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Defining a NOGEL for mutation induction in Muta™Mouse following exposure to N-Nitrosodimethylamine (NDMA)

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The N-nitrosamine, NDMA, is an environmental mutagen and has been identified as a contamination impurity in some commonly used drugs, resulting in several product recalls. NDMA was evaluated in an OECD compliant Muta™Mouse assay (28-day oral dosing) across 7 doses (0.02-4 mg/kg/day) using an integrated design that assessed mutation at the transgenic lacZ locus in various tissues and the endogenous Pig-a gene, along with micronucleus frequencies in peripheral blood. Liver pathology was determined together with NDMA disposition. Acute treatments were included to investigate the accumulation and/or additivity of individual dose effects on mutation induction. Liver was included since it is the most sensitive organ for tumour and mutation induction and bone marrow for reasons of comparison to the micronucleus endpoint (used to assess clastogenic potential). NDMA was negative for mutation induction in bone marrow (lacZ) and peripheral blood (Pig-a mutation or micronucleus induction) when tested up to 4 mg/kg/day. There were dose-dependent increases in lacZ mean mutation frequency in liver, lung and kidney following 28-day repeat dosing or in liver after a single dose (10 mg/kg). The No Observed Genotoxic Effect Level (NOGEL) was determined for these tissues and the dose response data were analysed using bench-mark dose modelling. NDMA mutagenicity in liver was not stochastic in terms of mutation additivity at the lacZ locus with evidence of an overall reduction in mutation frequency following repeat dosing compared with acute dosing for the same total dose. Liver toxicity was observed (≥1.1mg/kg/day) and these data will be discussed in terms of NDMA exposure, hepatic toxicity, and mutagenicity, together with bench-mark dose modelling. The results will be integrated using an adverse outcome framework and the implications for human risk assessment presented.

Keywords:
NDMA, Mutamouse, mutation, LacZ and Pig-a