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**SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS
SCCP**

Extended Opinion on

Parabens, underarm cosmetics and breast cancer

Adopted by the SCCP
by written procedure on 28 January 2005

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1. BACKGROUND

Parabens (4-Hydroxybenzoic acid, its salts and esters) are regulated by Cosmetic Directive 76/768/EEC, Annex VI, part 1, reference 12 and can therefore be used as a preservative up to a maximum concentration of 0.4 % in the finished product for 1 ester and up to 0.8 % for mixtures of esters. The substances are marketed with the symbol (+) and therefore may also be added to cosmetic products in concentration other than those laid down in Annex VI for other purposes apparent from the presentation of the product.

In its opinion of 17 February 1999 (SCCNFP/0125/99) concerning the restrictions on materials listed in Annex VI of Directive 76/768/EEC on cosmetic products, the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) stated that those substances indicated by (+) in Annex VI, when incorporated into cosmetic formulations for non-preservative functions, should be subjected to the same restrictions in usage levels and warnings as when used for preservative effects.

If a preservative marked with the symbol (+) is added for non-preservative purpose to a cosmetic product in a concentration higher than that laid down in the Annex VI, data to substantiate its safety should be submitted to the SCCNFP.

The European Commission has received publications on the possible link between underarm cosmetic products and the risk of breast cancer and a safety file prepared by the Norwegian Institute of Public Health with a safety assessment of parabens. In addition COLIPA¹ provided scientific critique of the publication by Darbre et al. (Concentrations of Parabens in Human Breast Tumours. Journal of Applied Toxicology 2004, 24, 5-13).

2. TERMS OF REFERENCE

The SCCP was asked to answer the following questions:

- 1. Do the data provided within the requests indicate a potential risk for the development of breast cancer in past users of underarm cosmetics?*
- 2. In particular, do the data provided indicate a potential risk for the development of breast cancer in past users of underarm cosmetics containing parabens?*
- 3. If yes, does the SCCP recommend any further restrictions with regard to the use of underarm cosmetics containing parabens?*
- 4. Do the data provided justify a concern that parabens when used up to the maximum authorized concentration in cosmetic products might pose a risk to the consumer?*
- 5. If yes, do the data provided justify a change in the maximum concentration for their use in cosmetic products and would this concentration apply to all parabens used (methyl-, ethyl-, propyl- and butylparaben)?*

¹ COLIPA – European Cosmetics Toiletry and Perfumery Association

3. OPINION

3.1. The link between breast cancer and the use of (paraben-containing) underarm cosmetics

Parabens are the alkyl esters of p-hydroxybenzoic acid and are allowed as antimicrobial preservatives for use in food products, medicinal products and cosmetics. The link between the use of underarm cosmetics and breast cancer has been promoted through a number of publications by Darbre and Harvey, in which the following facts were considered:

- underarm cosmetics are applied frequently to an area directly adjacent to the breast;
- they are not rinsed off, but have the opportunity to accumulate in the underarm and upper breast area;
- the upper outer quadrant of the breast is the most frequent site of carcinoma;
- estrogens are known to be involved in breast cancer;
- parabens have shown to exert some weak estrogenic effects;
- parabens have been reported to be included in 99% of all cosmetic products;
- methyl paraben has been measured in human breast tumours at a 12.8 ng/g level, while ethyl, propyl and butyl paraben were found at 2.0 - 2.6 ng/g in the affected tissue.

[Byford et al. 2002, Darbre 2003, Harvey 2003, Harvey and Everett 2004, Darbre et al. 2004a, Harvey and Darbre 2004].

These publications led to a number of "letters to the editor" and opened a discussion on the scientific evidence linking the use of underarm cosmetics to a higher incidence in breast cancer. The major remarks formulated were the following:

- (i) there were some important deficiencies in the study design:
 - lack of control tissue when measuring concentrations of parabens in breast tumours;
 - blank samples clearly contaminated with parabens;
 - high variability in individual blank values;
 - no study of the general therapeutic history of the tissue donors and no mention of the paraben-containing anti-cancer drugs the patients were using;
 - no study of donors' exposure to consumer products containing parabens;
 - brief descriptions of tissue handling;
- (ii) the most frequently occurring paraben was the methyl ester, which had shown to have the lowest estrogenic activity in the *in vitro* and *in vivo* estrogenicity studies;
- (iii) existing epidemiological data indicate the absence of an association between underarm cosmetics and breast cancer;
- (iv) the majority of underarm cosmetics do not contain parabens as preservatives (> 98%)

[Golden and Gandy 2004, Jeffrey and Williams 2004, Flower 2004].

Darbre et al. and Harvey formulated replies to these comments and therein clearly state that it had never been their aim to link tumour grade, quadrant incidence of the tumour or patterns of underarm cosmetic use in patients. Moreover, Darbre et al. acknowledge that the study on the concentrations of parabens in breast tumours could not identify either the route of entry or the source of the parabens. Carcinogenicity was not considered in the study and the presence of

parabens was not claimed to cause the breast tumours. Finally, they mention that epidemiological studies of underarm cosmetic use and breast cancer fell out of the scope of the paper and were, therefore, not discussed [Darbre et al. 2004b, 2004c, 2004d, Harvey 2004].

In September 2004, the Danish Institute of Food and Veterinary Research issued a report titled "Note on Parabens in Food, Cosmetics and Consumer Products". Therein, the authors also elaborate on the suggested relationship between the use of parabens in underarm cosmetics and the development of breast cancer. They came to the conclusion that there is no indication to support such a causal relationship [Anonymous 2004].

4. CONCLUSION

- *Do the data provided within the requests indicate a potential risk for the development of breast cancer in past users of underarm cosmetics?*

As discussed under point 3.1. of this opinion, there are insufficient data to establish a clear link between the use of underarm cosmetics and breast cancer. The authors of the studies that led to the suggestion of a connection between the use of underarm cosmetics and breast cancer, clearly state that they did not have the intention to prove such a link.

Two recent epidemiological studies on the use of underarm cosmetics in relation to breast cancer exist. The authors of these studies could not establish a relationship between the use of underarm deodorants and antiperspirants and the occurrence of breast cancer [Mirick et al. 2002, McGrath 2003].

Moreover, according to current knowledge in this field, age is the major risk factor with regard to the incidence of breast tumours, followed by family history of breast cancer [De Grève 2004]. The effect of hormones has been acknowledged, but not all cancers are estrogen receptor positive. In fact, it is strongly suggested that for the pathogenesis of a significant proportion of all breast cancers, hormones do not play a significant role. It is true, however, that estrogens might have a role through their mitogenic action to further stimulate the malignant transformation of premalignant cells [De Grève 2004]. For this reason, exposure to potent estrogens should be avoided whenever possible.

Further important clinical data are:

- breast cancer tumours occur most frequently in the upper quadrant of the breast (closest to the armpit). A clear relationship, however, has been found with the amount of gland tissue present at that location;
- it is clinically well-established that the circulation of blood/lymph goes from the breast towards the armpit and further towards different organs and tissues and not vice-versa, making an exchange process from the armpit towards the breast tissue highly speculative.

It is the opinion of the SCCP that, viewing the current knowledge, there is no evidence of demonstrable risk for the development of breast cancer caused by the use of underarm cosmetics.

- *In particular, do the data provided indicate a potential risk for the development of breast cancer in past users of underarm cosmetics containing parabens?*

With regard to their general toxicological profile, acute, subacute and chronic toxicity studies in rats, dogs and mice, have proven parabens to be practically non-toxic, not carcinogenic, not genotoxic or co-carcinogenic, and not teratogenic. Parabens are not expected to accumulate in tissues and the ester linkage of the parabens is expected to be readily hydrolyzed [SCF 1994].

In a number of *in vitro* studies, such as the recombinant yeast estrogen screen, parabens have proven to be able to bind to the estrogen receptor, to activate genes controlled by these receptors, and to stimulate cell growth and increase the level of immune reactive estrogen receptor protein. The estrogenic potency increases with increasing length and branching of the alkyl side chains (methyl < ethyl < propyl < butyl < isobutyl), but remains at all times 1000 to 1,000,000 times below the potency of 17 β -estradiol. Hydroxybenzoic acid, the common metabolite of all parabens, appeared to be inactive in the *in vitro* assays.

The *in vivo* estrogenic activities of parabens have been tested in uterotrophic assays employing either immature female rodents or adult ovariectomized female rodents after oral, subcutaneous or dermal administration. Again, butyl paraben appeared being more potent than propyl, ethyl and methyl paraben, and again the values remained several magnitudes of order below the potency of 17 β -estradiol. Conflicting results have been reported for p-hydroxybenzoic acid tested *in vivo*. One study claimed that it has no estrogenic effect; another study gives potency values 1000-fold below the 17 β -estradiol level [EFSA 2004, Anonymous 2004, Paulsen and Alexander 2003].

Taking into consideration the answer to the question 2.2 and viewing the fact that the estrogenic potential of parabens has been found to be very low, it is the opinion of the SCCP that, in the light of the present knowledge, there is no evidence of demonstrable risk for the development of breast cancer caused by the use of paraben-containing underarm cosmetics.

- *If yes, does the SCCP recommend any further restrictions with regard to the use of underarm cosmetics containing parabens?*

Not relevant (the answer to the previous question was negative).

Questions 4 and 5 have been answered in “Opinion on the safety evaluation of parabens”, doc. n° SCCP/0873/05 of 28 January 2005.

5. MINORITY OPINION

Not applicable

6. REFERENCES

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