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Acknowledgements

Carine Van Camp, Jenny Maes and Anna Hofele are acknowledged for their considerable administrative skills and support.
Juliette Albiac is acknowledged for her guidance through the process.

1. Executive Summary

A small consortium examined the potential utility of using Nuclear Hormone Receptors (NHR) to determine mechanistic approaches that could be applied for the assessment of developmental toxicity, and which might lead to the development of innovative non-animal testing methods.

The consortium worked through two workshops with invited experts to advise and help direct discussion.

The advancement of non-animal testing methods to determine chemicals that may impact upon reproductive development is demonstrated by the consideration of the increasing demands, both regulatory and societal, for such testing. Currently there are no generally accepted alternatives to animal assays.

In developing such alternatives, it was recognised in the workshops that approaches should be founded on fundamental mechanisms in order to enable more reliable inter-species extrapolation, particularly to predict human hazard. The consortium noted that signalling pathways from NHR were highly conserved between species and were critical targets for understanding the mode of action of developmental toxicants.

Consequently, the most promising focus for a mechanistic approach was to investigate the role of NHR in developmental toxicity and a well developed research case example on male reproductive effects was analysed. A generic paradigm was developed and agreed that would form the basis for application of new technologies for future research. These new "enabling technologies" allow investigation of processes and mechanisms that were not possible even a short time ago. The molecular biology and analytical capabilities represented by these technologies, such as toxicogenomic / proteomic analyses, cellular models and cell reporting assays, continue to develop rapidly and allow the development of new possibilities and approaches.

The consortium considered how to approach future research. Central to the approach was the functional and/or morphological definition of the toxicological endpoint as the starting point, triggering the self-selection of pathways/receptors that would be investigated. In this way, a project would not be biased by selection of particular receptors before knowing which were relevant to the observed effects. Projects would apply the enabling technologies in order to identify the relevant receptors and cell types involved in the defined lesion. This informatics-based approach would provide the foundation for development of improved, mechanism-based spin-off models for hazard assessment and screening.

There was a general agreement that the areas for research should be determined by the most common and important clinical effects/ morphological and functional changes observed in developmental toxicology studies and induced by xenobiotics. One approach proposed was to examine epidemiology data on developmental abnormalities for correlation with hormones. Debate on specific areas concluded that the focus should be on clinical findings of concern that were relevant to human health and should be feasible. Organ systems considered to be of potential value for such research included urinogenital, respiratory, musculoskeletal, circulatory/ cardiovascular and immune.

Technology is currently available to allow the expression of drug metabolising systems (eg. cytochrome P450s) in these cell lines; unlike many of the current *in vitro* systems which are

deficient in metabolising capacity. Hence, these cell lines would be appropriate also for chemicals whose toxicity is mediated via a metabolite.

A battery of these engineered cell lines would be required to cover the major effects of concern. There will be other mechanisms of action that will not be covered by an NHR approach, however similar bioinformatics-driven approaches would be applicable.

Recommendation

It was recommended that research is undertaken to further elucidate the role of NHRs in the mechanism of developmental toxicity. The mechanisms elucidated by such an approach should then be tested for their relevance to man through the use of *in vitro* systems.

If the resultant mechanism of action determined by the approach is of relevance to man, then cell based systems should be developed, which are capable of reporting on the ability or otherwise of chemicals to influence this mechanism.