A Decade of Toxicological Trends

Introduction

As with many other disciplines, toxicology has buzzwords and jargon that come and go, reflecting scientific trends. Although this can be useful to those closely involved in the field, these trends and buzzwords can be unhelpful to those trying to understand the discipline. To help unravel this, we asked senior toxicologists in the BTS and elsewhere to suggest the most popular trends and we then used the published literature to check those assumptions and establish a rank order of popularity. Here we count down the top ten buzzwords in toxicology with an emphasis on significance for public and environmental health.

At Number 10: Artificial Intelligence.

Artificial Intelligence, also known as AI, uses complex mathematics to learn from and make predictions based on what we already know. Some of the more advanced AI tools (referred to as machine learning or deep learning) can mimic human thinking by introducing an element of chance and then 'observing' the consequences. One of the most recognised examples of this is the chess computer Deep Blue that ultimately managed to beat a chess grand master by making unpredicted and apparently illogical moves that were outside of the established chess repertoire.
Another term often seen in association with AI is Big Data. Big data refers to large '*warehouses*' or databases that accommodate volumes of information outside of human comprehension. For example, big data is currently assimilating all of the known COVID-19 variants, their occurrence, geographical location and transmission. Since each COVID19 virus has around 30,000 DNA bases in its code and there have been more than 200 million people infected globally, it's easy to see how the volume of information can rapidly overwhelm regular computational methods. Within toxicology, discussions on the use of AI first appeared in 2011 but usage remains in its infancy. It seems probable that with time AI will be used to detect patterns in existing data as predictors of toxicity for new drugs, chemicals and agrochemicals.

At Number 9: Microphysiological systems

Microphysiological systems (MPS) are advanced laboratory cellular models that take cells usually derived from humans and grow them in 3D systems that mimic the structure of organs such as the liver and lungs. This introduction of 3D structure and other clever developments such as fluid movement to mimic blood supply has taken the traditional lab-based cell culture resource to new levels. The first publication that described MPS in a toxicology-relevant context was in 2010; since then, there has been a gradual increase in publications as MPS technologies advance, making them more relevant for toxicology. The attraction here is that human-based *in vitro* models could reduce animal testing and make tests for relevant to humans. However, it is proving incredibly complex to transition MPS from the bench into toxicologically relevant assays that can replace and improve on what we have now. This may explain the limited growth and recent decline in the number of MPS publications in the field of toxicology. However, the use of MPS in predictive toxicology risk assessment is expected to grow to provide more human-relevant and predicative assays to indicate safety profiles earlier and with more certainty.

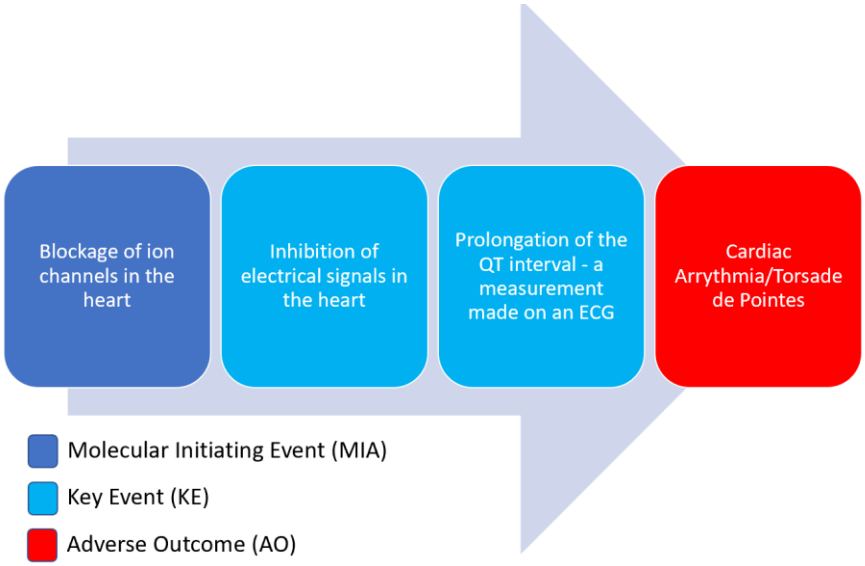
At Number 8: The 3Rs

The 3Rs concept was introduced by Russel and Burch in 1959 though publication of 'The Principles of Humane Experimental Technique' and refers to the replacement, reduction and refinement of animals in research wherever possible. As outlined above, there is substantial investment in

replacement of animal tests with other animal-free methods. However, in some areas such as drug development, the use of animals is still required to protect human safety. Here, the focus is on reducing the number of animals used, either by using methods that enable researchers to obtain comparable levels of information from fewer animals or to obtain more information from the same number of animals. Refinement of methods of animal use is aimed at enhancing the animal welfare standards. Animals are used in the safety and efficacy testing of all new drugs to meet regulatory requirements and to safeguard human health although researchers across all disciplines are working to establish alternative methods. The toxicologically relevant publications on the 3Rs have declined in ranking over the decade. This may seem surprising since interest in and adherence to the 3Rs remains highly topical. However, the trends we noted could suggest that the 3Rs as a concept is now embedded in research approaches and that it is not in itself a topic of research.

At Number 7: Adverse outcome pathways

Adverse outcome pathways (AOPs) are tools used in toxicology to illustrate a (sometimes) straight line from cause to effect. AOPs begin with a molecular initiating event (MIE) followed by a series of intermediate key event steps resulting in an adverse outcome (see illustration below). They are envisaged as predictive tools that use existing knowledge regarding the linkage between a specific molecular event and an adverse outcome. From the first AOP publications in 2012, there has been a steady increase, as the demand has grown for higher throughput assessment of chemicals with greater accuracy whilst minimising animal use. AOPs are useful in many fields and have assisted in defining the key events in skin sensitisation, providing a non-animal route for skin sensitisation testing.



An example of an Adverse Outcome Pathway, in this case for cardiac arrythmia caused by blockage of ion channels in the heart. These cardiac ion channels control electrical signalling which in turn regulate the cardiac action potential, as seen on an electrocardiogram (ECG). Several drugs have had the tendency to block cardiac ion channels, lengthening the QT and potentially leading to a fatal irregularity of the heartbeat (a ventricular arrhythmia called torsade de pointes).

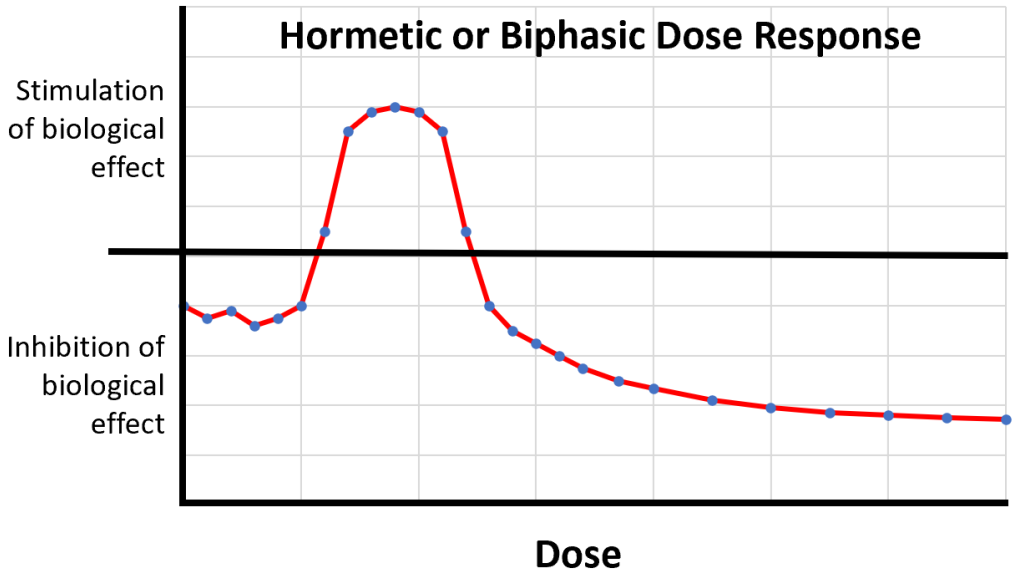
At Number 6: Read-across

Read-across is a predictive technique based on the principle that substances with similar chemical structures will have similar properties and thereby have similar toxicokinetic and toxicodynamic properties. Therefore, data from a source chemical, can be '*read-across*' to fill the data gap for a new chemical. Read-across can save time, money and avoids additional animal testing making it a desirable tool in toxicological assessment. The number of read-across publications increased gradually from 2009 until 2016, many of them describing and assessing the capabilities of read-across as a tool in risk assessment. This growth in publications may be due to the establishment of the REACH regulation that provided specific information requirements and guidelines for applying

read-across methods. The post-2016 drop in publications may be indicative of less activity in the research area as it has become a well-established methodology in toxicology.

At Number 5: Hormesis

Hormesis is a term that even some experienced toxicologists struggle to define! However, it is generally used to describe a biphasic dose response with a low dose causing stimulation or a beneficial response and a high dose being inhibitory or toxic (see illustration below). There are some reports that suggest that hormesis could be important but the number of hormesis publications per year over the last decade has seen a slow decline. This suggests that hormesis is becoming less important in toxicological research, and that toxicologists have deemed that there is not enough evidence to support the concept being an important part of chemical risk assessment.



A biphasic or hormetic dose response curve. Rather than a simple or linear relationship between dose and response, hormesis describes a biological response where at a low dose, the "toxic" or inhibitory agent actually becomes stimulatory or beneficial to the organism. In other words, something that is harmful at a high dose can be good for you at a low dose.

At Number 4: Personalised or precision medicine

Personalised or precision medicine refers to tailoring therapies to an individual patient based in their predicted response or risk of a disease, thus making the treatment as individualised as possible. Toxicologically relevant personalised medicine publications have undergone a substantial growth since 2009 with the increased availability of clinical, genetic, genomic, and environmental information from patients. In toxicology, these data help to determine the underlying mechanisms of disease so that the right drug and dose can be selected. An application of personalised medicine in toxicology is CYP 450 genotyping which can determine the rate at which certain types of medicines will be metabolised by an individual, which is dependent on their genetics. This information can be used to create specific dosing regimens to reduce adverse effects and improve drug efficacy. Personalised medicine has moved around the top four slots over the last decade, stabilising in third place for the last 5 years.

At Number 3: The microbiota

The microbiota refers to specific microorganisms usually in the context of the skin or gut. The microbiome describes the collection of genomes from all the microorganisms that are found in these environments. The importance of the microbiome in toxicology is mirrored by the substantial increase in publications in the field over the last decade. We have long focused on drug metabolism by the person themselves, but we now realise that drug metabolism by gut bacteria can affect both the efficacy and safety profile of drugs. The considerable variation in the microbiota from individual to individual may also account for the variation in drug metabolism. Over the last 10 years, there has been an explosion in microbiome-related publications in the toxicology field, although surprisingly the ranking of the microbiome has remained constant since 2014. As a relatively new player in the toxicology field, the impact of the human microbiome on toxicology is yet to be seen.

At Number 2: Genomics

Genomics is the analysis of the entirety of an organism's DNA. From a toxicological perspective, toxicogenomics is the application of genetics and molecular biology to describe the response to a compound. Compounds with similar toxicity mechanisms should perturb the transcriptome in a similar manner; these transcriptome changes can then be used as a predictive markers for toxicity outcome. Genomic publications have consistently been in the top four over the last 10 years settling at position 4, indicating genomics is fully integrated into toxicology and plays a significant role in advancing the scientific basis of toxicity risk assessment. Genomics has been evaluated for application in risk assessment within the context of reducing animal testing. It will be interesting to see if this potential application raises genomics up the rankings.

And finally, at Number 1: Zebrafish

Zebrafish is a member of the minnow family and is popular in biomedical research due to its low cost, ease of maintenance and its regenerative abilities. The first toxicologically relevant zebrafish paper was published in 1974 and concerned the impact of environmental toxicants and chemicals on non-mammalian species. It was only later when we realised that these fish conserve a lot of human relevant genes and pathways that it was proposed that in some cases, zebrafish research could be relevant for human health. The success of this approach and acceptance of zebrafish as a suitable model organism in toxicology over the last 10 years are evidenced in our study where zebrafish is the top concept in the decade studied. Zebrafish have been used extensively in developmental and environmental toxicology as they have a higher throughput *in vivo* screening capability than other experimental organisms, making them a useful early indicator of toxicity.

Summary and future directions

Toxicology, like other fields, has scientific trends that come and go with time. One notable trend is that the top four slots have been static over the past 4 years, suggesting that new ideas are introduced and increase in popularity until they find their place in scientific culture. This may suggest that relatively new entries such as AI have yet to find their steady state in the rankings.
It is interesting to speculate on what new trends will emerge over the coming decade. Tools/techniques such as CRISPR–Cas9, image analysis and next-generation sequencing may feature heavily in the general published literature, but do not yet feature highly in toxicology publications. This suggests that it takes time for these trends to be picked up and used.