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SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS

SCCP

Extended Opinion on

the Safety Evaluation of Parabens

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.

2. TERMS OF REFERENCE

The SCCP was asked to answer the following questions:

- 1. 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?*
- 2. 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)?*

3. OPINION

3.1. Recent Official Reports on Parabens

Parabens are the alkyl esters of p-hydroxybenzoic acid and are allowed as antimicrobial preservatives for use in food products, medicinal products and cosmetics.

Recently, three important official reports have been issued on the toxicity profile and safety of the use of parabens in consumer products. They were based upon a previous report of the Scientific Committee on Food [SCF 1994].

3.1.1. The Scientific Committee on Food (SCF), SCF 1994

- a) In a document issued 25 February 1994 on p-hydroxybenzoic acid alkyl esters and their sodium salts, the SCF reported that acute toxicity of parabens was only seen at high dosages. All the parabens produced similar symptoms with rapid onset of ataxia, paralysis and central nervous system depression, resembling anaesthesia, suggesting their toxicity is related mainly to the free acid. With non-lethal dosages, recovery is prompt.
- b) *In vitro* and *in vivo* mutagenicity studies provided no evidence of genotoxicity for methyl, propyl and butyl paraben. A carcinogenicity study with butyl paraben in the mouse was reported to be negative, although the study appeared not being performed according to the appropriate guidelines.
- c) Reproduction and teratogenicity studies in the rat with ethyl paraben (up to 10% in the diet) found no adverse effects on reproductive performance. Foetal anomalies, however, were observed, though without a clear dose-response relationship. For this reason, a new oral teratogenicity study in the rat was requested.
- d) The absorption, metabolism and excretion of parabens had been studied in rats, rabbits, dogs and humans. The methyl, ethyl and propyl esters of p-hydroxybenzoic acid appeared to be well absorbed and the ester linkage was assumed to be readily hydrolyzed. Urinary excretion of the unchanged esters was very low, usually less than 1% of the administered dose. Butyl paraben was suspected to follow a different metabolite pathway, but studies in dogs had shown no evidence of accumulation of either parent compound or metabolites in the tissues.
- e) A number of special studies revealed that the parabens (in particular propyl and butyl paraben) were able to induce cell proliferation in the forestomach and glandular stomach of rats. A supplementary study in the rat on propyl paraben, given as a solution instead of a ground powder, was requested.
- f) Finally, the report stated several subchronic and chronic toxicity tests conducted in rats, dogs and mice, resulting in a NOAEL-value of 1000 mg/kg bw/day. Based on this value, the EC Scientific Committee on Food established a temporary Acceptable Daily Intake (ADI) of up to 10 mg/kg as the sum of methyl, ethyl and propyl paraben and their sodium salts. That ADI was temporary since the Committee asked for some additional information with regard to the reproductive effects and more data on the cell proliferation effect of the compounds in the rat forestomach.

3.1.2. The European Food Safety Authority (EFSA), EFSA 2004

- a) Newly available studies on the developmental toxicity of methyl paraben in rats, mice, hamsters and rabbits were evaluated and no evidence of developmental toxicity up to 300 mg/kg bw/day (rabbits) or 550 mg/kg bw/day (rodents) was observed.
- b) In the re-evaluation of the proliferative effects of parabens on forestomach cells in rats, it was concluded that this effect only occurred above a certain threshold exposure that is not reached in man.
- c) An evaluation was also undertaken of the estrogenicity of parabens *in vitro*. However, for methyl, ethyl and propyl paraben, such activity was not detectable *in vivo* using uterotrophic assays (oral and s.c.) in mice and rats. On the contrary, for butyl and isobutyl paraben (not used in food), a positive effect was seen after s.c. injection. For the major metabolite, p-hydroxybenzoic acid, no effect was present.
- d) Dietary administration of methyl and ethyl paraben to juvenile male rats had no effect on sex hormones and reproductive organs at dosage levels up to 1000 mg/kg bw/day. Thus the NOAEL for methyl and ethyl paraben is 1000 mg/kg bw/day. For propyl paraben impaired spermatogenesis, reduced testosterone levels and reduced sperm cell count numbers were observed and a LOAEL of 10 mg/kg bw/day was established.
- e) The EFSA report came to the conclusion that the ADI of up to 10 mg/kg remains in place for the sum of methyl and ethyl paraben and their sodium salts on the basis of a NOAEL of 1000 mg/kg. For propyl paraben on the other hand, this ADI was not considered appropriate. An ADI for the propyl ester could not be established because of the lack of a clear NOAEL.

3.1.3. The Danish Institute of Food and Veterinary Research, Anonymous 2004

In September 2004, the Danish Institute of Food and Veterinary Research issued a report entitled "Note on Parabens in Food, Cosmetics and Consumer Products".

This document refers to the EFSA report for a full overview of the available toxicity data on parabens, and focuses on the problems of endocrine disrupting potential, effects on the male reproductive system, skin penetration of parabens, breast cancer & paraben-containing cosmetics, possible interactions between different xenoestrogens, and possible low doses effects.

The authors repeat the conclusions of the EFSA report [EFSA 2004] and do not raise additional concerns with regard to the use of parabens in cosmetics [Anonymous 2004].

3.1.4. The Norwegian Institute of Public Health (NIPH), Paulsen and Alexander 2003

In 2003, the NIPH published a report briefly summarizing the toxicity of the parabens and studying in particular the alleged endocrine disrupting potential of the molecules. The authors conclude that:

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- a) Different parabens have varying estrogenic potential in cell cultures and animal studies, but their potency is 1000 to 1,000,000 times lower than the potency of 17 β -estradiol or testosterone.
- b) In order to perform a revised and complete risk evaluation, data on reproduction in long-term animal experiments, data from multiple generation experiments and more detailed knowledge on the pharmacokinetics of parabens under use conditions, are required.
- c) A preliminary risk assessment followed by the calculation of the Margin of Safety (MoS) for the use of parabens as a preservative in cosmetic products, leads to worst case MoS's of 122 and 73 for adults and children, respectively.

In these calculations, the following parameters were considered:

- NOAEL (developmental toxicity of propyl and butyl paraben)	10 mg/kg bw/day
- total global exposure to all cosmetic products:	17.7 g
- percutaneous absorption (based on human <i>in vitro</i> studies):	3.5%
- contribution of dietary parabens:	not considered (very small)
- mean human body weight:	60 kg
- maximum permitted concentration of paraben mixture:	0.8%
- larger body surface per body mass of children versus that of adults:	factor 1.7
- extensive biotransformation of parabens into p-hydroxybenzoic acid (liver, skin):	not accounted for

- d) Neither interactions, additive or synergistic effects, nor effects at doses below the ones tested, are likely.

3.2. Toxicity Profile of the parabens used in cosmetic products

Viewing the availability of the four above-mentioned official reports, the toxicity profile of the parabens will only be briefly summarised in the current report and more detailed sections will be dedicated to the specific potential problem areas.

3.2.1. General toxicology

Based on acute, subacute and chronic toxicity studies in rats, dogs and mice, parabens have been proven to be practically non-toxic, not carcinogenic, not genotoxic nor co-carcinogenic, and not teratogenic. A NOAEL value of 1000 mg/kg bw/day was accepted for all esters.

Parabens are not expected to accumulate in tissues and the ester linkage of the parabens is expected to be readily hydrolyzed [SCF 1994].

3.2.2. Estrogenic effects of parabens

In a number of *in vitro* studies, such as the recombinant yeast estrogen screen, parabens have proven being able to bind 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. p-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 claims 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].

3.2.3. Effects of parabens on the male reproductive system

Methyl, ethyl, propyl and butyl paraben have been examined for effects on the reproductive organs in the male offspring of rats and mice.

Male neonatal Wistar rats s.c. injected with **butyl paraben** at 2 mg/kg bw/day on postnatal days 2 to 18 showed no detectable effects on any reproductive parameter [Fisher et al. 1999]. This study, however, demonstrated only very minor effects for compounds such as genistein, bisphenol A and octylphenol administered at high dosages.

On the contrary, 10 mg/kg bw/day administered to post-weaning male Wistar rats for eight weeks through their diet caused a decrease of the cauda epididymal sperm reserve, a decrease in sperm count, in daily sperm production and in serum testosterone [Oishi 2001].

In another study, pregnant Sprague Dawley rats were s.c. injected with daily dosages of 100 or 200 mg **butyl paraben**/kg bw from gestational day 6 to postnatal day 20, and the offspring were examined. Both tested dosages showed clear effects, amongst which a decrease in sperm count and sperm motile activity in the epididymus [Kang et al. 2002].

Administered to ICR (Cjr:CD-1) mice in the diet for 10 weeks at dosage levels of 14.4, 146 and 1504 mg/kg bw/day, **butyl paraben** showed some clear effects at the two highest dosage levels, including increased epididymal weights, despite of a decrease in testis spermatid count and in serum testosterone levels. The authors were unable to explain this discrepancy [Oishi 2002a].

In 2002, Darbre et al. published a study on the estrogenic activity of **isobutyl paraben** *in vitro* and *in vivo* (subcutaneous administration). The authors conclude that the studies clearly show that isobutyl paraben is more potent, but the doses used in the *in vivo* test were not higher than the ones tested for all other parabens (1.2 and 12 mg isobutyl paraben/mouse, equivalent to approximately 24 and 240 mg/kg bw). [Darbre et al. 2002].

As far as **propyl paraben** is concerned, a four-week administration via the diet (0, 10, 100, 1000 mg/kg bw/day) to the Wistar rat showed similar effects as caused by butyl paraben, though at a dosage of 100 mg/kg bw/day. The propyl ester caused only minor effects at 10 mg/kg bw/day. No dose-response relationship was observed [Oishi 2002b].

Recently, **methyl** and **ethyl paraben** have been tested for effects on secretion of sex hormones and the Wistar rat male reproductive system. Dosages of 103 and 1030 mg/kg bw/day failed to induce adverse effects [Oishi 2004].

Taking together the above-mentioned studies, it is clear that butyl paraben shows the highest potency with regard to effects to the male reproductive system. This is in accordance with the results of the estrogenicity tests. It was also concluded that, in order to define an exact NOAEL for propyl paraben, additional studies were necessary [EFSA 2004, Anonymous 2004].

Very recently, a detailed developmental toxicity evaluation of **butyl paraben** given by oral gavage to Sprague-Dawley rats became available [Daston 2004]. Dosage levels of 0, 10, 100 and 1000 mg/kg bw/day were administered on gestation days 6-19 (sperm positive day being gestation day 0). Foetuses were evaluated on gestation day 20. The highest dosage level caused decreases in maternal weight gain (significant during gestation day 18-20 interval). Maternal food consumption was, however, also decreased in that group for the gestation days 6-20 interval. No differences from the control group could be observed in any of the developmental parameters including embryo/foetal viability, foetal weight, malformations or variations. The maternal NOAEL for butyl paraben was established on 100 mg/kg bw/day. It was further concluded that butyl paraben does not have the potential to cause developmental toxicity in the Sprague-Dawley rat at oral dosages up to 1000 mg/kg bw/day [Daston 2004].

3.2.4. Breast cancer and the use of paraben-containing cosmetics

The suggested link between the use of (paraben-containing) underarm cosmetics and breast cancer has been discussed and refuted in a separate SCCP opinion on Parabens, underarm cosmetics and breast cancer [SCCP/0874/05]. This issue will therefore not be reconsidered in the present opinion.

4. CONCLUSION

- *Is the concern justified that parabens, when used up to the maximum authorized concentration in cosmetic products, might pose a risk to the consumer?*

Methyl and ethyl paraben

Previous toxicological data have led the EU Scientific Committee on Food to establish an Acceptable Daily Intake (ADI) level of 10 mg/kg bw/day as the sum of methyl, ethyl and propyl p-hydroxybenzoic acid esters and their sodium salts [SCF 1994].

With the most recent findings on the alleged estrogenic effects of the parabens and more importantly with the newly discovered effects on the male reproductive system, as described under point 3.3 of this opinion, the European Food Safety Authority reviewed the safe use of parabens in food. The Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food came to the conclusion that the ADI remained unchanged for methyl, ethyl paraben and their sodium salts, but that for propyl paraben no ADI could be established, by lack of a clear NOAEL value.

Therefore, it is the opinion of the SCCP that methyl and ethyl paraben can be safely used up to the maximum authorized concentration as actually established (0.4%).

Propyl, butyl and isobutyl paraben

Propyl paraben

- The developmental rat study provided for propyl paraben failed to indicate a clear NOAEL value, but it suggested that the potency of propyl paraben is clearly lower than the potency of butyl paraben [Oishi 2002b]. For the latter, a NOAEL value of 2 mg/kg bw/day was proposed. This value was obtained in a study where the compound was orally administered to male Wistar rats for 17 days and the investigated reproductive parameters included testicular weight, aquaporin-1 immunoexpression, rete testis distention and efferent duct epithelial cell height [Fisher 1999].
- The LOAEL-value for propyl paraben in Wistar rats was shown to be 10 mg/kg bw/day [Oishi 2002a].
- The major adverse effects of concern caused by propyl paraben involve the male reproductive system. It must not be forgotten, however, that the majority of cosmetic products will be used by females. Especially the cumulative cosmetic exposure value of 17.79 g/day is a clear overestimation for the normal male population.

Butyl and isobutyl paraben

- For butyl paraben a NOAEL value in Cjr:CD-1 mice (oral study) of 2 mg/kg bw/day has been proposed [Oishi 2002b].
- Very recently, a developmental study on butyl paraben became available. In that study, it was shown that the maternal NOAEL of butyl paraben was 100 mg/kg bw/day and that the compound did not have the potential to cause developmental toxicity in the Sprague-Dawley rat.
It is known that potent estrogens interfere with the development of the reproductive system, placental function, embryonic growth, embryo viability and maintenance of pregnancy [Daston et al. 1997]. Although indirectly, these parameters could be responsive indicators of estrogenicity. This leads to the suggestion that butyl paraben did not have a strong estrogenic potential during the developmental study.

It is the opinion of the SCCP that the available data do not enable a decisive response to the question of whether propyl, butyl and isobutyl paraben can be safely used in cosmetic products at individual concentrations up to 0.4%.

Therefore industry is requested to provide the complete developmental toxicity dossier of these three esters of p-hydroxybenzoic acid. The reason for this request is that the current opinion is based upon extended literature data and there is a significant possibility that additional *in vivo* data have been generated within industry without having been submitted to the SCCP.

- *If yes, do the available data 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)?*

Methyl and ethyl paraben

For the methyl and ethyl p-hydroxybenzoic acid esters, the maximum authorized concentrations remain unchanged.

Propyl, isopropyl, butyl and isobutyl paraben

As the present discussion is based solely upon data in the literature, it is the SCCP's opinion that more information is needed in order to formulate a final statement on the maximum concentration of propyl, isopropyl, butyl and isobutyl paraben allowed in cosmetic products.

More specifically, the following data are requested before end of March 2005:

- full descriptions of available *in vitro* percutaneous absorption studies;
- a complete dossier with regard to the reproductive and developmental toxicity of propyl, isopropyl, butyl and isobutyl paraben, with special focus on the male reproductive system.

5. MINORITY OPINION

Not applicable

6. REFERENCES

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7. ACKNOWLEDGEMENTS

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