MUT/2020/06

COMMITTEE ON THE MUTAGENICITY OF CHEMICALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT

Section 400 - Pig-a gene mutation assay - DRP & Validation report

- **The comments below were sent to the OECD.**
- **Do members have any further comments?**

PHE Secretariat
February 2020

National Experts or National Co-ordinators please complete the following:

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Please include "GC" for General Comments, the paragraph number or line number. Please include only numbers in the left two columns.

Paragraph #	Line #	Expert Comments	response
GC		This assay would appear to be a valuable addition to the battery of tests for the investigation of genotoxicity. Some of its positive attributes from a regulatory perspective are • the ability (indeed, recommendation) to combine with other tests, primarily repeated-dose toxicity studies but also other *in vivo* genotoxicity studies. This should minimise the use of animals used specifically to investigate *in vivo* mutagenicity (and also the cost); • the encouraging performance measurements in terms of sensitivity and specificity, etc., when compared with the bone marrow TGR assay and rodent cancer in haematopoietic tissues; • the use of rats for the assay will be complementary to the use of toxicokinetic data to support or demonstrate bone-marrow exposure, since TK studies are also usually conducted in rats; therefore there will be no need to discuss possible inter-species differences in bone-marrow exposure between rats and mice, as can be the case when *in vivo* micronucleus tests in mice are evaluated; • the cumulative effects of repeated-doses, resulting in the accumulation of mutant frequencies, that should maximise the sensitivity of the test. Further assessment of the test's regulatory potential will be possible when more details on the protocol are available (for example, the criteria for a positive / negative result and how difficult these are to interpret, how outliers are dealt with).	
GC		The demonstration of adequate bone marrow exposure is obviously vital for concluding on the validity of a negative result in the Pig-a assay as proposed and will raise similar regulatory issues as have been experienced with the *in vivo* micronucleus test; this will need to be addressed in a test guideline. Furthermore, it may not detect substances that are mutagenic only in other tissues.	

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GC		The sensitivity of the assay is increased with repeated, longer-term exposure; a small number of mutagenic chemicals were not detected following single or shorter-term exposures. The number of studies of short-term exposure that gave an inconclusive result was also rather high (Table VIII, page 130-137). Whilst it might be desirable to retain flexibility of dose duration in the test guideline, the preference to use longer-term exposures, or justify the use of shorter-term exposures, could be addressed in future guidance to support the use of the test to meet regulatory information requirements.	
AP: GC		The evidence provided is very persuasive that "… the development of the Pig-a assay towards a Test Guideline should move forward". However, little appears to be known really about the basic mechanisms of the assay e.g. what are the target cells (and their DNA repair capacity) and what are the target DNA sequences? Is there any evidence that this assay is able to detect more readily certain types of mutations e.g. those occurring at AT rather than GC base pairs? What is the relative sensitivity for detecting point mutations vs frameshifts and indels?	
NC: GC		There are a lot of questions regarding basic mechanisms and uncertainty around the results, especially shorter term exposures. A lot more discussion and feedback is needed on the above points before agreeing to move this assay forward for TG development.	

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