Session 6: Epigenetics in risk assessment: academia, industry and regulator perspective

45 | Epigenetics in risk assessment: academia, industry and regulator perspective

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There is a growing body of evidence demonstrating that chemicals can affect epigenetic processes in organisms (e.g. DNA methylation, histone tail modifications, microRNAs, etc.) and subsequently alter the way an organism responds to a stressor. These epigenetic effects may result in long-term impact on phenotypes, fitness, health and disease in living organisms both within generations (from embryogenesis to adulthood) and in a trans-generational fashion. Despite the substantial amount of research published in this area, a number of questions remain to be answered, particularly in the context of long-term impact on human health and ecological risk assessment of chemicals.

Three keynote speakers from Academia, Industry and Government will address these questions and give views on how epigenetic effects might fit into current tiered risk assessment frameworks.

46 | Environmentally induced epigenetic toxicity: potential public health concerns

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Epigenetic changes regulate gene expression without mutating DNA and can be modified by environmental chemicals. To determine whether, or not, environmentally induced epigenetic toxicity is of real concern to public health there are some important considerations, including dose, route, metabolism, and timing of exposure; mixture effects; human variability; adaptive versus adverse outcomes; and mechanisms and model systems. We have recently reviewed the current evidence for environmentally induced epigenetic toxicity in human cohorts and rodent models and highlighted the research considerations and implications of this emerging knowledge for public health and regulatory toxicology. Many hundreds of studies have investigated such toxicity, yet relatively few have demonstrated a mechanistic association among specific environmental exposures, epigenetic changes and adverse health outcomes in human epidemiological cohorts and/or rodent models. While this small body of evidence is largely composed of exploratory in vivo high-dose range studies, it does help to begin identifying putative biomarkers and assays that may be useful for biomonitoring such exposures and toxicities, and testing the epigenetic toxicity potential of environmental exposures. In addition, current OECD human health related Test Guidelines (TGs) have the potential for adaptation to incorporate adverse epigenetic endpoints that would begin to address regulatory concerns and develop formal epigenetic toxicity TGs. Collaboration between scientists from academia, industry, and governmental and regulatory bodies will promote further research within a regulatory context, and drive the development and implementation of epigenetically relevant integrated testing strategies or policies for the continued protection of public health.

47 | International regulatory needs for development of an IATA for non-genotoxic carcinogenic chemical substances

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Although regulatory requirements for carcinogenicity testing of chemicals vary according to product sector and regulatory jurisdiction, the standard approach starts with a battery of genotoxicity tests. If any of the in vivo genotoxicity tests are positive, a lifetime rodent cancer bioassay may be requested, which allows the detection of non-genotoxic carcinogens (NGTxC). However, under most chemical regulations the cancer bioassay is rarely requested, specific requests to obtain information on non-genotoxic mechanisms of carcinogenicity are few, and there are no OECD approved screening methods. When the in vitro genotoxicity battery is negative, usually no further carcinogenicity testing is requested. Consequently NGTxC might remain unidentified and therefore the risks they may pose to human health will not be managed. In contrast to genotoxic carcinogens NGTxC act through a large variety of specific mechanisms, often underpinned by epigenetic mechanisms, and a panel of tests covering multiple biological traits will be needed. The development of an Integrated Approach to Testing and Assessment (IATA) of NGTxC could assist regulatory decision makers. We examine what NGTxC are and discuss chemical regulatory requirements and limitations. With a strong drive to reduce animal testing and costs in mind, it is essential that proper and robust alternatives for animal testing (3Rs) methods for addressing non-genotoxic modes of action are developed and used. Therefore relevant in vitro mechanisms and assays are described and tentatively organized in levels of information, indicating both a possible structure of the future IATA for NGTxC and associated OECD Test Guideline development priorities.

48 | Report on EFSA scientific colloquium on epigenetics and risk assessment

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Epigenetics is a relatively new scientific field and scientists are still debating what it really entails. What we know is that epigenetics involves changes surrounding the DNA in cells that affects how genes are read but without changing the underlying DNA sequence.

The issue of epigenetics and its impact on human health and life span was prominently discussed at EFSA's second scientific conference "Shaping the future of food safety, together" in October 2015. About 100 scientists, risk managers and policy makers from 20 countries including five non-EU countries met in Valencia, Spain, on 14 and 15 June, to continue this discussion and to look at the potential role of epigenetics in risk assessment.

The overall objective of the discussions was to identify the potential role of epigenetics in risk for food and feed and also the wider environment. In dedicated discussion groups, participants addressed various issues including: whether or not epigenetic processes should be considered in risk assessment; the need to address molecular mechanisms, methods to investigate epigenetic effects and the use of epigenetic biomarkers; as well as the need to identify existing data gaps and research needs.

The main take-home message from the colloquium was to ask and seek answers to those questions that will increase our understanding of epigenetics. What do epigenetic modifications mean? How do we study them? What is the size of such modifications that we need worry about? Cooperation and collaboration between the various scientific disciplines and with the clinical side of epidemiology have proven to become necessary strategic elements to improve scientific risk assessment.

Christer Hogstrand chaired Discussion Group “Epigenetics and environmental risk assessment: mechanisms, testing and data gaps” at the colloquium. He reports in his capacity as an academic scientist and does not necessarily reflect EFSA’s view.