ID 06.5

Applying transcriptomic benchmark modelling for toxicological decision making

Richard A. Currie

Product Safety Science Strategy, Syngenta International Research Center, Jealotts Hill, Bracknell, RG^{426}EY, UK.
Richard.currie@syngenta.com

Risks from chemical exposure are managed using reference doses extrapolated from a Point of Departure (PoD) that is derived from the no observed effect concentrations, or by calculating the benchmark dose (BMD) of pathological observations seen in standardised animal studies. This approach is founded on the premise that humans and ecological species will be sufficiently protected by ensuring chemical exposure is below the dose at which a defined observable endpoint is expected. Pathological observations in animal studies have been used, since at least the 1940s, to determine these PoDs. However, using traditional animal studies is low throughput and resource intensive, resulting in only a limited number of known chemicals having been evaluated.

The application of omics methods to the risk assessments of industrial chemicals and agrochemicals has been proposed by the scientific community for two decades. However, although research has demonstrated that it may be possible to use omics data to derive a PoD, in practice it has not been used. To aid this uptake process, recently Johnson et al (Toxicol. Sci. 190(2), 2022, 127) proposed a logical framework that outlined 4 key principles that must be accepted to give confidence in using omics data to set a PoD: (1) transcriptomics is a reliable tool to detect altered gene expression caused by a chemical treatment; (2) altered gene expression is an indicator of adverse or adaptive biological responses to a stressor; (3) a benchmark dose based PoD can be set using a concerted molecular change (CMC) in transcriptomics data measured in a short term in vivo studies; and (4) these transcriptomic PoD supports a human health protective risk assessment.

The first two principles are well supported by published literature. Recently, the latest in a series of ECETOC workshops on use of omics data, explored the third principle. It explored a number of case studies and concluded that 'omics data, when developed within the extant robust frameworks for data generation and analysis, can be used to derive a PoD. Here I will show that BMD analyses of CMCs in transcriptomics data from multiple tissues in a 14-day rat dietary toxicity studies supports human health protective risk assessments for several of our recent crop protection development candidates. Therefore, we can conclude that transcriptomics data can be used to set endpoints for human health risk assessments of repeat dose systemic toxicity.

Keywords:
toxicogenomics; benchmark dose modelling; point of departure; crop protection