Developmental neurotoxicity

A.Terron

European Food Safety Authority, Parma, Italy

Although starting as a small tube of ectoderm, embryonic development is a very complex biological process and human brain must undergo a series of time correct sequence of stages. Each of these physiological processes is vulnerable to adverse effects from exposures to toxic environmental chemicals. Humans are indeed more susceptible to developmental neurotoxicity (DNT) and some of the human brain functions are difficult to explore and quantify in animal experimentation i.e. cognitive function, skills, behaviour. The use of animal experiments has limitations given the recognised molecular and species differences with the additional intrinsic difficulty in interpreting such a complex studies with so many endpoints measured (OECD TG 426). Moreover, DNT testing is dependent on triggers from systemic toxicity testing in adult rodents, which may not be sensitive enough as some processes are specific for brain development only and are not present in the adult brain. Indeed, only few environmental substances have been actually tested for DNT. The consequence is a knowledge gap in chemical testing as well as in the mechanistic understanding for DNT. Over the last decade a number of scientific initiatives have concluded that developmental of *in vitro* assays and other alternative methods could provide the basis for non-*in vivo* based testing strategy and support a mechanistic shift using a human relevant test system like the human pluripotent stem cells. It is now important to understand what the scientific premises are and how to move from the academic perspective to the regulatory switch from a risk assessment based on identification of apical endpoints to a more mechanism-based risk assessment. From a strategic view, it is now necessary to come to a conclusive consensus on defining alternative methods to be assembled in a DNT testing battery able to explore the key cellular processes critical to normal brain development and define the next steps for regulatory use. Although uncertainties still exist precluding a straightforward replacement from in vitro to in vivo, recent data indicate that in vitro efficient models are available and should now considered for regulatory application. As a scientific consensus already exists, what we need now is to move on with testing to fill the gaps on methods performance, and regulatory acceptance of the methods. The ultimate aim is to build a predictive, valid and flexible model, able to respond to different regulatory-based problem formulations.