During the 26th Plenary meeting of 9 December 2003, the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) adopted the attached "Proposal for Recommended Mutagenicity / Genotoxicity Tests for the Safety Testing of Cosmetic Ingredients to be included in the Annexes to Council Directive 76/768/EEC".

The Commission services invite interested parties for their comments.

Please send your comments before 19 February 2004 to the following e-mail address :

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THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

PROPOSAL

FOR

RECOMMENDED MUTAGENICITY / GENOTOXICITY TESTS FOR THE SAFETY TESTING OF COSMETIC INGREDIENTS TO BE INCLUDED IN THE ANNEXES TO COUNCIL DIRECTIVE 76/768/EEC

(SCCNFP'S NOTES OF GUIDANCE)

adopted by the SCCNFP during the 26th plenary meeting of
of 9 December 2003

1. INTRODUCTION

In the risk assessment of substances it is necessary to address the potential effect of "mutagenicity". It can be expected that some of the available data had been derived from tests conducted to investigate harmful effects on genetic material ("genotoxicity"). Hence, both the terms "mutagenicity" and "genotoxicity" are used in this document. (1)

The chemical and structural complexity of the chromosomal DNA and associated proteins of mammalian cells, and the multiplicity of ways in which changes to the genetic material can be effected makes it difficult to give precise, discrete definitions.
Mutagenicity refers to the induction of permanent transmissible changes in the amount or structure of the genetic material of cells or organisms. These changes may involve a single gene or gene segment, a block of genes or whole chromosomes. Effects on whole chromosomes may be structural and/or numerical.
Genotoxicity is a broader term and refers to potentially harmful effects on genetic material which are not necessarily associated with mutagenicity. Thus, tests for genotoxicity include tests which provide an indication of induced damage to DNA (but not direct evidence of mutation) via effects such as unscheduled DNA synthesis (UDS), sister chromatid exchange (SCE), DNA strandbreaks, DNA adduct formation or mitotic recombination, as well as tests for mutagenicity. (1)

The term mutation refers to a permanent change in the amount or structure of the genetic material of an organism, which may result in a heritable change in the characteristics of the organism. These alterations may involve individual genes, blocks of genes, or whole chromosomes. Mutations involving single genes may be a consequence of effects on single DNA bases (point mutations) or of larger changes, including deletions and rearrangements of DNA. Changes involving chromosomes as entities may be numerical or structural. 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.

Modification by chemicals of the segregation of chromosomes during both mitotic and meiotic cell division can lead to malsegregation and thus to aneuploidy. This is a type of mutation which involves a change in chromosome number from the normal diploid or haploid status of a species, whereas polyploidy represents an increase in chromosome number which is an exact multiple of the haploid number, e.g. triploidy (3n) and tetraploidy (4n). Aneuploidy makes a major contribution to human embryonic loss and some birth defects such as Down Syndrome (trisomy of chromosome 21). Chemicals which induce aneuploidy as their predominant mutagenic effect are termed aneugens. A wide range of chemicals (primarily those which modify the spindle of the dividing cell) such as colchicine, benomyl, trichlorphon and griseofulvin have been shown to induce aneupoloidy in test systems ranging from *in vitro* cultured mammalian cells and somatic tissue of intact animals, to germ cells of rodents. Currently, evidence for the carcinogenicity of aneugens is limited. However a large number of aneugens are inducers of malignant transformation in Syrian hamster cells *in vitro*. Given the association between aneuploidy and heritable effects in germ cells, and potential carcinogenicity, the Committee concludes that the testing of chemicals for potential aneugenic activity should be included in genotoxicity testing strategies. Data from studies of induced aneuploidy have been used for the classification of chemicals in the EU and thus the advice provided here is timely.

It is therefore apparent that information on the three levels of mutation, namely gene, clastogenicity (i.e. structural chromosome aberrations) and aneuploidy (i.e. numerical chromosomal aberrations), is necessary to provide comprehensive coverage of the mutagenic potential of a chemical.

This is also the case when assessing carcinogenic potential, since all three types of mutation have been shown to be associated with the activation and expression of oncogenes, and loss or inactivation of tumour suppressor genes and other classes of genes implicated in carcinogenesis.
Genotoxic (or genotoxicity) refers to agents, which interact with the DNA and/or the cellular apparatus which regulates the fidelity of the genome, e.g. the spindle apparatus, and enzymes such as the topoisomerases. It is a broad term that includes mutation as well as damage to DNA or the production of DNA adducts, by the chemical itself or its metabolites. Genotoxic effects also include unscheduled DNA synthesis (UDS), sister chromatid exchange (SCE) and mitotic recombination. However the detection of such effects does not in itself provide direct evidence of inherited mutations. (2)
(Committee on Mutagenicity: Guidance on Strategy for Testing of Chemicals for Mutagenicity. UK Department of Health, London, December 2000, pp.5-7)
The Committee reaffirms its view published in 1989 that there is currently no single validated test that can provide information on all three end-points, namely gene mutation, clastogenicity and aneuploidy and thus it is necessary to subject a given substance to several different assays (2).

Stage 1 Tests

1. Bacterial Test for gene mutation
2. Test for clastogenicity and for indication of aneugenicity
   i) *in vitro* metaphase analysis or
   ii) *in vitro* micronucleus test[*]
3. Mammalian cell mutation assay (currently, the preferred choice in the mouse lymphoma assay)

Test 3 is not required for those substances where there will be little or no human exposure (2)

A recent publication by IWGT Expert Group (15), representing industries and universities, has stated:

The group agreed upon a number of principles, such as the need for an elementary data set that addresses the three major genetic endpoints, namely mutagenicity, chromosome breakage (clastogenicity), and aneugenicity. For hazard evaluation, data are needed from an elementary data set providing information on (1) gene mutations, (2) structural chromosome aberrations, and (3) numerical chromosome aberrations. The tests conducted to evaluate effects on these endpoints need to be properly conducted, i.e. according to existing guidelines, IWGT recommendations or best scientific practice.

As defined by Art.2 of Council Directive 76/768/EEC (21) all cosmetic products imply a large and continuous human exposure which must not cause any damage to human health
Article 2: "A cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use ".

[*] **If there are indications of aneugenicity in the metaphase analysis (e.g. hyperdiploidy, polyploidy) or positive results in the micronucleus test, there is a need to confirm whether the compound is an aneugen by using an appropriate staining procedure**

2. MUTAGENICITY TESTING REQUIREMENTS IN DIFFERENT SECTORS

2.1. BIOCIDES

A recent approved Directive of the European Parliament and of the Council, concerning the placing of biocidal products on the market, states in its Art. 2 that "under the conditions of use, the biocidal product shall pose only a low risk to humans, animals and the environment".
The common core data set for active substances considered by this Directive requires, among the toxicological and Metabolic studies (6.6. of Annex IIA):

6.6.1. *In vitro* gene mutation study in bacteria
6.6.2. *In vitro* cytogenicity study in mammalian cells
6.6.3. *In vitro* gene mutation assay in mammalian cells
6.6.4. If positive in 6.6.1, 6.6.2 or 6.6.3, then an *in vivo* mutagenicity study will be required (bone marrow assay for chromosomal damage or a micronucleus test)
6.6.5. If negative in 6.6.4 but positive *in vitro* tests then undertake a second *in-vivo* study to examine whether mutagenicity or evidence of DNA damage can be demonstrated in tissue other than bone marrow
6.6.6. If positive in 6.6.4 then a test to assess possible germ cell effects may be required (22).

2.2. FOOD ADDITIVES

The EU Scientific Committee on Food (3) recommends that a battery of four tests should be used, two at gene level (in prokaryotic and eukaryotic cells) and two at the chromosome level (*in vitro* and *in vivo*) (see Table 1).

Table 1

FOOD ADDITIVES
EC Scientific Committee on Food

Measurements of:

1. a test for induction of gene mutations in bacteria
2. a test for induction of chromosome aberrations in mammalian cells *in vitro*
3. a test for induction of gene mutations in mammalian cells *in vitro*
4. positive results in any of the above *in vitro* test will normally require further assessment of genotoxicity *in vivo*

2.3. FOOD CONTACT MATERIALS

The CEC Scientific Committee on Food requests three *in vitro* mutagenicity studies for packaging materials. A test for gene mutations in bacteria, a test for gene mutations in cultured mammalian cells (20).

2.4. COSMETICS

As stated on page 14 of SCC "Notes of Guidance for Testing of Cosmetic Ingredients for Their Safety Evaluation" (19) the safety evaluation Procedure as applied by the SCCNFP refers to the ingredients in Annexes III, IV, VI and VII of Directive 76/768/EEC :

- Annex III is a list of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- Annex IV is a list of colouring agents allowed for use in cosmetic products;
- Annex VI is a list of preservatives which cosmetic products may contain;
- Annex VII is a list of UV filters which cosmetic products may contain.
-

All these ingredients, for their chemical properties, might present a risk to human health and therefore require an adequate design of toxicological studies, including the mutagenicity studies. These ingredients, moreover, are largely, routinely and extensively used by the consumers, as they are applied to a considerable part of the body and for a long period of the lifetime.

3. SPECIFIC CONSIDERATIONS ABOUT THE TESTS

3.1. LIMITED EFFECTIVENESS OF BACTERIAL TESTS

There are circumstances where the performance of the bacterial reverse mutation test does not provide sufficient information for the assessment of genotoxicity. This may be the case for compounds that are highly toxic to bacteria (e.g., some antibiotics) and compounds thought or known to interfere with mammalian cell-specific systems (e.g., topoisomerase inhibitors, nucleoside analogues, or certain inhibitors of DNA metabolism). In these cases, usually two *in vitro* mammalian cell tests should be performed using two different cell types and two different endpoints, i.e., gene mutation and chromosomal damage. Test approaches currently accepted for the assessment of mammalian cell gene mutation include tests for mutation: 1) at the tk locus using mouse lymphoma L5178Y cells or human lymphoblastoid TK6 cells; 2) at the hprt locus using CHO cells, V79 cells, or L5178Y cells; or 3) at the gpt locus using AS52 cells. When such additional tests are performed because of the high level of toxicity of the test chemical to bacteria, it is still important to perform the bacterial reverse mutation test because some antibacterial agents, albeit highly toxic to the tester strains, are genotoxic at very low, sub-lethal concentrations in the bacterial reverse mutation test (e.g., nitrofuran antibiotic) (4).

3.2. LIMITED SENSITIVITY OF TWO ASSAYS

Combination of assays for gene mutation in bacteria and for chromosomal aberrations (plus aneuploidy) in mammalian cells may not detect a small proportion of agents with the potential for *in vitro* mutagenicity. Thus a third assay, comprising an additional gene mutation assay in mammalian cells, should be used, except for compounds for which there is little or no human exposure. Certain mammalian cell gene mutation protocols that have been widely employed, particularly some of those involving the use of Chinese hamster cells, are now considered to be insufficiently sensitive, predominantly on statistical grounds. Of the available systems, measuring mutations at the thymidine kinase (tk) locus in L5178Y mouse lymphoma cells has gained broad acceptance and has the advantage of detecting not only gene mutations but also various sizes of chromosome deletions"(2).

3.3. THE NEED TO INCLUDE THE *IN VITRO* MICRONUCLEUS TEST

The genome may sustain a wide spectrum of damage leading to possible permanent changes in DNA sequence. Generally, the DNA lesions induced by chemical mutagens need the cell to pass through the cell cycle before being expressed as cytological endpoints. Presence of DNA damages may alter mechanisms involved in the control and regulation of cell cycle leading to different cellular responses in relation to the nature and/or the number of lesions (5).
The expression of molecular damages is complex and may be expressed under different cytological levels.
Structural chromosomal aberrations (CA) result from breakages and/or breakage – rejoining events that occur during the G0/G1 or G2 stages of the cell cycle but are visualized when cells are at the metaphase stage (6).
Micronuclei (MN) arise during cell division from either chromosome laggards in anaphase or from chromosome fragments. Therefore, micronuclei may contain a whole chromosome and/or an acentric fragment. The cytokinesis block assay based on the inhibition of actins in the division furrow by cytochalasin-B allows the identification of cells having divided once in culture (7).
Moreover by combining both assays with fluorescence in situ hybridisation (FISH) using pancentromeric or chromosome specific probes, it is possible to distinguish between stable chromosome rearragements, chromosome loss, chromosome breaks and chromosome non-disjunction (8,9).
The simultaneous use of these cytogenetic methodologies will enable to reach a higher sensitivity for the adequate and refined hazard assessment of mutagens and will lead to a better understanding of the biological mechanisms involved (10,11).

4. SCCNFP OPINION

NOTES OF GUIDANCE

3-4.6 MUTAGENICITY/GENOTOXICITY

In the safety evaluation of cosmetic ingredients it is necessary to address the potential effect of "mutagenicity/genotoxicity"; somatic cell mutagens are considered, moreover, to be involved in neoplastic transformations
.
Mutagenicity refers to the induction of permanent transmissible changes in the amount or structure of the genetic material of cells or organisms. These changes may involve a single gene or gene segment, a block of genes or whole chromosomes. Effects on whole chromosomes may be structural and/or numerical.

Genotoxicity is a broader term and refers to potentially harmful effects on genetic material which are not necessarily associated with mutagenicity. Thus, tests for genotoxicity include tests which provide an indication of induced damage to DNA (but not direct evidence of mutation) via effects such as unscheduled DNA synthesis (UDS), sister chromatid exchange (SCE), DNA strandbreaks, DNA adduct formation or mitotic recombination, as well as tests for mutagenicity (1).

At present, no single validated test method can provide information on all the above mentioned genetic endpoints; their diversity usually precludes the detection of more than one of them in a single system (12, 23).

Several *in vitro* and *in vivo* mutagenicity/genotoxicity tests are available : they have been described in OECD Guidelines (12) as well as in Annex V to Directive 67/548/EEC (13).
As a general recommendation, the SCCNFP is of the opinion that the base level of evaluation of the potential for mutagenicity/genotoxicity of a cosmetic ingredient to be included in Annexes III,IV,VI and VII of Council Directive 76/768/EEC (19) should include tests to provide information on the three major genetic endpoints, namely (1) mutagenicity at a gene level, (2) chromosome breakage and/or rearrangements (clastogenicity),and (3) numerical chromosome aberrations (aneugenicity): these three base level of information represent the actual consensus of international groups of scientific experts (15, 23),and of an expert advisory committee (2).
Moreover, by considering that Salmonella assay (Bacterial Reverse Mutation Test) does not detect all compounds with mutagenic potential (2, 4, 23) an additional gene mutation assay in mammalian cells is necessary for the evaluation of those chemicals like the cosmetic ingredients to which a large fraction of the consumers, for a great part of their lifetime is exposed.
The need to include two test for detection of gene mutations is recognized also for the evaluation of food additives (3), of substances to be used in food contact materials (20) and of biocides (22).

Therefore the SCCNFP, for the *in vitro* base level testing of cosmetic ingredients indicated above, recommends four assays, represented by the following test systems:

STAGE 1 : *IN VITRO* TESTS

1. Tests for gene mutation
1.1. Bacterial Reverse Mutation Test (OECD 471, 21st July 1997; EC B.13/14, 19th May 2000)
1.2. *In vitro* Mammalian Cell Gene Mutation Test (currently, the preferred choice is the mouse lymphoma assay) (OECD 476 21st July 1997; EC B.17, 19th May 2000)

2. Tests for clastogenicity
2.1. *In vitro* Mammalian Chromosome Aberration Test (OECD 473, 21st July 1977; EC B.10 19th May 2000)

3. Tests for aneugenicity and non-disjunction

3.1. *In Vitro* Micronucleus Test (Guideline proposed to OECD) (18)

There could be instances for which the base level of all four *in vitro* tests seems not necessary or should be modified: in these cases a scientific justification for deviation from the battery of tests, and the decision taken should be given.

Certain structurally alerting molecular entities are recognised as being casually related to the carcinogenic and/or mutagenic potential of chemicals. Examples of structural alerts include alkylating electrophilic centers, unstable epoxides, aromatic amines, azostructures, N-nitroso-groups, aromatic nitro-groups.
For some classes of compounds with specific structural alerts, it is established that specific protocol modifications/additional tests are necessary for optimum detection of genotoxicity. The additional testing needed when the chosen 4-test battery yields negative results for a structurally alerting test compound could consist of such modifications.

In Vitro Metabolic Activation

Cells should be exposed to the test substance both in the presence and absence of an appropriate metabolic activation system. The most commonly used system is a cofactor-supplemented post-mitochondrial fraction (S9) prepared from the livers of rodents (usually rat) treated with enzyme-inducing agents such as Aroclor 1254 or combination of phenobarbitone and beta-naphthoflavone. The post-mitochondrial supernatant fraction is usually used at concentrations in the range from 10 to 30 percent v/v in the S9 mix. The choice and concentration of a metabolic activation system may depend upon the class of chemical being tested. In some cases it may be appropriate to utilize more than one concentration of post-mitochondrial fraction. For azo dyes and diazo compounds, using a reductive metabolic activation system may be more appropriate (16, 17).

In vivo studies

There are several reasons for mutagenicity testing beyond the *in vitro* base level may be required. Normally, when some concern is raised by positive results from *in vitro* tests, further testing may be justified.

The selection of the *in vivo* assays cannot be defined a priori and depends on the positive results observed in the *in vitro* assays.

Nevertheless, before undertaking any *in vivo* testing, a thorough review is needed of the *in vitro* test results of the substance (with its toxicokinetic profile), available information on its chemistry and toxicological profile, as well as data on analogous ingredients. Finally, it is obvious that a particular *in vivo* test should be conducted only when it can be reasonably expected from all the properties of the test substance and the proposed test protocol that the specific target tissue will be adequately exposed to the test substances and/or its metabolites.

In June 2003, a new strategy for testing oxidative hair dye ingredients for their potential genotoxicity/mutagenicity/carcinogenicity has been adopted by the SCCNFP (14). This strategy imposes six *in vitro* tests instead of the four mentioned above, viewing the fact that several permanent hair dyes formulations contain aromatic amines or may form them during the oxidative reaction.

The *in vitro* level 1 of genotoxicity/mutagenicity testing strategy recommended by the SCCNFP for different classes of cosmetic ingredients to be included in the technical annexes of Directive 76/768/EEC is represented in table 2.

Table 2

IN VITRO MUTAGENICITY / GENOTOXICITY TESTING STRATEGY RECOMMENDED BY SCCNFP

(Notes of Guidance (SCCNFP/0690/03)

<table>
<tr><td colspan="4">COSMETIC INGREDIENTS (ANNEXES: III, IV, VI, VII)</td></tr>
<tr><td colspan="2">1</td><td>2</td><td>3</td></tr>
<tr><td>BACTERIAL REVERSE MUTATION</td><td>MAMMALIAN CELL GENE MUTATIONS</td><td>STRUCTURAL CHROMOSOME ABERRATIONS</td><td>NUMERICAL CHROMOSOME ABERRATIONS</td></tr>
<tr><td colspan="4">POSITIVE / NEGATIVE</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td colspan="2">UV ABSORBING INGREDIENTS (ANNEX VII)</td><td colspan="2">HAIR DYES (ANNEX III)</td></tr>
<tr><td>PHOTOMUTAGENICITY TEST (Bacterial, Mammalian cells)</td><td>PHOTOCLASTOGENICITY TEST (Chromosome aberrations, Micronucleus)</td><td>DNA DAMAGE ASSAY, UDS, SCE, COMET, DNA ADDUCTS, STRAND BREAKS, ETC</td><td>IN VITRO CELL TRANSFORMATION (SHE Cells)</td></tr>
<tr><td colspan="2"></td><td colspan="2">HAIR DYES' REACTION PRODUCTS</td></tr>
<tr><td colspan="4">↓</td></tr>
<tr><td colspan="4">IN VIVO TESTS IF NEEDED</td></tr>
</table>

5. BIBLIOGRAPHY

1. EUROPEAN CHEMICAL BUREAU: Technical Guidance Document on Risk Assessment. European Commission, EUR 20418EN, 1 April 2003
2. COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT: Guidance on a strategy for Testing of Chemicals for mutagenicity. December 2000;
3. Guidance on Submission on Food Additive Evaluations by the Scientific Committee on Food: SCF/CS/ADD/GEN/26/Final, 12th July 2001
4. FDA; Toxicological Principles for the Safety of Food Ingredients. Red Book 2000, July 7th 2000.
5. SHACKELFORD, R.E., KAUFMANN, W.K. & PAULES, R.S.(1999) Cell cycle control, checkpoint mechanisms and genotoxic stress. Environ. Health Perspect. 107,p. 5-24.
6. VAN DELFT, J., BAAN, R.A. & ROZA, L.(1998) Biological effect markers for exposure to carcinogenic compound and their relevance for risk assessment. Crit. Rev. Toxicol. 28, p: 477-510
7. ELHAJOUHJI, A., TIBALDI, F. & KIRSCH-VOLDERS, M. (1997) M. Indication for thresholds of chromosome non-disjunction versus chromosome lagging induced by spindle inhibitors *in vitro* in human lymphocytes. Mutagenesis, 12 (3), p: 133-140.
8. TUCKER J.D. & PRESTON, R. J. (1996) Chromosome aberrations, micronuclei, aneuploidy, sister chromatid exchanges and cancer risk assessment. Mut. Res. 365, p: 147-159.
9. TUCKER, J. (1998) Use of chromosome translocations for measuring prior environmental exposures in humans, in Biomarkers : Medical and workplace applications, edited by Joseph Henry Press, p: 117-132.
10. LAURENT, C. ,(2000) Cancérogenèse: facteurs génétiques et environnementaux. Guide Pratique du Cancer edited by the « Association Belge contre le Cancer and Editions Kluwer ». Chap 4, pp 1-36,
11. LAURENT,C., (2001) Biomonitoring as a tool in exposure assessment. In : Risk Assessment : occupational exposure. pp 25 – 39. Editors : G. Vollmer, L. Gianonni, L. Olsen, B –Sokull-Klütgen and S. Munn. European Commission - Joint Research Center.
12. OECD Guidelines for the Testing of Chemicals (2000): Introduction to the OECD Guidelines on Genetic Toxicology Testing and Guidance on the Selection and Application of Assays pp.1-18, Vol.2 Paris;
13. Testing Methods for Classification, Packaging and Labelling of Dangerous Substances in the European Union (1997). Methods for the Determination of Toxicity. pp. 111-274
14. Updated Recommended Strategy for Testing Hair Dyes for Their Potential Genotoxicity/Mutagenicity/Carcinogenicity. SCCNFP/0720/03 Final, 24th –25th June 2003.
15. MULLER,L., et al.,(2003)Strategy for genotoxicity testing and stratification of genotoxicity test results- report on initial activities of the IWGT Expert Group. Mutation Research 540 177-181.
16. MATSUSHIMA,T., et al., Factors modulating mutagenicity microbial tests.(Ed.). Norpoth, K.H. and Garner, R.C.(1980) Short-term test systems for detecting carcinogens,(Springer, Berlin-Heidelberg-New York) pp.273-285.
17. PRIVAL, M.J., et al (1984) Mutagenicity of Benzidine and Benzidine-congener dyes and selected monoazo dyes in a modified Salmonella assay. Mutation Research 136:33-47.
18. PARRY,J.M.(1997) A proposal for a new OECD Guideline for the *in vitro* micronucleus test. EEMS (draft)
19. The SCCNFP Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation. SCCNFP/0690/03, 20 October 2003.

20. Guidelines of the Scientific Committee on Food for the presentation of an application for safety assessment of a substance to be used in food contact material prior to its authorisation. SCF/CS/PLEN/GEN/100 Final, 19 December 2001.
21. Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to Cosmetic Products. O.J. L 262, 27 September 1976, p. 169.
22. Directive 98/8/EC of the European Parliament and the Council of 16 February 1998 concerning the placing of biocidal products on the market. OJ L 123, 24 July 1998, p. 1.
23. DEARFIELD, K.L. et al. (2002) Genotoxicity risk assessment : a proposed classification strategy. Mutation Research 521, 121-135.