

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COM)

Guidance documents: Revised format. Draft guidance on significance of mutagenicity for human health.

Introduction

1. The draft format for COM guidance documents has been amended to include an expanded introduction and a structure which allows for development of statements on individual genotoxicity tests and the overall and components of the testing strategy.
2. A draft text covering the significance of mutagenicity for human health has been included. This is based on the text developed for the cumulative paper (MUT/2010/09).

COM discussion

3. Members are asked to comment on the revised documents.

Secretariat May 2010

Guidance Statements

The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) is an expert advisory committee whose members are appointed by the Chief Medical Officer for England and the Chair of the Food Standards Agency following an appointments exercise involving public advertisement. Members serve in their own capacity as independent experts and observe a published code of practice including principles relating to the declaration of possible conflicting interests.

The remit of the committee is to advise all U.K. government departments and agencies with an interest in the safety of chemicals across various sectors, on all aspects of the mutagenicity and genotoxicity of chemicals. The Secretariat is provided by the Health Protection Agency (who lead) and the Food Standards Agency (FSA). Other government departments with an interest provide assessors to the Committee; these are specifically from the Department of Health, the Department of Environment, Food and Rural Affairs (Defra), the Chemicals Regulation Directorate (CRD) of the Health and Safety Executive (HSE) (responsible for legislation regulating chemicals, pesticides, biocides and detergents), the Veterinary Medicines Directorate (VMD: a Defra agency responsible for the licensing of veterinary drugs) and the Medicines and Healthcare Regulatory Agency (MHRA; a DH agency responsible for the licensing of human medicines). In addition there are assessors from the Scottish Government, the Welsh Assembly Government and the Northern Ireland Assembly).

The role of the COM is advisory. It has no regulatory status, although its advice may be provided to an agency that does have such a role (e.g. HSE CRD for occupational aspects and for pesticides etc). Its remit is to advise on all aspects of mutagenicity and genotoxicity of chemicals, and this may involve advice on a specific chemical, and also on testing strategies and research. The COM also has a general remit to advise on important general principles or new scientific discoveries in connection with mutagenic and genotoxic hazards (the inherent property of the substance) or risk (the likelihood of mutagenic or genotoxic effects occurring after a given exposure) and to present recommendations for genotoxicity testing. In practice the bulk of the work of the Committee relates to assessing genotoxicity tests and providing advice on mutagenic hazard of chemicals.

These guidance documents present COM conclusions on these topics and are considered accurate at time of publication. As the science which underpins each of these statements advances, the COM may

consider it necessary to review a statement and issue a revised version.

An overview of the human health consequences of mutation.

Assessment Strategies

[A Strategy for Testing of Chemicals for genotoxicity](#) 2000 G01 v 3

A summary statement which presents the Committee's recommended general approach to assessing the genotoxicity of a chemical and approach to devising a testing strategy for chemicals with limited or inadequate genotoxicity data. .

[Stage 0; Prescreening considerations prior to testing.](#) G02

Details of the Committee's suggested advice on examining the physico-chemical properties, structural alerts for genotoxicity and pre-screening high throughput assays.

[Stage 1; A strategy for *in vitro* assessment of the genotoxicity of chemicals](#) G03

Details of the recommended principal and supporting assays for investigating the mutagenicity of chemicals *in vitro*.

[Stage 2; A strategy for *in vivo* assessment of the genotoxicity of chemicals including germ cell genotoxicity](#) G04

Details of the recommended *in vivo* studies for further investigation of chemicals testing positive for mutagenicity *in vitro*

[Assessment of Threshold for *in vivo* Mutagens](#) 2010 G05 v 1

A statement providing definitions relating to thresholds for *in vivo* mutagens, examples of substances where a threshold mode of genotoxicity has been agreed and approaches to the determination of threshold doses for *in vivo* genotoxins.

Genotoxicity Tests

These Statements are not intended as new or alternative guidelines on the conduct of genotoxicity studies. They are intended to provide an overview of the Committee's advice on these tests. Statements may also offer comments on new and emerging tests.

In vitro bacterial tests for gene mutation.

Details of the Committee's advice on these tests which are core tests in Stage 1 of the testing strategy

In vitro mammalian cell micronucleus assay for clastogenicity and aneuploidy.

Details of the Committee's advice on this test which is a core test in Stage 1 of the testing strategy.

In vitro chromosomal aberration assay in mammalian cells (metaphase analysis) for clastogenicity and aneuploidy

Details of the Committee's advice on this test which is not part of the core strategy.

In vitro mouse lymphoma assay for gene mutation

Details of the Committee's advice on this test which is not part of the core strategy

In vitro assays using human reconstructed skin

Details of the Committee's advice on these tests which is not part of the core strategy

In vitro alkaline comet assay for DNA damage

Details of the Committee's advice on this test which is not part of the core strategy

In vivo Transgenic rodent mutation assay

Details of the Committee's advice on this test which is a core test in Stage 2 of the testing strategy

In vivo Rodent bone marrow MN (and peripheral blood) and CA assays.

Details of the Committee's advice on these tests which are core tests in Stage 2 of the testing strategy

In vivo Rodent comet assay

Details of the Committee's advice on this test which is a core test in Stage 2 of the testing strategy

In vivo Rat liver UDS assay

Details of the Committee's advice on this test which is not part of the core strategy

In vivo supplementary genotoxicity tests in testing strategy

Details of the Committee's advice on supplementary genotoxicity tests which may be part of Stage 2 of the testing strategy.

[Syrian hamster embryo cell transformation assay](#) 2002 G11 v 1
Summary text Summary text Summary text
Summary text Summary text Summary text Summary text

[Considering high dose positive *in vivo* mutagenicity data in the bone marrow assays that may not be biologically significant with regard to considering a chemical to be an *in vivo* mutagen](#) 2003 G13 v 1
Summary text Summary text Summary text Summary text
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[The use of toxicogenomics in toxicology](#) 2004 G14 v 2
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[The cII transgenic mutation assay](#) 2005 G15 v 1
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[Use of target organ mutagenicity data in carcinogen risk assessment](#) 2005 G16 v 1
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[Comparison of the relative performance of the *in vivo* rat liver uds assay and the *in vivo* comet assay](#) 2006 G17 v 1
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[Risk factors affecting the formation of chromosomal aberrations and micronuclei in peripheral blood lymphocytes](#) 2006 G18 v 1
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Significance of chemical induced mutation for human health (April 2010)

Introduction

1. A mutation in the germ cells of sexually reproducing organisms may be transmitted to the offspring, whereas a mutation that occurs in somatic cells may be transferred only to descendent daughter cells. Mutagenic chemicals may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutations, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer.

Evidence for chemical inherited genetic changes

2. A full description of the impact of mutation on human health and classification of inherited defects is beyond the scope of this guidance and the reader is referred to published reference text books.(Turnpenny and Ellard, 2005, Lynch, 2009) In brief, there are many thousands of monogenic (single gene) genetic disorders which have been identified. Detailed information can be found in the online Mendelian Inheritance in man database (www.ncbi.nlm.nih.gov). There is no convincing evidence for chemical induced inheritable germ cell mutations in human populations (Lynch, 2009), although developments in molecular epidemiology may help to address the need for improved study designs (Elespuru and Sankaranarayanan, 2007).
3. There is evidence that exposure of women during pregnancy to *in vivo* mutagens (e.g. anti cancer drugs such as busulfan, cyclophosphamide, cytarabine, 6-mercaptopurine and daunorubicin/doxorubicin) can lead to transplacental exposure of the fetus with subsequent teratogenic effects.(Bishop et al., 1997). There is also convincing evidence from studies using experimental animals that *in vivo* mutagens can cross the placental barrier and increase mutation frequency in the fetus. Examples include ethyl nitrosourea (Mei et al., 2005), cisplatin (Munoz et al., 1996) urethane (Nomura, 2008) and polycyclic aromatic hydrocarbons such as 7,12-

dimethylbenz[a]anthracene, 3-methylcholanthrene and benzo(a)pyrene (Donovan et al., 2004). In addition biomonitoring for DNA damage (using the comet assay) in peripheral blood lymphocytes sampled from umbilical cord blood taken from newborn infants shows significantly higher DNA damage in infants whose mothers were active smokers compared to infants born to mothers who did not smoke (de Assis et al., 2009).

4. There is less evidence for paternal exposure to *in vivo* mutagens resulting in inherited genetic changes. Studies of sperm from smokers show evidence for increased levels of oxidative DNA damage and benzo(a)pyrene diol epoxide DNA and evidence that these adducts are transmitted to embryos (Chang, 2008). A number of epidemiological studies have documented evidence for an association between paternal smoking and childhood leukaemia (Chang, 2008). However overall the evidence for an association between paternal smoking and childhood leukaemia is limited (Wigle et al., 2008)

Mutagenic effects in carcinogenesis

5. DNA damage in a somatic cell may result in a somatic mutation, which may lead to malignant transformation (cancer). A substantial proportion of the known human carcinogens exhibit *in vivo* mutagenic activity (<http://monographs.iarc.fr/ENG/Classification/crthallist.php>). A mutagenic mode of action for carcinogenesis has been reported for a number of these genotoxic carcinogens where a detailed assessment has been published (e.g. cyclophosphamide (McCarroll et al., 2008) and chromium (IV) (McCarroll et al., 2010)). Characterisation of gene mutations in human tumours, in common with the known mutagenic profiles of genotoxins in experimental systems, may provide further insight into the role of environmental mutagens in human cancer (Phillips and Arlt, 2009). Mutational inactivation of tumour suppressor genes and activation of oncogenes are associated with development of a wide range of cancers. (Dixon and Koprass, 2004).

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