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A framework for interpreting *in vitro* genotoxicity data: Using mechanistic data to interpret positive results

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Non-animal methods are increasingly being used for regulatory decision making by agencies worldwide because of their potential to reliably and efficiently produce information that is fit for purpose while reducing animal use. The prediction of genotoxic hazard to humans usually follows a stepwise approach, beginning with an *in vitro* battery consisting of a gene mutation test in bacteria, an *in vitro* test for chromosomal damage and/or gene mutation in cultured mammalian cells. Depending on the *in vitro* test results and regulatory requirements, the *in vitro* battery may be followed in some cases by *in vivo* testing.

When the standard battery of two or three *in vitro* genotoxicity tests was retrospectively analysed it was found that a high percentage of *in vivo* non-genotoxic or rodent non-carcinogenic compounds gave positive results in at least one *in vitro* test. The *in vitro* chromosome damage assays gave a high percentage of misleading positive results, often related to choice of cell line and confounded by differing methods of estimating cytotoxicity. To better interpret *in vitro* genotoxicity results, it has been suggested that all available information including *in silico* and *in vitro* data should be considered in a holistic weight of evidence approach. Clarification of the mechanism of action (MoA) of the test chemicals proves particularly valuable for decision-making.

This poster presents illustrative case studies showing how MoA assessment using non-animal methods such as the ToxTracker system, as well as other non-animal methods, can provide information on the potential genotoxic mode of action. Examples are presented where results from *in vitro* genotoxicity tests can be rationalised with a holistic data driven approach, potentially reducing the need for *in vivo* follow-up testing. Mode of action information allows for a more accurate and concrete assessment of genotoxicity. Investigation of MoA using targeted methods without animal testing has great potential to clarify positive *in vitro* genotoxicity test results, thereby avoiding *in vivo* follow-up testing.

Keywords:

In vitro positives, Mode of action, ToxTracker, Reduce *in vivo* follow-up.