BTS Annual Congress 2023 symposium report – Hannah Coghlan

From the 17th to the 19th of April 2023, I attended the British Toxicology Society (BTS) annual congress, held at the Park Regis Hotel in Birmingham. I was very fortunate to be awarded the BTS Pre-Doctoral Student Bursary to support my attendance, which also allowed me to present an oral communication on some of my PhD research. The conference was a fantastic opportunity to discuss hot topics in toxicology with others and gain a better understanding of the applications and importance of toxicology outside of my field. In particular, I found Symposium 3: 'Clinical Toxicology Workshop' incredibly interesting as it provided a different perspective on the importance of toxicology than those I am used to. The symposium was chaired by Dr. James Coulson and co-hosted by the Clinical & Human Toxicology Speciality Section of the BTS and the British Pharmacological Society. The session consisted of three presentations on various aspects of clinical toxicology, followed by an oral communication discussing a case study of clinical toxicology.

The first session, presented by Dr. Laurence Grey of University Hospital Llandough, was entitled 'Introduction to Clinical Toxicology' and formed a fascinating insight into clinical presentations of drug toxicity. Dr. Grey discussed the concept of toxidromes – a set of symptoms or clinical manifestations of poisoning that can provide indication of the mechanism of toxicity and inform diagnosis and identification of possible xenobiotic causes. A particularly interesting toxidrome presented was that of the serotonin toxidrome 'serotonin syndrome' which involves a set of symptoms associated with increased serotonergic activity in the central nervous syndrome and its stimulation of smooth muscle. These include increased body temperature – which itself poses a significant health risk as it can cause organ failure -, confusion, flushing, tremors, unstable blood pressure and pulse, hypertonia, hyperreflexia and bowel symptoms. Dr. Grey noted that, during diagnosis of toxicity or poisoning, diagnoses are often made with rudimental observations, but treatment must be rapid to maximise its efficacy; therefore, immediate, life-threatening symptoms (e.g., high body temperature) are first treated to improve the patient's condition while an antidote or treatment for the cause of toxicity is identified. Interestingly, it was also pointed out that polypharmacy and multimorbidity can complicate diagnosis of toxicity as toxidromes may not be distinct and that, although we tend to focus on pharmaceuticals as a cause of toxicity, non-pharmaceuticals can also cause poisoning.

The second presentation was by Dr. Dominic Williams of AstraZeneca, entitled 'Liver safety at the transition between pre-clinical and clinical trials'. As my own research focuses on the prediction of liver safety concerns in preclinical species, I found this particular presentation incredibly interesting. Dr. Williams first provided an overview of drug-induced liver injury (DILI), including a range of causes, mechanisms and varied presentations. The first stages of toxicology screening were then discussed, with high-throughput screening first being used to predict a compound's probability of DILI risk based on common mechanisms of DILI, such as inhibition of important transporter proteins (e.g., BSEP) and mitochondrial toxicity. This investigation then progresses to the development of a tailored DILI risk prediction based on factors such as compound structure, mechanism and *in vitro* safety data. An *in silico* approach to modelling DILI utilising various experimental endpoints, including plasma C_{max} and bioactivation potential, was also described. However, it was noted that, despite the value offered by many types of *in vitro* models, no single model meets all needs of current toxicology studies. For this reason, *in vitro* safety assessment often uses simple, 2D *in vitro* models for high-throughput screening, before progressing to more complex, 3D *in vitro* models to gain a stronger mechanistic understanding of DILI risk and improve preclinical-clinical translation. Dr. Williams then presented a case report of a compound currently in development for the treatment of cancer. In this case, *in vivo* preclinical studies utilising animal models did not predict DILI risk, although elevations in the liver damage biomarkers alanine transaminase (ALT) and bilirubin were detected in a number of patients in early clinical trials. These biomarker elevations had a rapid onset

but also rapidly resolved, which suggested that this toxicity may not be a case of Hy's law DILI, which is a safety rule that suggests that fatal DILI is of high risk if a drug causes hepatocellular damage (indicated by ALT) with jaundice (indicated by bilirubin). *In silico* modelling using the software, DILIsym, indicated that elevations of the two biomarkers were unrelated to each other and lead to the hypothesis that they were caused by two different mechanisms. Proteomics and experimental data confirmed that downregulation of the efflux transporter protein MRP2 was the mechanism of bilirubin accumulation, while elevated bile acid levels in the liver and reduced apoptotic body removal was determined to be the mechanism of ALT elevation. Dr. Williams completed his presentation by reiterating that translation from *in vitro* toxicity to clinical biomarkers of toxicity is crucial, and that *in silico* modelling can be valuable in assisting hypothesis generation and experimental design.

The third session of this symposium was entitled 'Environmental pollution and cardiovascular disease: why is it all up in the air?' and was presented by Dr. Mark Miller of the University of Edinburgh. I enjoyed this session as, as mentioned by Dr. Grey during his presentation, although discussions on toxicity often focus on pharmaceuticals, many environmental pollutants can also cause organ toxicity. The presentation began on the sobering fact that deaths from ambient air and toxic chemical pollution are increasing, with pollution being responsible for around 9 million deaths yearly and up to 10% increased risk of certain diseases (e.g., cardiovascular disease and cancer). Dr. Miller discussed how, although approximately 90% of the worlds population currently live in areas with air pollution levels above those considered 'acceptable', recent studies have identified physiological effects of pollution at far lower levels. A particular concern is the presence of particulate matter released by vehicle exhausts that can carry harmful chemical species and deposit in the lung alveoli. A study was then discussed which found that controlled exposure to dilute vehicle exhaust – approximately equivalent to cycling for 2 hours in heavy traffic – increased blood clotting and cardiac ischaemia and decreased vascular relaxation (to the same level as a life-long smoker) and fibrinolysis. This exemplified that even relatively short-term exposure to pollutants can significantly impact health.

The final presentation of the symposium was an oral communication presented by Prof. Timothy Gant of the UK Health Security Agency (UKHSA) entitled 'Case Report of Chemical Investigation of Incidents of Hepatitis of Unknown Origin in Children in 2022'. The presentation detailed efforts by the UKHSA to establish if chemical toxicity was the cause of 274 cases of hepatitis, including 15 liver transplants, in children between April and July 2022, which was highly publicised and point of public discussion at the time. Prof. Gant stated that the cases did not present a clear toxidrome, and it was hypothesised that COVID-19, genetic, infection or chemical exposure could be the cause. UKHSA initially attempted to identify chemical causes of this liver toxicity via an agnostic chemicals analysis using a combination of ICP-MS metal analysis, untargeted LC-MS/GC-MS and a range of targeted assays using samples liver samples from hospitalised patients. However, as these liver samples were obtained at various timepoints following hospitalisation, it was considered that any causative chemicals would likely have been cleared from the body prior to disease presentation and sample collection. Furthermore, a number of therapeutics were identified by this analysis that were not reported by clinicians; despite this, these chemicals were ruled out as causative agents as the presentation of hepatitis did not match the identified drugs (e.g., paracetamol) and it was likely these had been administered therapeutically but not recorded. Prof. Gant explained that, ultimately, no chemical cause of these cases of hepatitis were identified, and recent publications suggest that co-exposure to the AAVE2 and another virus, possible HLA associations, and reduced immune protection in children as a result of COVID-19 lockdowns may be associated with these cases. However, although it was not determined that there was a chemical cause to this liver injury, it was

interesting to learn more about how the causes of unexplained disease outbreak are investigated by government and healthcare agencies.

I would like to reiterate my thanks to the BTS for my receiving the Pre-Doctoral Student Bursary which allowed me to attend and present at the 2023 Annual Congress, and for organising such a great event.