Current Perspectives and Recent Cases](#)

Postponed to 2022. A new joint meeting with [UKELA](#).

A one-day event of discussion and case studies to bring together practicing lawyers and legal academics, with toxicologists and scientists, to increase understanding between the two and to understand each other's strengths and limitations.

[Airmon 2022](#)

The 10th International Symposium on Modern Principles of Air Monitoring and Biomonitoring. This symposium is the leading international forum at which recent progress in workplace, residential and environmental exposure assessment strategies and associated analytical air sampling and biomonitoring methodologies can be discussed and takes place in Bristol, United Kingdom between **7th–10th November 2022**.

Abstract submissions for oral presentations and poster presentations are now open. Abstract submission closes on Friday 20th May 2022.

Submissions are welcome in any areas of air monitoring and biomonitoring including:

- Air sampling / Air samplers / Analytical measurements / Biomonitoring
- Direct reading instruments / Emerging measurement requirements
- Epidemiology / Exposure assessment and modelling
- Method comparability/ Harmonisation/ Quality assurance standardisation/ Validation
- Sensors
- Test chamber workplace simulation studies

Meeting Reports

Plastics, From Cradle to Grave – and Resurrection II

A virtual meeting was held jointly by the RSC (Toxicology, Food & Environmental Chemistry groups) and the SCI on June the 9th 2021. Further to the successful conference held in 2019, a follow up one was organised to expand on the key themes, looking at where we have come from, where we have got to and where we want to go.

This conference brought together academic and industrial speakers with the aim of focussing on assessing challenges and opportunities for researchers, industry and Government. There was a thematic link between the current use of plastics, toxicology and standardisation, the complex issues with respect to fit for purpose sampling and analysis, and the future of plastic usage.

Presentations and speakers included:

- Plastics, packaging and politics update 2021 - Stuart Foster, Chief Executive Officer, Recoup
- Implications of the WHO Microplastics in drinking water 2019 report - Peter Marsden, Principal Inspector Drinking Water Inspectorate, UK (Recently retired)
- Microplastic removal in drinking water processes: coagulation flocculation - Dr Pablo Campo-Moreno, Cranfield University, Lecturer in Applied Chemistry
- The potential impact of microplastic pollution on the environment and human health - Dr Natalie Welden, University of Glasgow
- Microplastics in Scottish Waters: what has been done and what needs to be done? - Prof Colin Moffat, Marine Scotland Chief Scientific Advisor, Scottish Government
- Benefits and risks of plastics in healthcare (will include associated pollutants in plastics) - Dr Anne Woolridge, Independent Safety Services Ltd (ISSL)
- Plastic-free London Project: Campaign Issues - Mike Simmonds
- Compostable packaging and food waste management - David Newman, Managing Director, Bio-based and Biodegradable Industries Association (BBIA)
- Reducing Plastics in the Environment - Judy Proctor, Environmental Agency

One of the highlights of the meeting was a presentation by Dr Natalie Welden:

The Potential Impact of Microplastic Pollution on the Environment and Human Health



Dr Natalie Welden, is a Lecturer in Environmental Science and Sustainability, School of Interdisciplinary Studies, University of Glasgow and is a marine biologist and ecotoxicologist with a decade's research experience in the field of microplastic pollution. Her previous publications have explored the chemical and mechanical breakdown of large plastic debris, including polymer fibres, the transport and deposition of microplastics, and their uptake and impacts in aquatic species. Within her

work, there has been a key focus on the effects of microplastic fibres on nutritional state and survivorship in commercially important species, as well as on potential solutions to the issue of plastic pollution. Natalie's solutions-focused outlook has resulted in numerous projects with stakeholders, recently collaborating with the Women's Institute in support of their "End Plastic Soup" campaign and subsequent "In a Spin" report which publicised the issue of microplastic fibre pollution and explored how we in the UK treat our clothes, and a partnership with innovation start up Matter and white goods manufactures Beko on an Innovate UK funded project aimed at reducing microplastic fibre pollution from domestic washing machines.

Despite over a decade of high interest in microplastic pollution, there is still so much we don't know. While we have found microplastics in remote places, including snow, mountain lakes and in deep-sea sediments, it appears that the highest levels of contamination are generally close to areas of high anthropogenic activity, in proximity to their main sources. Wildlife in these areas appears to be the most readily affected too. From a brief scan of the literature, you can find records of interactions between microplastics and organisms from across the aquatic food web and, increasingly, in terrestrial species. However, not all species are affected equally. Feeding mode, feeding rate and morphology all influence plastic ingestion, as does the size of the organism in relation to the size of the microplastics available. Retained microplastic is also affected by residence time in the gut. Animals with large or simple guts may easily egest microplastics, limiting the potential for plastic aggregation to that consumed over a short period. But it can be an entirely different matter for those with complex and small structures. Indeed, it appears that microplastics and their effects are more prevalent in lower trophic organisms, which are typically smaller, morphologically complex animals.

Still, we only have a rough idea of what the implications of uptake by these organisms might be. Across the literature we see a patchy account of numerous effects observed across multiple species (although many of these can be grouped under similar themes) for example: changes in mortality, feeding, behaviour, growth, reproduction, histology, enzyme activity and even gene expression. However, the results of microplastic exposure vary greatly between species and there are regular reports of studies which demonstrated

no significant effects whatsoever. As a result, we must be careful when extrapolating from the reported observations.

Early observations of plastic in species for human consumption have unsurprisingly drawn a lot of public interest and, subsequently, there have been numerous papers and associated news reports regarding our exposure to plastics via food and drink in addition to airborne sources. Nevertheless, it is difficult to draw conclusions from the available data. If we wish to assess the risk to human health posed by microplastics we need to know the impact that they may have on humans, the level of exposure at which these effects might be seen, and the current level of exposure that we experience (do we or could we meet the thresholds at which damage occurs?).

In determining the potential effect of microplastic ingestion, there are a number of suggested outcomes in the literature. For example, it has been suggested that microplastic exposure could lead to responses including inflammation, genotoxicity, oxidative stress, apoptosis and necrosis. But many of these effects have been suggested as a result of observations of plastics in the human body from non-environmental or extremely concentrated sources, such as from the wear of prosthetics or the inhalation of fibres by factory workers.

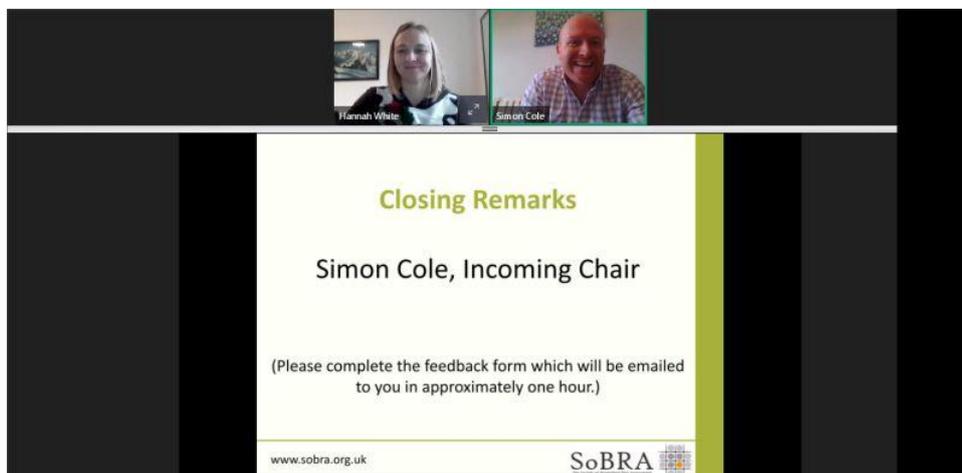
When we consider the level of microplastic to which we are exposed there is a more developed evidence base. We are aware of numerous exposure routes, some of which are recorded in multiple studies from which we might develop preliminary estimates of exposure. Subsequently, there have been cautious attempts to place a value on our daily inhaled and ingested particle counts. For example, Cox et al., in the *Journal Environmental Science and Technology* (2019) suggest a nominal value of between 126 and 142 particles consumed per day and 132 and 170 inhaled particles per day for adults, based on a typical US diet. But this accounting is by no means exhaustive.

However, we're currently unable to go much further, unable to fully determine the current risk or to establish safe threshold levels. As a result, we may struggle to recommend reasonable, measurable targets for microplastic reduction and face barrier when engagement with potentially reluctant stakeholders regarding measures to reduce microplastic outputs.

In many cases, we are ahead of the science when it comes to our response to microplastics. Public opinion has moved much faster than the evidence base and, while some of the resulting legislation will have a definite positive effect, we are lacking information on vital decision-making aspects such as comparative lifecycle assessments to underpin some of the suggested responses. Nevertheless, we shouldn't let minor data gaps stop us from making the small and sensible changes, and we should support constructive interactions with stakeholder throughout the plastic lifecycle to enable the sustainable use of plastic materials.

SoBRA December 2020 Conference

SoBRA's first virtual conference! Thank you to all those who tuned in to hear the outgoing Chair Hannah White outline the Society's activities of 2020 and the plans for 2021. The incoming Chair is Simon Cole.



[View programme & presentations](#)

BTS virtual Congress 2021

The BTS Congress also went virtual. The RSC Toxicology Group supported a session on "Experimental data and uncertainty modelling", which was chaired by RSC Toxicology committee member Dr Paul Russell (Unilever).

The presentations and speakers included:

- Characterising uncertainty within in vitro models for safety assessment in early drug discovery - Dr Delyan Ivanov (AstraZeneca, UK)
- Integration of experimental data into skin allergy modelling - Dr Gavin Maxwell (Unilever, UK)
- Determining points of departure from multivariate experimental data - Dr Imran Shah (EPA, North Carolina, USA)
- In silico screening for endocrine disruption hazard identification - Dr Elena Fioravanzo

Planning is already underway for the 2022 BTS Congress with RSC Toxicology proposing a session on 'Confidence in predictive models' to complement and build on the successful 2021 session.

Poster Prize at Exposure Science 2021

The 8th UK & Ireland Occupational and Environmental Exposure Science Meeting 2021 was held virtually on 10th June 2021. Presentations and speakers included:

Keynote lecture: Prof Andrew Meharg (Queen's University Belfast) - Human Exposure to Inorganic Arsenic in Rice

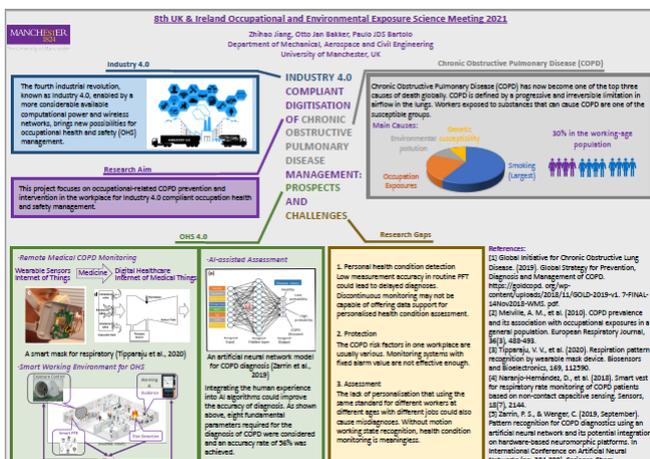
Prof. Kraichat Tantrakarnapa (Mahidol University, Thailand) - TAPHIA: Thailand Air Pollution and Health Impact Assessment

Kate Jones (Health and Safety Executive, UK) - HBM4EU: Biomonitoring exposure to chromates

Dr Miranda Loh (Institute of Occupational Medicine, University of Edinburgh) - Exploring interventions for reducing SARS-CoV-2 in hospital environments

Plus, there were short overviews from the poster presenters. RSC Toxicology sponsored a poster prize that was awarded to Zhihao Jiang for his poster on 'Industry 4.0 Compliant Digitisation of Chronic Obstructive Pulmonary Disease Management: Prospects and challenges'.

"As my first international conference, I found the 8th UK & Ireland Occupational and Environmental Exposure Science Meeting 2021 a highly relevant and very useful event for me. All the technical presentations were excellent and inspiring. The event attracted researchers in exposure science from all over the world and offered an opportunity for them to share, which is quite precious, especially during this hard time of COVID-19. In this meeting, high quality lectures covering different topics in the field were delivered, and that could help widen horizons and inspire thinking. Additionally, there was a series of presentation accompanying a variety of excellent e-posters. As a winning entrant, I'd like to say it was a tough competition and I learnt a lot from the others' work. I'm very pleased to receive the best poster award, especially considering the high quality of the other posters. I'm looking forward to participating in the next edition and I'll fully recommend this conference to my colleagues. Best wishes, Zhihao."



Zhihao Jiang UKI
OEEES 2021.pdf

Sustainability

A sustainable future for chemistry encompasses a wide range of disciplines, technologies, applications and behaviours. The RSC has collated a collection to showcase the innovation and insights of leading companies that are making the shift to a more sustainable future, both in their own operations and through supporting change in supply chains, regulation and consumer behaviour.

Faces of Toxicology



For those of you who have not yet checked out these videos, a playlist can be found [here](#). This video series aims to showcase the variety of careers available in toxicology. The series begins with an animated overview of toxicology as a science followed by individual toxicologists talking about their work. The Toxicology Group Committee is working to add further videos, so if you are interested in being a 'face' of toxicology, please [get in touch](#).

We are continuing to add new videos; another (Dr Hazem Matar) should be added shortly. Some of the videos are now available on the RSC's education platform [A Future in Chemistry](#).

Chemistry Humour

I tried writing jokes about the periodic table...
... but I realised I wasn't quite in my element.

Oxygen, hydrogen, sulphur, sodium, and phosphorous walk into a bar.
"OH SNaP!" says the bartender.

More required ... or maybe not!

Dr John Hoskins and Phenylketonuria Therapy



John Hoskins was an analytical chemist and longstanding member of the Toxicology Group Committee and a past chairman. Sadly, he passed away earlier this year while still very much interested in the work of the RSC. John was always good company and source of information.

For many years John was an independent consultant on aspects of fibre toxicity originating from his later years of employment at the Medical Research Council (MRC). However, in the first period of his career after obtaining a PhD in the Australian National University in Canberra, John was a member of the MRC Unit of Metabolic Studies in Psychiatry at the University of Sheffield and then the Toxicology Unit in Carshalton and Leicester. At this time, he studied aspects of amino acid metabolism including the possibility of treating phenylketonuria (PKU), a classic genetic disorder. PKU is caused by a deficiency in phenylalanine hydroxylase (PAH), resulting in neurotoxic levels of excess phenylalanine due to its lack of conversion to tyrosine. At the time a plant enzyme phenyl ammonia lyase (PAL) was known to convert phenylalanine to cinnamic acid and so it was hoped that if a similar enzyme was administered orally to patients it would survive digestive proteolysis long enough to reduce the levels of the amino acid from food protein in the gut and therefore in subsequent plasma levels. To explore the potential in patients, John and his colleagues in the then Public Health Laboratory Services and an adjacent NHS children's hospital, encapsulated yeast PAL in semipermeable gelatin for oral administration. Firstly, to test its safety and impact in normal individuals, volunteers in the MRC Toxicology Unit (of which I was one) consumed VERY large steak dinners (chips were optional) followed by PAL capsules. Blood samples and questionnaires showed no apparent adverse effects. Following on from this, multiple administration of PAL to a PKU patient showed a significant decrease in plasma phenylalanine subsequently demonstrating it as the basis for a potential therapy regimen [1].

Over the next three decades a number of academic and company research groups, particularly in Canada and the USA, methodically tackled the many practical problems remaining after the initial proof of concept that PAL could be an enzyme substitution therapy for PKU. Adequate supply of PAL enzymes was resolved by recombinant techniques and mouse models of PKU were developed for careful experimental in vivo studies. Sustained intraperitoneal use caused immune responses and it was still difficult to prevent significant digestive loss if given orally. Eventually, crystal structures of PAH and PAL enzymes enabled structure-based engineering and mutants to attach polyethylene glycol molecules to stabilize and protect modified PAL enzymes while maximising activity and minimising immunogenicity following parenteral administration. After clinical trials the final product was authorised by the FDA in 2018, not only lowering plasma phenylalanine

levels after subcutaneous injection but long-term improving clinical assessments of neurological performance [2]. So far, an orally active form is not available for patients.

In a 2018 review paper, major collaborators described in detail this story and acknowledged the role John had played and emphasized the importance of academic-industry collaborations [3]. In these times, when huge amounts of research data is being generated, it's nice to know that not all old work is reported as new!

Andy Smith, MRC, Leicester

References

[1] Hoskins JA, Jack G, Wade HE, Peiris RJ, Wright EC, Starr DJ, Stern J (1980) Enzymatic control of phenylalanine intake in phenylketonuria. *Lancet* 1(now vol 395), 392-394

[2] <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pku-rare-and-serious-genetic-disease>

[3] Levy HL, Sarkissian CN, Scriver CR (2018) Phenylalanine ammonia lyase (PAL): From discovery to enzyme substitution therapy for phenylketonuria. *Mol Genet Metab* 124, 223-229