Guidance on a strategy for genotoxicity testing of chemicals

Stage 0: preliminary considerations prior to genotoxicity testing

Please refer to the G-Strategy for an executive summary and introduction to this document.

Numbers in round brackets refer to references at the end of this document. A full list of references can be found in the main guidance.

28. The intrinsic chemical and toxicological properties of the test chemical must be considered before devising the genotoxicity testing programme. Manufactured nanomaterials present particular considerations with regards to genotoxicity testing and these are discussed in a separate document 'Test Guidance Strategies for Genotoxicity Testing of Manufactured nanomaterials' (34).
29. The physico-chemical properties of the test chemical (for example, acid dissociation constant (pKa), partition coefficient, solubility, volatility and stability in, and potential reactions with, solvents/vehicles) and its purity can affect the ease of conduct and results of in vitro tests. For example, the tolerance of cells to acidic chemicals can be enhanced by neutralisation but this may affect the inherent reactivity of chemicals with DNA (69). Potential reactions of the test chemical with solvent/vehicle should also be considered (for example, cisplatin reacts with dimethyl sulfoxide (DMSO)) (47). Alternatively, low solubility may limit the feasibility of undertaking some or all of the in vitro mutagenicity tests recommended in this strategy. The potential for auto-oxidation of the test chemical in the culture medium can also affect the outcome of in vitro genotoxicity tests (92). It is noteworthy that the toxic properties of test chemicals, such as target organ effects, or irritancy or corrosivity in contact with skin or mucous membranes and their toxicokinetics and metabolism will influence the choice of route of administration and the highest dose level achievable in Stage 2 in vivo mutagenicity tests.

Quantitative structure activity relationships (QSAR)

30. The expected mutagenic potential of a chemical can be assessed from its chemical structure, which may provide structural alerts for mutagenicity. The COM has previously agreed that where no genotoxicity data is available, initial assessment of potential genotoxicity can be based on publicly available QSAR models. A range of QSARs have been developed to predict genotoxicity and COM considered updated information on these models in February 2018. It was concluded that whilst it remained useful to evaluate data generated from QSAR models, in particular as a negative predictor for screening purposes, no changes to the previously recommended guidance (detailed more fully in the 2011 version of the COM Guidance document, 32) were warranted.

31. Overall, QSAR approaches for the prediction of genotoxic activity can be a valuable tool to aid in the high throughput screening of compounds, the provision of assessments for chemicals for which no genotoxicity test data is available and also prioritisation for genotoxicity testing. QSAR can also aid in the interpretation of genetic toxicology tests. Expert judgement is needed when reaching conclusions on mutagenic hazard on the basis of QSAR information alone, and such predictions cannot replace the need to undertake the in vitro and in vivo genotoxicity tests required to derive conclusions on mutagenic hazard and risk. In reaching conclusions, data from well conducted in vitro or in vivo genotoxicity tests should be attributed a much higher weight of evidence than QSAR predictions, although all information should be assessed on a case-by-case basis.

Screening tests

32. With regard to this guidance, genotoxicity screening tests refers to high throughput or scaled-down tests which have been designed to be rapid, economical, reproducible, require only small amounts of test chemicals (typically below 50 mg) and have a high concordance with comparator genotoxicity end points in genotoxicity tests; these tests are also often referred to as pre-screening tests. None of the available genotoxicity screening tests have reached the stage of development where they could routinely be used to replace data generated from guideline-compliant in vitro genotoxicity testing. COM therefore does not recommend any particular test for screening purposes.

33. A number of in vitro systems for use as screening tests have been proposed and are described in full in the previous version of the COM Guidance (32). It is recognised that a screening strategy can be useful for companies to carry out preliminary investigations or to prioritise compounds. However, COM is unable to give recommendations concerning screening tests as developments in the field are rapid.

References

Numbers refer to the complete list of references in the main guidance document.

32. DOH (2011). Guidance on a strategy for genotoxicity testing of chemicals. Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (accessed March 2021)

34. DOH (2021b). 'G9 test guidance strategies for genotoxicity testing of manufactured nanomaterials.' Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment. Awaiting publication.

47. Fischer SJ, Benson LM, Fauq A, Naylor S and Windebank AJ (2008). 'Cisplatin and dimethyl sulfoxide react to form an adducted compound with reduced cytotoxicity and neurotoxicity.' NeuroToxicology 29, pages 444-452

69. Hiramoto K, Nasuhara A, Michikoshi K, Kato T and Kikugawa K (1997). 'DNA strand-breaking activity and mutagenicity of 2,3-dihydro-3,5-dihydroxy-6-methyl-4-H-pyran-4-one (DDMP), a Maillard reaction product of glucose and glycine.' Mutation Research 395, pages 47-56

92. Long L, Kirkland D, Whitwel, J and Halliwell B (2007). 'Different cytotoxic and clastogenic effects of epigallocatechin gallate in various cell-culture media due to variable rates of oxidation in culture media.' Mutation Research 634, pages 177-183