Advancing Alternatives Methods at the US FDA

Main author: Suzanne Fitzpatrick (United States Food and Drug Administration- US FDA)

Co-authors: George E.N. Kass, Jose V. Tarazona

INTRODUCTION

Most chemical risk assessments are conducted today based on the paradigm developed in the second half of the 20th century. The hazard assessment provides health-based guidance values, mostly derived from animal toxicity data, and in the risk characterisation an assessment is made whether or not a proportion of the population will be exposed to levels which are considered of concern from a health risk point of view. Numerous international and national efforts currently focus on new methodologies and tools, the so-called New Approach Methodologies or NAM

METHODOLOGY

These NAMs are designed to support the next generation risk assessment (NGRA) that will involve a shift from traditional observational in vivo tests towards a more informed and targeted evaluation of chemicals that capitalises on the understanding of the mechanisms behind adverse effects. The US FDA together with the US EPA have been pioneering the 'Advancing the Next Generation of Risk Assessment' (NexGen) effort together by setting up the key programmes ToxCast and Tox21 which paved much of the risk assessment paradigm shift towards NGRA. Tox 21 is a partnership between the FDA, NCATS, EPA and NIEHS. These agencies recently signed an updated Memorandum of Understanding that expanded this collaboration to additional NAMS including. elegans, zebra fish, A.I. in silico modelling, organoids and microphysiological systems. In 2017 FDA published it FDA Predictive Toxicology Roadmap that clearly established a pathway for accepting NAMS into regulatory assessments. In2020, the FDA established its Alternative Methods Work Group that included senior regulators from all six FDA programmes. This work group established a public website to track, in real time, the FDA's progress on NAMS.

RESULTS

EFSA has been following closely the developments and regulatory application of NAMs over the past decade as part of its scientific strategy. Over the past years, EFSA has been investing considerably in developing and incorporating NAM approaches, particularly Read-Across, PB-TK modelling and in vitro assays for data-gap filling, regulatory chemical risk

assessment and for the developments of new open access tools. More recently, EFSA developed a roadmap for developing its NAM strategy further.

An important consideration is that such efforts and investments in NAMs and the NGRA should not be done in isolation but within an international framework. This will not only help to streamline the different activities and avoid duplications but also will be the only way to secure worldwide acceptability of NAMs for regulatory purposes. This has triggered generic regulatory initiatives like APCRA (Accelerating the Pace of Chemical Risk Assessment), covering several case-studies as proof of concept for the use of NAMs in the regulatory context. However, there are also specific needs in the food and feed area.

DISCUSSION

With this in mind, EFSA and FDA decided to join forces and collaborate in order to facilitate the incorporation of NAMs in food safety assessments. Three main common priorities have been identified. The first and generic priority is global acceptance of NAMs in food related chemical risk assessments; this would be implemented through developing guidance on how to incorporate NAM results as part of the safety assessment. The second and more specific priority focuses on setting the foundations for using NAM-based non-guideline scientific publications in regulatory risk assessments. The last challenging priority is the (R)evolution of the risk assessment paradigm, facilitating the integration of mechanistic information in the hazard and risk characterisations; establishing alternative approaches to combine NAMs with other data to derive safe levels (e.g. MoE); and improving our knowledge on interindividual variability to cover sensitive populations. This collaborative proposal has been presented to the International Liaison Group for Methods on Risk Assessment of Chemicals (ILMERAC), and several organisations in America, Asia and Europe have already indicated interest in joining forces.