Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM)
GACS meeting October 1st 2015

David Lovell

(Chair, St George’s Medical School, University of London)
Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM)

• Assesses and advises on mutagenic risks to humans,
• Advises on important general principles or new scientific discoveries in connection with mutagenic risks,
• Co-ordinates with other bodies concerned with the assessment of mutagenic risks
• Makes recommendations for mutagenicity testing.
• COM is a non-statutory body, and was established in its present form in 1978.
COM (1)

- Advisory Non-Departmental Public Body (ANDPB)
- status as an ANDPB primarily due to its ratio of non-public/public composition of members
- Thirteen members
- Chair (David Lovell),
- 5 academics (including chair and chair of COC ex-officio)
- 3 Employees of companies
- 3 Independent consultants
- 2 lay members
- COC is an internal DH expert advisory committee (DOH)
- COT is a committee of independent experts (FSA)
COM(2)

- Meets 3 times a year
- Joint secretariat: Public Health England (PHE), Food Standards Agency (FSA),
- Assessors from interested Government bodies
- Open and closed sessions.
- Public meeting (entrance by pre-arrangement)
- Limited public comment in meetings
- Declaration of interest
- CVs and Interests posted on web site
COM terms of reference


To assess and advise on the mutagenic risk to man of substances which are:

a. used or proposed to be used as food additives, or used in such a way that they might contaminate food through their use or natural occurrence in agriculture, including horticulture and veterinary practice or in the distribution, storage, preparation, processing or packaging of food;

b. used or proposed to be used or manufactured or produced in industry, agriculture, food storage or any other workplace;

c. used or proposed to be used as household goods or toilet goods and preparations;

d. used or proposed to be used as drugs, when advice is requested by the Medicines and Healthcare products Regulatory Agency;

e. used or proposed to be used or disposed of in such a way as to result in pollution of the environment.

To advise on important general principles or new scientific discoveries in connection with mutagenic risks, to co-ordinate with other bodies concerned with the assessment of mutagenic risks and to present recommendations for mutagenicity testing.
COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT

DRAFT TEMPLATE FOR COM 2012

This template shows the breadth of expertise available to the Committee and is intended to aide members in discussing future needs with regard to expertise necessary to fulfil the terms of reference of the COM. The complement of COM is 12 members (10 specialists and two lay members), attendance of COC chair (ex-officio capacity) and one chair. A deputy chair has been appointed from October 2011. The committee resolves to implement or follow where possible – use of in vitro tests, merging of assays, bolt on comet/Micronucleus tests (MNT) to toxicology studies in order to advance Replacement, Refinement and Reduction of Animals in Research.

Chair: Leadership, presentation of questions/referrals to members, representation of COM views to media. Expertise in mutagenicity.

Input from or advice to COT/COC on Toxicity or Carcinogenicity of chemicals.

Committee evaluation of specialist advice. Overall advice on risk of Mutagenicity.

1. Questions for committee referrals.
2. Advice to CMO/Chair Food Standards Agency, Government Departments.

Structure Activity Relationships, Pre-test screening methods

Metabolism and activation of chemicals. Use of kinetics in mutagen risk assessment. Evaluation of DNA/protein adducts

In-vitro genotoxicity testing

In vivo genotoxicity testing

Specialist knowledge of gene mutation, clastogenicity, aneugenicity, germ cell genotoxicity, cell transformation.

Development and evaluation of new test methods. Development of novel genotoxicity testing strategies. Assessment of mutagenic risk

 Provision of lay summaries of scientific advice and input to drafting of documents.
Definitions
Mutagen: An agent which causes changes in genetic material which are transmitted from generation to generation.

Genotoxin: An agent which damages genetic material or interferes with its transmission during cell division.

Clastogen/Aneugen: An agent which interferes with the transmission of genetic material in cell division.
‘Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection.’

Bruce N. Ames, William E. Durston, Edith Yamasaki & Frank D. Lee (1973)

Proceedings of the National Academy of Sciences 70 2281-2285.
About us

What we do

The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) advises government on the mutagenicity of chemicals used in pesticides, pharmaceuticals and other products.

COM provides independent advice to government departments and agencies on the potential mutagenicity and genotoxicity of chemicals (whether they are likely to cause mutation in cells), from natural products to new synthetic chemicals used in pesticides or pharmaceuticals. It also advises on strategies for reducing the risk from these chemicals.
Papers

2013

- MUT/2013/01 Food Standards Agency funded research project on combined effects of aneugens benzydamines and other aneugens which act by disrupting microtubule assembly. (Discussed in closed session therefore not published on website).
- MUT/2013/02 Draft statement on photogeneotoxicity testing.
- MUT/2013/03 Update on the development and validation of the Ig-A gene mutation assay.
- MUT/2013/04 Swimming pool disinfection by-products and genotoxicity assessment.
- MUT/2013/05 Summary of biomonitoring data.
- MUT/2013/06 Review of current approaches to germ cell testing.
- MUT/2012/07 OECD draft test comet.

2012
Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

Alcoholic beverages COM/02/55
Actonif COM/03/93
Acrylamide COM/05/91
Acrylamide COM/07/91
Aneuploidy COM/00/52
Benzimidazoles COM/07/93
Cell Transformation Assays COM/12/94
2-chlorobenzylidene malononitrile and CS spray COM/98/92
cfl Transgenic Mutation Assay COM/05/92
Chlorophenols COM/12/91
Chromium Picolinate COM/04/92
Comet assay COM/88/93
Guidance Documents
Guidance

A strategy for testing of chemicals for genotoxicity

From: Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
First published: 1 December 2011
Part of: Committee on Mutagenicity: statements and guidance

5 guidance statements on testing chemicals with no or inadequate genotoxicity data.

Documents

Guidance on a strategy for genotoxicity testing of chemical substances
PDF, 419KB, 71 pages
This file may not be suitable for users of assistive technology. Request a different format.

Guidance on a strategy for genotoxicity testing of chemical substances: prescreening considerations

1989

Guidelines for the Testing of Chemicals for Mutagenicity

2000

GUIDANCE ON A STRATEGY FOR GENOTOXICITY TESTING OF CHEMICAL SUBSTANCES

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Stage 1: Preliminary Considerations Prior to Genotoxicity Testing (Figure 1)

- Physico-chemical and Toxicological Properties
- Structure Activity Relationships
- Screening Tests

Stage 1: In Vitro Genotoxicity Testing (Figure 2)

- Overview of Strategy
- Description of Stage 1 Tests - General Aspects
- Discussion of Stage 1 Tests - Core Tests
  - In Vitro Bacterial Test for Gene Mutation
  - In Vitro Mammalian Cell Mutations Test for Carcinogenicity and Mutagenicity
  - In Vitro Chromosomal Aberration Assay in Mammalian Cells (Metaphase Analysis) for Carcinogenicity and Aneuploidy
- In Vitro Mouse Lymphoma Assay for Gene Mutation and Carcinogenicity
- In Vitro CHG/PIF Assay for Gene Mutation
- In Vitro Assays using Human Reconstituted Skin
- In Vitro Alkaline Comet Assay for DNA Damage

Stage 1: Summary (In Vitro Genotoxicity Testing)

- Overview of Strategy
- Discussion of Stage 2 Initial Testing Strategy - General Aspects
- Discussion of Stage 2 Recommended Tests in Vitro Genotoxicity Tests
  - Rodent Micronucleus and Chromosome Aberration Assay for Carcinogenicity and Aneuploidy
  - Transgenic Mammalian Test, Metaphase Analysis (TGCM) for Carcinogenicity
  - Rodent Comet Assay for DNA Damage
  - Assay-Cor-Human Test (H-UCM) Assay for DNA Damage

Stage 2: Supplementary Tests

Stage 2: Summary (In Vitro Genotoxicity Testing)

V: Possible Future Developments

Annex 1: Sensitivity and Specificity Data Considered by COM

Annex 2: Tabulation of Genotoxicity Tests in Stages 1 and 2 and Mutagenicity and Genotoxicity End Points Detected

Annex 3: Rationale for Selection of Ames Test and In Vitro Micronucleus Assays as the Two Principal In Vitro Tests
Figure 2: Screening (Stage 0) and in vitro tests (Stage 1)

Stage 0:
Structure Activity Relationships (SAR), pre-screening tests, and physico-chemical properties (substance/impurities)

Stage 1 Core Tests:
1. Bacterial gene mutation (Ames test)
2. Clastogenicity and aneugenicity (in vitro micronucleus test)

NEGATIVE results in all Stage 1 tests

EQUIVOCAL result in any Stage 1 test

POSITIVE result in any Stage 1 test

Consider other factors that indicate additional evaluation is required:
- Structural alerts,
- Results of other tests (e.g. rodent tumours)

Consider:
- Reproducibility
- Historical control data
- Mode of Genotoxic Action (MoGA)
- Results of stage 0
- Misleading positive results (e.g. bacterial specific metabolism, or excessive mammalian cell cytotoxicity)

Substance is not mutagenic

Insufficient evidence to assess the mutagenicity of the substance

Substance should be considered to be an in vitro mutagen

Proceed to Stage 2 only where in vivo testing is permitted*

* In situations where in vivo testing is prohibited, further in vitro testing should be considered
## Assessment Strategies

| Guidance on the significance of chemical-induced mutation for human health | 2012 | G6 | V1 |
| A Strategy for Testing of Chemicals for Genotoxicity. | 2011 | G strategy | V3 |
| The strategy recommended by COM for testing chemicals with no existing genotoxicity data. |
| Stage 0: Prescreening considerations prior to testing. | 2011 | G0 | V1 |
| Link to the Committee's advice on examining the physico-chemical properties, structural alerts for genotoxicity and screening high throughput assays. |
| Stage 1: A strategy for in vitro assessment of the genotoxicity of chemicals. | 2011 | G1 | V1 |
| Link to the Committee's recommended approach to in vitro testing. |
| Stage 2: A strategy for in vivo testing of the genotoxicity of chemicals including germ cell genotoxicity. | 2011 | G2 | V1 |
| Link to the Committee's recommended strategy for in vivo genotoxicity testing. |
| Stage 3: Guidance on a strategy for chemicals with inadequate genotoxicity data. | 2011 | G3 | V1 |
| Details of the Committee's recommended approach to genotoxicity testing and hazard assessment of chemicals with inadequate genotoxicity data. |
| Impurities: An interim statement on an approach to assessment of impurities. | 2011 | G4 | V1 |
| Assessment of Threshold for in vivo Mutagens | 2010 | G5 | V1 |
| 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. |

Guidance on the Significance of Chemical-induced Mutation for Human Health

“An important concept is that for those chemicals which cause disease through mutagenicity, it is not possible to identify a threshold dose below which the effect does not occur, and that even low exposures can be associated with a small increase in risk.”

“Mutations have the potential to result in the development of cancer and, if they occur in the germ cells, may also affect future generations. There is a clear causal association between exposure to some mutagens and increased incidence of cancer in humans. The impact of germ cell mutations on human health is less well understood, and currently there are no clear causal associations. There is evidence, however, for heritable genetic effects of mutagenic chemicals in animal models.”

Guidance on a strategy for testing of chemicals for mutagenicity.

“For most chemicals recognised as \textit{in vivo} somatic cell mutagens no further genotoxicity testing is necessary since they will be assumed to be potential genotoxic carcinogens and potential germ cell mutagens. However in some specific cases germ cell studies may be undertaken to demonstrate whether a somatic cell mutagen is, or is not, a germ cell mutagen.” COM (2000)
During 2014 the Committee:

- Produced a statement on Mutational Spectra
- Considered the Tox-Tracker assay
- Reviewed the mutagenicity of alcohol
- Commented on OECD Test Guidelines Programme
  - Draft TG in vitro Syrian hamster embryo (SHE) cell transformation assay
  - Draft TG474 Mammalian erythrocyte micronucleus test
  - Draft TG475 Mammalian bone marrow chromosomal aberration test
  - Draft TG473 in vitro Mammalian chromosome aberration test
  - Draft TG487 in vitro Mammalian cell micronucleus test
  - Draft TG in vivo Mammalian alkaline comet assay
  - Draft TG genotoxicity testing for manufactured
- Carried out Horizon Scanning (informal)
During 2015 the Committee:

- Statement on the mutagenicity of alcohol and its metabolite (acetaldehyde)
- Potential role of oxidative damage in alcohol's mutagenic and carcinogenic mode of action
- Threshold for Chromium VI? (Environment Agency)
- 3-D tissue models
- Cycloastragenol TA-65 (ACNFP) telomere amplification
- OECD guidelines
Horizon Scanning

- Integration of \textit{in vivo} genotoxicity assays in repeat dose toxicity testing (and transgenics)
- Epigenetics and epimutations
- Mitochondrial DNA mutations
- Human mutation rates and disease
- Development of the Pig-A assay in human erythrocytes
- Quantitative approaches to genotoxicity dose-response data
COM Project Board (Triennial) Review

Scope / Terms of Reference for the Review

Stage One: To establish whether there is a continuing need for the functions performed by COM and, if so, whether these functions should be delivered by an alternative delivery model;

Stage Two: If it is agreed that the functions of COM should continue to be delivered as an ANDPB, the review will then consider its governance arrangements to ensure COM is compliant with recognised principles of good corporate governance.

Note: The structure, efficiency and effectiveness of COM will be considered during both stages.
Annex A - Call for Evidence Form

Confidentiality

Information provided in response to this consultation, including personal information, may be published or disclosed in accordance with the access to information regimes (these are primarily the Freedom of Information Act 2000 (FoIA) and the Data Protection Act 1998 (DPA)).

If you want the information that you provide to be treated as confidential please be aware that under the FoIA there is a statutory Code of Practice with which public authorities must comply and which deals, amongst other things, with obligations of confidence. In view of this, it would be helpful if you could explain why you regard the information you are providing as confidential. If we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. An automatic confidentiality disclaimer generated by your IT system will not, of itself, be regarded as binding on the Department.

The Department will process your personal data in accordance with the DPA and in the majority of circumstances this will mean that your personal data will not be disclosed to third parties.

About You

Name: 

Organisation: 

Email/postal address: 

Would you categorise your response as from:
- Individual
- Public sector organisation
- Charitable/voluntary sector healthcare organisation
- Private sector
- None of the above

Please state: 

If your response is from an umbrella organisation representing a wider membership, please indicate the approximate number of members consulted and the number of responses received: 

Please indicate what relationship you have with COM, if applicable: 

Questions

There is no need to answer all nine questions unless you wish to do so. For those which you do answer please provide evidence to support your answers wherever possible. If you wish to send supporting documentation please email as an attachment to TR.COM@dh.gsi.gov.uk
Future Issues

- Triennial Review
- New testing methods
- Next Generation Sequencing (NGS)
- Human genetic architecture
- Epigenetics and epimutations
- Human germ cell mutagens
- Hazard Identification v. Risk Assessment
- Qualitative v. quantitative assessment of results
- Margin of Exposures (MOE)
- Thresholds v. Benchmark Doses
- Diseases other than cancer