

## Toxicology Group Newsletter – Autumn/Winter 2011

Dear Members

Welcome to the second edition of the Toxicology Group newsletter for 2011. Thank you to everyone who has contributed.

We begin with a stimulating commentary by John Hoskins on the book 'Silent Spring', written almost 50 years ago by Rachel Carson, and its aftermath. This controversial work had an immediate impact on scientists, environmentalists, politicians and the general public which is still reverberating to this day. In 2012, the 50<sup>th</sup> Anniversary of its publication, it is hoped that the Toxicology Group will host a joint symposium, with 'Silent Spring' as its central theme, to examine all aspects of the tenet, and to review developments in environmental toxicology

There are also several 'Meeting Reports' covering the Group Meeting on the 'Toxicology of Nanoparticles', the 2011 EUROTOX Congress, and a link to Abstracts from the Autumn BTS Meeting.

In addition, Professor Shirley Price has provided an introduction to the Register of Toxicologists. Increasingly, as scientists, we need not only to provide general evidence of our continuing professional development (CPD) to maintain our Chartered status, but also to demonstrate to the outside world specific achievements in our chosen field. This is perceived as being particularly important in mainland Europe, and it should be noted that Members of the UK Register of Toxicologists gain automatic membership of the HEUROTOXH Register of Toxicologists (ERT).

I hope you find topics of interest in this edition - please let us know if there are other areas which you would like to see covered in future issues. Moreover, if you have any articles (and photographs) which you wish to submit for publication, or reaction to the Commentary which we hope will become a regular feature of the Newsletter, please e-mail them to me at the address given below.

Finally, on behalf of the Committee and the Toxicology Group Membership I should like to thank Kate Jones for all the hard work she has put into editing the Newsletter up till now, this in addition to the already onerous task of Secretary. It has recently been agreed that the two positions need be separated, and I will be responsible for editing the next few issues of the Newsletter until a permanent Editor has been appointed.

Lorna Wren  
RSC Toxicology Group Newsletter Editor (acting)  
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### The Committee:

#### Chair:

John MacLachlan (Glasgow  
Caledonian University)

#### Treasurer:

David Hart (AkzoNobel)

#### Secretary:

Kate Jones (HSL)

#### Members:

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Lorna Wren (Consultant)

#### Contents include:

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- Upcoming Meetings
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## **Silent Spring at 50: is Rachel Carson really dead?**

Fifty years on and we're still here. The human race has survived!

Yet in 1962 Rachel Carson predicted that technology would wipe us out by the 1980s. Then, her seminal work 'Silent Spring' published just two years before her death, described how man [*sic*] would destroy the biosphere and himself along with it. At the end there would be a "silent spring" in which "no birds sing". The book is rightly regarded as a classic and has been read by millions, and it led to a description of her as the first apocalyptic.

Everywhere, she wrote, were the signs of death - sickness, the disappearance of the birds, infertility, death of baby animals, failure of fruit crops because the bees had gone. No fish swimming in the streams. This, she considered, was no supernatural event - it had been done by man - and it would happen through the spraying of pesticides. The economic system with its attendant politics and regulation would promote the catastrophe. Poisonous chemicals, the lethal products of industry, would be the agents of destruction. Causing most damage, she perceived, were the two "sinister" partners man-made radiation and man-made chemicals in the unbroken chain of "evil" and death. These "unnatural", "synthetic" creations were rendering toxic the air, the water and the soil. Worst of the two were the chemicals, "unnatural" and "synthetic" creations. For the first time since man had appeared on earth he was now exposed to hazardous chemicals from the moment he emerged from the womb to the moment of death.

The worst chemical of them all was, in her eyes, DDT. The properties of DDT had been discovered in the 1930s and since then it had saved millions of lives. It appeared safe, it allowed farmers to stop using more obviously toxic arsenic-based pesticides and, in countries where malaria was endemic, it was the solution to the problem. But unfortunately it killed the good insects as well as the bad ones. Carson

was a passionate environmentalist who reasoned that wiping out the insects would eventually lead to the horror scenario of a 'silent spring'. This downside of DDT helped the cause of environmental groups whose lobbying led eventually, in 1972, to the EPA banning DDT, despite the considerable evidence that had been presented of its safety. A ban was enacted in spite of the EPA's own administrative law judge declaring: *"DDT is not a carcinogenic hazard to man...DDT is not a mutagenic or teratogenic hazard to man...The use of DDT under the regulations involved here [does] not have a deleterious effect on freshwater fish, estuarine organisms, wild birds or other wildlife."* For the environmentalists the ban was a great victory.

The politics that Carson so derided when used in support of 'big-industry' were also used by her to hasten the end of DDT. Carson had argued that DDT and other pesticides were not only harming wildlife but killing people too. Ignoring the science and insisting that DDT was a carcinogen, a claim she backed with obviously spurious examples, garnered public interest. This, together with the Delaney Clause passed by Congress some years earlier, which proscribed any chemicals in food suspected of causing cancer, led to the ban. Four decades and many studies later DDT has still not been shown to be a human carcinogen.

Although the ideas Carson expressed on carcinogens were not original, she was the first to reach a national audience. She pronounced on the essential non-carcinogenicity of nature saying that its role in cancer causation was negligible. For her, natural carcinogens were "few in number", limited to a few radioactive rocks, arsenic and UV from the sun and that evolution had shaped and directed us within the environment. 'Benevolent nature' was the result. She felt that the rot really set in with World War II when the planet became contaminated through "unnatural" production of radiation and great numbers of "sinister" chemicals. "Sinister" because they were "synthetic", artefacts of human intelligence manufactured in test-tubes and were substances which had no natural equivalents and to which no life could adjust. Man had created "the vast majority of carcinogens" and

could therefore get rid of them. She demanded their eradication to avoid the build-up of tiny doses that constituted the crucial threat to our lives.

In her lifetime she was a much-respected marine biologist, conservationist and writer but her last major work 'Silent Spring' defines her memory.

Its message was simple: '*we are responsible for the "sea of carcinogens" in which we swim.*'

**Submitted by: John Hoskins**

## MEETING REPORTS

### Toxicology of metallic nanoparticles

On 24<sup>th</sup> June 2011, the RSC Toxicology group held a one-day meeting on the 'Role of metals in the toxicity of nanoparticles: Informing the regulation of nanoparticulate safety'. The aim was to give an overview of the recent research in this area and to collate the toxicological opinions, particularly with reference to regulation. The current concern over the potential toxicity of nanoparticles (environmental, clinical and engineered) is often based on presumptions and uncertainties in their various modes of action. Greater understanding of the specific mechanisms would aid the risk assessment process.



Dr Andy Smith (MRC, Leicester) introduced the meeting giving his view of the current lack of knowledge of toxicological mechanisms for

metallic nanoparticles (NPs) and the tendency to presumption of the mode of action by grouping certain species. He posed a number of questions for the day including:

- How might metallic nanoparticles contribute to toxic and carcinogenic processes?
- Does the nano state have a specific role to play, other than as a provider of metallic ions?

Professor Ken Donaldson (University of Edinburgh) then covered a number of studies that had looked at various aspects of metallic nanoparticulate toxicology and presented data that he had compiled from a number of sources. First, he presented a number of data that demonstrated that smaller particles were better translocated (e.g. gold where a 10-fold increase in translocation across the lung air/blood barrier was seen for a 10-fold reduction in particle size) and caused greater inflammation. The inflammation was related to surface area in a linear response, across a number of particle types. He then went on to discuss the role of surface chemistry – different metal oxide NPs with the same surface area showed markedly different free radical activity. For insoluble particles, positive acid zeta potential seems to increase inflammation responses. For soluble particles, the toxicological impact seems directly related to the toxicity of the soluble species, for example  $\text{Cu}^{2+}$  and  $\text{Zn}^{2+}$  ions (from metal NPs) are highly toxic and inflammogenic whereas  $\text{Mg}^{2+}$  ions are not. Professor Donaldson finished his presentation with a discussion of metallic nanofibres and whether they fit the 'asbestos paradigm', where the toxicity is related to the high aspect ratio (AR) of the fibre. Metallic nanofibres can exist as nanorods (AR up to 5) and nanowires (AR up to 1000). Inflammation tests have shown that there is very little response to fibres less than 5  $\mu\text{m}$  in length; beyond this 'trigger point' there is a dramatic increase in inflammation, with an apparent length related increase up to ~20  $\mu\text{m}$  after which the response plateaus.

Professor Terry Tetley (Imperial College, London) followed with a presentation on the reactivity of NPs in the lung, specifically at the

alveolar interface. It is estimated that 50% of inhaled nano-sized objects will reach the alveoli. The alveolar surface consists of two cell types, type one (AT1) epithelial cells which cover 95% of the alveolar surface and type 2 (AT2) which are progenitors to AT1 cells. Professor Tetley's research group has undertaken a range of *in vitro* experiments, looking for AT1 cell responses to NP challenge. Little difference in IL-8 response was seen on dosing with TiO<sub>2</sub>, Ag, Wc or ZnO NPs. However IL-6 response was increased for all NPs and all doses with responses still elevated after 48 hours recovery (except for ZnO) although Ag and ZnO caused cell death at the higher doses. Polydispersed 244 nm Ag particles caused a significant increase in IL-8 whereas other smaller Ag particles (5 – 44 nm) with various coatings (sugar, PVP, citrate) didn't alter IL-8 release. The use of foetal calf serum (FCS, widely used in tissue culture) can also influence cell death and IL-6/IL-8 release – for CuO NPs the TD<sub>50</sub> was reduced 3-fold in the presence of FCS compared to without, whereas for ZnO the TD<sub>50</sub> was doubled in the presence of FCS (TiO<sub>2</sub> was unaffected). Experiments looking at the effect of different forms of TiO<sub>2</sub> on AT1 cell mediator releases showed that nanopowder (~600 nm) was no more likely to result in IL-6, IL-8 or MCP-1 release than standard TiO<sub>2</sub> (~950 nm), pure anatase (~300 nm) or pure rutile (~150 nm).

Next, Professor Jamie Lead (University of Birmingham) gave an overview of research into silver nanoparticles in the environment. In the environment NPs acquire coatings of organic matter (humus), this can cause aggregates of around 2.5 µm to disaggregate into ~30 nm particles over a 30-day period. Silver NPs were shown to be highly toxic to *pseudomonas sp.* when incubated in media alone but there was no observed effect on growth when incubated in humus-containing media. By contrast humus had no effect on the high toxicity of silver nitrate. The media causes aggregation so the high toxic response of silver NPs is therefore not explained by dissolution.

Professor Frank Kelly (King's College, London) presented results from a study on ambient particulate matter (PM) toxicity. It has been estimated that 29,000 deaths are due to

airborne particles. In cities, most of the particulate matter comes from traffic pollution and the problem has been exacerbated by the increase in the use of diesel. Particles consist of a carbonaceous core with components adsorbed onto the surface (organics e.g. PAHs, metals, biological material e.g. endotoxin). Three sites (semi-rural, urban residential and high urban traffic) were studied for oxidative potential of the PM collected at each site – the high urban traffic area showed greater oxidative potential (both as a fraction of PM and per unit volume air) than the other sites. The RAPTES (Risk of Airborne Particulates: A hybrid Toxicological- Epidemiological Study) study aims to assess the metal content and redox activity of ambient PM during human volunteer challenge. Volunteers were exposed to an underground train platform environment as well as a traffic intersection and an urban garden. Ambient iron-containing PM concentrations were 100x greater and PM<sub>0.18</sub> concentrations were 300x greater in the underground scenario. Nasal lavage samples showed that post-underground levels of iron PM deposits were three times greater than for the other scenarios. There was also evidence of increased redox activity of the PM deposited in the nasal cavity and this activity was correlated to the iron content of the nasal lavage fluid.



Continuing the iron theme, Dr Shareen Doak (University of Swansea) is studying the genotoxicity of iron oxide NPs. Ultrafine superparamagnetic iron oxide nanoparticles (USPION) have potential medical applications in MRI imaging, drug delivery and magnetic tumour ablation. There are three different

composition types –  $\text{Fe}_3\text{O}_4$ ,  $\gamma\text{-Fe}_2\text{O}_3$  and  $\alpha\text{-Fe}_2\text{O}_3$  and the supramagnetic properties rely on a particle size of  $<35$  nm. *In vitro* experiments showed that serum content had an impact on apparent hydrodynamic diameter (at 1% serum average diameter was 9x greater than at 10% serum for the same nominal 10 nm particles). Cellular uptake of dextran-coated  $\text{Fe}_2\text{O}_3$  was three times greater in 1% serum than 10% and also three times greater than dextran-coated  $\text{Fe}_3\text{O}_4$ . However uncoated  $\text{Fe}_2\text{O}_3$  was absorbed to the same extent as uncoated  $\text{Fe}_3\text{O}_4$  and the amount of serum did not affect uptake.  $\text{Fe}_2\text{O}_3$  particles were shown to cause dose-dependent increased oxidative DNA adducts and the cellular response was similar to iron overload in hepatocytes.

Dr Patrick Case (University of Bristol) concluded the day's presentations with a study on cobalt and chromium NPs *in vitro* and *in vivo*. Metal-on-metal (MoM) replacement joints are becoming increasingly common as younger patients receive implants. Although MoM implants have been used since the 1930s, two new adverse reactions have been observed. Within five years of surgery, 1% of patients suffer 'pseudotumours' destroying local tissues, or local 'hypersensitivity' immune reactions. Long-term risks include melanoma (up 43%), kidney (up 22%) and bladder (up 15%) cancers after 10 years. *In vitro*, CoCr NPs were more cytotoxic and caused more DNA damage than an equivalent micron-sized particle dose. *In vivo*, blood and urine levels of Co or Cr are increased post-operation from six months to at least 2 years. Chromosomal aberrations also increase. In 2010 a medical device alert was issued describing the potential adverse immune reactions. In cases where replacement surgery is required, corrosion of the implant has been observed.

Following the presentations there was a brief discussion of the issues. The general consensus was that nanoparticle toxicology seemed to be very complicated! There seemed no apparent clear case for groupings although "low toxicity" NPs might be filtered out on surface area/inflammation ratios. It is also perhaps reasonable that nanofibres are considered on their physical properties, such as aspect ratio. It is clear that NPs are not a

single entity and surface reactivity may be important in determining toxicology. Routes of entry also seem to be relevant and *in vitro* experiments may not always reflect what is seen *in vivo*.

**Submitted by: Kate Jones**

### **Eurotox 2011, Paris, 28<sup>th</sup> -31<sup>st</sup> August 2011**

The 47<sup>th</sup> Congress of the European Societies of Toxicology (Eurotox) was held at the Palais des Congrès de Paris. Paris, heralded as 'the city of love', or perhaps more appropriately as the work place of Marie Curie, did not fail to disappoint as the venue of the conference. I was fortunate enough to receive funding from the Royal Society of Chemistry to attend. As a final year PhD student, the conference was an invaluable opportunity to communicate with my peers, network with future employers and experience a truly international conference with around 1500 delegates from around the world.



Held on the 28<sup>th</sup>-31<sup>st</sup> August, the conference opened with a welcome note from the conference president, Dr. Nancy Claude (Servier Group, France) and president-elect, Prof. Ruth Roberts (AstraZeneca, UK).

My conference experience commenced with a symposium evaluating the monitoring and assessment of adverse epigenetic effects by

chemicals, this followed in the afternoon by another addressing **'Emerging health issues from chronic pesticides exposure'**. In between these two sessions was the (HESI) Health and Environmental Sciences Institute keynote lecture given by Prof. Alan Boobis OBE entitled: **'Risk assessment needs 21<sup>st</sup> century rationality as well as 21<sup>st</sup> century science'**. The talk highlighted the issues surrounding the unpredictability of animal models especially concerning studies of mixtures, and the transition towards a greater reliance on *in vitro* and *in silico* models. He also summarised an ILSI HESI project which intends to address these important issues.

On the first day I also presented a poster entitled **'Analysing species differences of the Aryl Hydrocarbon Receptor in response to persistent organic pollutants'**. As part of my project, I use *in vitro* work to calculate the potency of a range of environmental pollutants which can be directly applied to risk assessment.



In the evening I was again fortunate enough - and this time not at the expense of the RSC members! - to attend the gala dinner cruise along the river Seine. Sailing past the Eiffel tower at night was a truly spectacular moment, but perhaps more significantly the cruise provided me with the opportunity to speak to some of the delegates at the conference including the President-elect.

The second day symposium started with **'What's new in genotoxicity testing?'** with several interesting talks initially discussing the

reliability of *in vitro* models before shifting towards legislative aspects with regards to synchronisation between regulators. This was followed by a talk on cosmetics testing in which Dr. Raffaella Corvi (European Commission, Italy) discussed the proposed removal from the market by 2013 of all cosmetic products which have undergone animal testing (EU Cosmetics Directive). The general conclusion was that despite investment in, and development of, *in vitro* models, it is expected that this deadline will be extended until an appropriate replacement can be properly implemented.

During lunch, the Society of Toxicology (SOT) vs. Eurotox debate was held. This year the opposing sides had to discuss whether biomarkers would eventually replace histopathological evaluation to determine adverse responses ..... with Eurotox defending. Perhaps unsurprisingly the vote went in the direction of 'against', but both parties delivered excellent arguments.

The afternoon symposium discussed tools for the establishment of Human Toxicity Values (HTVs). One particular talk by Dr. Sean Hays (Summit Toxicology, USA) introduced and explained biomonitoring equivalents, identifying them as a valuable resource which could be the future of risk assessment by helping to fully utilise biomonitoring data.

**'Xenobiotic receptors and long-term toxicity'** was the symposium subject on the final day of talks. Prof. Roland Wolf OBE (University of Dundee, UK) examined the role of Constitutive Androstane Receptor (CAR) and Pregnane X Receptor (PXR) in xenobiotic toxicity and examined the possible repercussions on P450 enzymes when these genes are (directly or indirectly) knocked out.

Overall I found the conference to be very interesting and although I've mentioned only a few examples of the talks I attended, I thought all of the speakers gave excellent lectures. I would like to thank the Royal Society of Chemistry and its members for funding my registration at the conference and reiterate how constructive the conference has been to my career in toxicology.

The conference proceedings are published in *Toxicology Letters, 2011, Vol. 205S*.

**Submitted by: Richard Wall**

**BTS Autumn Meeting, Nottingham,  
5-6<sup>th</sup> September 2011**

Abstracts from the BTS Autumn meeting are now available on the BTS website in the 'Members Only' Section  
[www.thebts.org](http://www.thebts.org)

## UPCOMING MEETINGS/WORKSHOPS OF INTEREST TO MEMBERS

BOHS Autumn Scientific meeting, 14<sup>th</sup>-15<sup>th</sup> November 2011, Leeds Metropole Hotel  
<http://www.bohs.org/AutumnScientific2011/>

Joint Meeting of SoBRA/RSC Toxicology Group, 21<sup>st</sup> December 2011, Burlington House, London on **Current Issues in Contaminated Land Risk Assessment** including the SoBRA AGM  
<http://www.rsc.org/Membership/Networking/InterestGroups/Toxicology/ForthcomingEvents.asp>

EUROTOX 2012, Stockholm, 17<sup>th</sup>-20<sup>th</sup> June 2012  
<http://www.eurotox2012.org/?id=50>  
Register before 11<sup>th</sup> February 2012 to be eligible for the early-bird fee!

## COMMITTEE NEWS

The next meeting of the Committee will be in December 2011.

Lorna Wren is to act as Newsletter Editor for the next year, allowing Kate Jones to concentrate on her role as Secretary to the Toxicology Group. Any items for inclusion in the next Newsletter (Spring/Summer 2012), or suggestions for areas which Members would like to see covered in future issues should be submitted as soon as possible.

## REGISTER OF TOXICOLOGISTS

In response to the need for international harmonisation and mutual recognition of qualifications, the UK Register of Toxicologists, sponsored by the Society of Biology and the British Toxicology Society, was established in 1993.

By identifying professional toxicologists with suitable qualifications and experience, it is intended that the Register fosters competence in practice and makes publicly available authoritative sources of information on toxicological matters. The attainment of registration is seen as a significant milestone in a career in toxicology and will become increasingly desirable for career progression. The designation "Registered Toxicologist" is not lightly given and is maintained by regular (5 yearly) review of continuing education and practice in toxicology.

Members of the UK Register of Toxicologists gain automatic membership of the EUROTOX Register of Toxicologists (ERT).

There are currently in excess of 200 members on the Register. Membership is predominantly UK-based but there are a number of other countries represented within the membership.

The disciplines are also very varied but the Register would like to invite members of the Royal Society of Chemistry to apply to join the Register and strengthen the links already forged with the RSC.

Registration fees are as follows:

**Application fee:** £30 for SOB/BTS members and £50 for non-members.

**Annual retention fee:** £25 for members and £45 for non-members.

**Re-registration application fee:** £20 for members and £40 for non-members.

The Panel meets twice at the Society of Biology, in March and September, to review new applications, applications for re-registration

and discuss any matters arising. There is one business meeting annually.

The Panel, as of September 2011, comprises:

*Professor Shirley Price (Chair)*  
*Professor Robert Chilcott (SoB representative)*  
*Dr George Kowalczyk (RSC representative)*  
*Dr Atholl Johnston (RCPATH representative)*  
*Dr Eian Massey (BTS Representative)*  
*Dr Christine McAlinden*  
*Dr Lesley Stanley (BTS Representative)*  
*Dr Cliff Collis (Secretariat)*

If you would like to register please go to the website for full details and an application form, or contact the Administrator of the Register directly.

Website: <http://www.toxreg.org.uk/>

Other contact details are as follows:

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**Submitted by Professor Shirley Price, Chair.**

## PUBLICATIONS/REPORTS

UKIEG (UK Internal Environments Group)  
Newsletter October 2011, soon to be found on:  
<http://ukieg.yolasite.com/>

Toxicity and Assessment of Chemical Mixtures [NB - The Toxicology Group responded to this consultation]

[http://ec.europa.eu/health/scientific\\_committees/consultations/public\\_consultations/scher\\_consultation\\_06\\_en.htm](http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scher_consultation_06_en.htm)

BSI - A Guide to the Detection, Characterization and Identification of manufactured nano-objects in complex matrices PAS 139  
<http://www.bsigroup.com/en/Standards-and-Publications/How-we-can-help-you/BSS/-/-/BSS/PS/Our-services/Current-projects/PAS-139/>

EFSA Scientific Committee; Scientific Opinion on Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain. EFSA Journal 2011; 9(5):2140 [36 pp.].  
[www.efsa.europa.eu/efsajournal.htm](http://www.efsa.europa.eu/efsajournal.htm)

A joint JRC-EASAC Report, September 2011 - Impact of Engineered Nanomaterials on Health: Considerations for Health-Benefit Assessment  
[http://ihcp.jrc.ec.europa.eu/our\\_activities/nanotechnology/nanoreport-10-11/JRC-EASAC-report.pdf](http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/nanoreport-10-11/JRC-EASAC-report.pdf)

Chemical Hazards and Poisons Report, Issue 20, Centre for Radiation, Chemical and Environmental Hazards, HSE, September 2011  
[www.hpa.org.uk/chemicals/reports](http://www.hpa.org.uk/chemicals/reports)

## DISCLAIMER

Please note that the opinions expressed in this Newsletter do not necessarily reflect those of the Toxicology Group Membership or the RSC