

**COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT****Mouse Lymphoma Assay****(Wang J et al Toxicological Sciences 2009 109(1):96-105;)**

1. The Committee, recommended in its guidance on a strategy for testing the use of the mouse lymphoma assay (or an alternative test of equivalent statistical power) as the third *invitro* test in Stage 1.
2. In the appended paper, the authors investigated genetic alterations in LY5178T/TK<sup>+/-</sup> mutants with either slow or large colony growth characteristics from studies investigating the mutagenicity of 3 -azido-3 -deoxythymidine (AZT), mitomycin C (clastogens) and taxol (aneugen). Colonies which exhibited significant Loss of Heterozygosity (LOH) in chromosome 11 were selected for further investigation. The increased mutation frequency in the studies ensured that a high proportion of mutants selected were due to chemical treatment. TK gene dosage, G-banding analysis for chromosomal changes and FISH for detection of chromosome 11 numerical changes were undertaken. The results showed complex genetic changes with all three test substances with evidence for deletion, recombination and aneuploidy. The absence of a functional P53 gene in LY5178T/TK<sup>+/-</sup> cells is in part responsible for survival of cells with larger scale DNA damage. The authors noted the study did not provide information on the efficiency with which these genetic alterations were detected.
3. The COM strategy suggested the MLA is suitable for regulatory use for detection of gene mutations and provides complimentary rather than equivalent data to metaphase analysis. More recently the COM has seen data to suggest that the MLA can detect clastogens and in some instances aneugens (the latter at high dose levels resulting in high levels of cytotoxicity)
4. The authors suggest that these new data provide evidence for the utility of the MLA in a mechanistically based genotoxicity hazard identification battery. Depending on the question that is being addressed and the importance of understanding the mutations induced by a particular chemical, the strategy of combining cytogenetic and molecular analysis of mutants can be used in hazard assessment.
5. The COM previously advised in the COM strategy that there were advantages in using assays that primarily identify individual mechanisms of genetic damage. However on a case-by-case basis the strategy suggested by Wang and colleagues may have some value.
6. What are COM members' views on the data provided and the proposal outlined by Wang J et al?