

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

OPINION

CONCERNING

**CHEMICAL INGREDIENTS IN COSMETIC PRODUCTS CLASSIFIED
AS**

CARCINOGENIC, MUTAGENIC OR TOXIC TO REPRODUCTION

ACCORDING TO THE CHEMICALS DIRECTIVE 67/548/EEC

adopted by the SCCNFP during the 18th Plenary meeting
of 25 September 2001

1. Term of References

1.1. Background

Council Directive 76/769/EEC is related to the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations.

Directive 94/60/EC amending for the 14th time Directive 76/769/EEC stipulates that “*substances appearing in Annex I to Council Directive 67/548/EEC and classified as carcinogens category 1 or 2, mutagens category 1 or 2, toxic for reproduction category 1 or 2, may not be used in substances or preparations placed in the market for use by general public in individual concentrations equal to or more than the concentration specified in Annex I to Directive 67/548/EEC, or concentration specified in Annex I to Directive 88/379/EEC relating to the classification, packaging and labelling of dangerous preparations*”.

The list of concerned substances was updated in Directives 97/56/EC and 1999/43/EC, respectively the 16th and 17th Amendments to Directive 76/769/EEC, and latest by Directive 2001/41/EC of the European Parliament and of the Council. By derogation these provisions do not apply to cosmetic products, which are regulated by Directive 76/768/EEC.

1.2. Request to the SCCNFP

In view of the classification of chemical substances as carcinogenic, mutagenic, or toxic for reproduction according to Council Directive 67/548/EEC, SCCNFP has been requested to give an opinion on the following :

- Does the SCCNFP consider that such substances pose a significant threat to the health of the consumer when used in cosmetic products?
- Does the SCCNFP propose any restrictions or conditions for the use of such substances in cosmetic products?

1.3. Definition of terms

Chemical substances classified as carcinogenic, mutagenic and toxic to reproduction are divided into 3 categories. The following definitions are reproduced directly from Annex VI of the Council Directive 67/548/EEC.

Carcinogenic substances

Category 1

Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Substances classified as carcinogenic, mutagenic, or toxic for reproduction

Category 2

Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:
appropriate long-term animal studies,
other relevant information.

Category 3

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

Category 3 actually comprises 2 sub-categories:

- (a) *substances which are well investigated* but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;
- (b) *substances which are insufficiently investigated.* The available data is inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

Mutagenic substances**Category 1**

Substances known to be mutagenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and heritable genetic damage.

Category 2

Substances which should be regarded as if they are mutagenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of heritable genetic damage, generally on the basis of:
appropriate animal studies,
other relevant information.

Category 3

Substances which cause concern for man owing to possible mutagenic effects. There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in Category 2.

Substances toxic to reproduction**Category 1**

Substances known to impair fertility in humans. There is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility.

Substances known to cause developmental toxicity in humans. There is sufficient evidence to establish a causal relationship between human exposure to the substance and subsequent developmental toxic effects in the progeny.

Category 2

Substances which should be regarded as if they impair fertility in humans. There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of:

clear evidence in animal studies of impaired fertility in the absence of toxic effects, or, evidence of impaired fertility occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of other toxic effects,
other relevant information.

Substances which should be regarded as if they cause developmental toxicity to humans. There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity, generally on the basis of:

clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of other toxic effects,
other relevant information.

Category 3

Substances which cause concern for human fertility, generally on the basis of:

results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of other toxic effects, but where the evidence is insufficient to place the substance in category 2,
other relevant information.

Substances which cause concern for humans owing to possible developmental toxic effects, generally on the basis of:

results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of other toxic effects, but where the evidence is insufficient to place the substance in category 2,
other relevant information.

2. Toxicological Evaluation and Characterisation

2.1. Strategy

The present opinion proposes to prohibit the use in cosmetic products of substances classified according to Council Directive 67/548/EEC as carcinogens category 1 or 2, mutagens category 1 and 2, or toxic to reproduction category 1 or 2 and substances with similar potentials. Substances classified according to Council Directive 67/548/EEC as carcinogens category 3, mutagens category 3, or toxic to reproduction category 3 and substances with similar potentials, should not be used in cosmetic products unless it can be demonstrated that their levels do not pose a threat to the health of the consumer.

The industry should be asked :

- To submit information to SCCNFP of cosmetic products which may contain carcinogenic or mutagenic substances or substances toxic to reproduction category 1 or 2, either because such substances may occur as part of a natural ingredient or as impurity in a component or may be formed during the production process.
- To submit information to SCCNFP on the presence of category 3 carcinogens, mutagens or substances toxic to reproduction in cosmetic products
- To submit information to SCCNFP on substances with similar potentials as those classified according to Council Directive 67/548/EEC as carcinogens, mutagens or toxic to reproduction if they are present in cosmetic products.

2.2. General

The classification of a substance as carcinogenic, mutagenic, or toxic to reproduction according to Council Directive 67/548/EEC represents a hazard classification. Some substances classified as carcinogenic category 1 or 2 represent a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk). These substances can be identified by the specific risk phrase used for labelling (R49: May cause cancer by inhalation). A substance classified as a category 3 carcinogen could be a substance which has been well investigated but the evidence that it will cause cancer in humans is limited, or a substance which has been insufficiently investigated. Classification of substances as mutagen category 3 and toxic to reproduction category 3 is based on limited evidence of the respective effects in humans or insufficient investigation. SCCNFP considers that it is important also to include category 3 substances in the present opinion.

According to the Council Directive 1999/45/EC certain preparations although not considered dangerous, may nevertheless present a threat to the health for users. Since the classification of a substance may take place several years after a hazard has been identified, it follows that in order to protect consumers, substances with similar potentials as substances classified as carcinogenic, mutagenic, or toxic to reproduction according to Council Directive 67/548/EEC should have the same restrictions. It is envisaged that some of these substances are present in cosmetic products.

Moreover, some category 1 and 2 substances may be present in cosmetic products as part of a natural ingredient, an impurity in one of the components or may be formed during the manufacturing process. In such cases, it must be demonstrated that the levels of concerned substances in the product do not pose a threat to the health of the consumer.

2.3. Safety evaluation**2.3.1. Assessment of human exposure**

The calculations should be based on the use of cosmetics and retention factors given in the Notes of Guidance for Testing of Cosmetic Ingredients for Their Safety Evaluation (1).

2.3.2. Effects of concern

Substances classified as carcinogenic, mutagenic, or toxic to reproduction and substances with similar potentials represents a health hazard and ought not to be present in cosmetic products. However, even though such substances are not intentionally added, they may be present as a part of a natural ingredient, as an impurity in one of the components, or may be formed during the manufacturing process.

Council Directive 67/548/EEC does not take into account the wide range in toxic potency that can be observed both in human epidemiological studies and in animal experiments. Thus, in cases where a carcinogenic or mutagenic substance, or a substance toxic to reproduction is present in a cosmetic product, it is necessary to perform a risk assessment to determine if a maximum level of the substance in the product can be established that does not represent a threat to the health of the consumer.

In order to assess potential risks of carcinogens, mutagens, or substances toxic to reproduction in humans, determination of the dose-responses is necessary. Traditionally, it has been considered that for toxic effects induced by non-genotoxic mechanisms it is possible to identify a no-effect level, while for toxic effects induced by genotoxic mechanisms the prudent view of non-threshold dose-response relationships has been adopted. The threshold paradigm implies that some exposure can be tolerated by an organism with essentially no elicitation of a toxic response. In the case of non-threshold endpoints, it is assumed that there is no level of exposure that does not pose a small, but finite, probability of inducing the toxic effect.

Risk assessment should be made on a case-by-case basis. Moreover, information on differences in toxico-kinetics and toxico-dynamics should always be taken into consideration. The default approach of risk assessment for a threshold toxic effect involves margins of safety (MOS) considerations. The total exposure from all product types is estimated for the substance and converted to a total systemic exposure dose (SED) based on knowledge of the skin absorption of the substance. This value is then compared with the no-observed adverse effect level (NOAEL) for the effect. The default approach for a non-threshold toxic effect involves determination of a dose-descriptor (e.g. T25 (2-4)) and conversion of the dose descriptor to the corresponding human dose descriptor (e.g. HT25). This is done by dividing with the appropriate scaling factor for interspecies dose scaling, based on comparative metabolic rates. Subsequently, the lifetime cancer risk at the SED is calculated with the use of the human dose descriptor by linear extrapolation, unless sufficient evidence for a non-linear dose-response curve is available.

2.4. Conclusions

SCCNFP considers that chemical substances identified as carcinogens, mutagens, or toxic to reproduction when present in cosmetic products are of concern to the health of the consumer. EU classifies carcinogens and mutagens and substances toxic for reproduction according to the Council Directive 67/548/EEC in 3 categories, i.e. substances identified from human studies and thus known to cause effects in humans (category 1), substances identified from animal studies and regarded as if they cause similar effects in humans (category 2) and substances that are of concern because of possible toxic effects in human (category 3). In addition, substances with similar potentials as those classified by EU may be identified. The use of such substances should also be restricted in the same way as substances classified according to the Directive 67/548/EEC.

SCCNFP acknowledges that cosmetic products may contain small amounts of carcinogens, mutagens, or substances toxic to reproduction even if such substances are not intentionally added to the product. In these cases, it will be necessary to perform risk assessment on a case-by-case basis to establish that the product does not pose a threat to the health of the consumer.

Substances classified in categories 1 and 2 have more stringent restriction within EU than substances classified as category 3. The reason follows from the criteria for classifications. Many category 3 carcinogens are non-genotoxic and it may be possible to determine a dose that can be tolerated with essentially no elicitation of a toxic response. Other category 3 carcinogens may pose a significant risk if present in a cosmetic product, but sufficient data to classify the substance in category 1 or 2 was not available when the substance was classified. Similar considerations also apply for category 3 mutagens and substances toxic to reproduction. On this basis SCCNFP considers that the same restrictions may not be applicable on all category 3 substances.

2.5. References

1. The rules governing cosmetic products in the European Union (2000). CosmetLex Vol 3. Cosmetics legislation. Cosmetic products. Notes of Guidance for Testing of Cosmetic Ingredients for Their Safety Evaluation, European Commission
2. EC 2000. *Guidelines for setting specific concentration limits for carcinogens in Annex 1 of directive 67/548/EEC. Inclusion of potency considerations.* Commission working group on the classification and labelling of dangerous substances. Brussel.
3. Dybing E, Sanner T, Roelfzema H, Kroese D, Tennant RW (1997), T25: A simplified carcinogenic potency index: Description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity. *Pharmacol Toxicol.* 80: 272 - 279.
4. Sanner T, Dybing E, Willems MI, Dinant Kroese ED (2001). A simple method for quantitative risk assessment of non-threshold carcinogens based on the dose descriptor T25. *Pharmacol Toxicol.* 88: 331 - 341.
5. Commission Directive 93/21/EEC of 27 April 1993 adapting to technical progress for the 18th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

3. Opinion of the SCCNFP

SCCNFP considers that the presence of carcinogens, mutagens, or substances toxic to reproduction in cosmetic products is of concern to the health of the consumer.

Substances classified according to Council Directive 67/548/EEC as carcinogens category 1 or 2 (except substances only carcinogenic by inhalation), mutagens category 1 and 2, or toxic to reproduction category 1 or 2 and substances with similar potentials, must not be intentionally added to cosmetic products.

Substances classified according to Council Directive 67/548/EEC as carcinogens category 3, mutagens category 3, or toxic to reproduction category 3 and substances with similar potentials, must not be intentionally added to cosmetic products unless it can be demonstrated that their levels do not pose a threat to the health of the consumer.

If a carcinogen, mutagen, or a substance toxic to reproduction is present in a cosmetic product from its presence in a natural ingredient, as an impurity, or because it is formed during the manufacture, it must be demonstrated that the product does not pose a threat to the health of the consumer.

4. Other considerations

Not applicable.

5. Minority opinions

Not applicable.