EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Consumer Products

SCCP

# OPINION ON

# Parabens

COLIPA n° P82

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCCP adopted this opinion at its 16th plenary of 24 June 2008

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

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SCCP

Questions concerning the safety of consumer products (non-food products intended for the consumer).
In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

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## 1. BACKGROUND

Between January 2005 and October 2006, the Scientific Committee on Consumer Product (SCCP) adopted three opinions on parabens:

- The first opinion (SCCP/0874/05) addressed parabens and breast cancer: "*Extended Opinion on Parabens, underarm cosmetics and breast cancer".*

- The second opinion "(SCCP/0873/05) was "*An extended opinion on the Safety Evaluation of Parabens*" with the following conclusions:

  "*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."*

- The third opinion (SCCP/1017/06) discussed a COLIPA[1] submission intended to fulfil the 2005 SCCP request for additional data.
  Several remarks were formulated and the tests provided by were found to contain too many shortcomings in order to be considered as scientifically valid, wherefore the SCCP declared *the conclusions of opinion SCCP/0873/05 to remain unchanged*.

Upon industry's request, a hearing took place in October 2007, in which the dossier was defended. The current opinion describes the outcome of the industry hearing and some additional publications.

## 2. TERMS OF REFERENCE

*Does the SCCP consider the continued use of propyl, isopropyl, butyl and isobutylparaben in a concentration up to the existing 0.4% weight/weight as individuals or 0.8% when used in combination in cosmetic products safe for the consumer?*

[1] COLIPA - The European Cosmetic Toiletry and Perfumery Association

# 3. OPINION

## 3.1 Historical background

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

In the SCCP opinion of January 2005 with regard to the safety evaluation of parabens, an overview of the general toxicological profile of the different p-hydroxybenzoic acid esters was provided, together with a discussion of the available literature with regard to the putative estrogenic effects of the esters and their alleged effects on the male reproductive system (SCCP/0873/05).

Important to retain is that the studies dealing with the reproduction toxic effects of the different parabens were nearly all performed by the same laboratory. These results are available only in the form of scientific publications issued over a period of 4 years (Oishi 2001, 2002a, 2002b, 2004). The SCCP noted that the Oishi publications contained insufficient detail and therefore requested full test descriptions of all available *in vivo* reproduction studies. Industry initiated repeat studies of the Oishi experiments in what they called a more robust setting to refute the conclusions made. Together with additional *in vitro* dermal absorption studies, these repeat studies were submitted to the SCCP and discussed in 2006 (SCCP/1017/06). The major discussion points in this opinion were situated in the fields of (i) reproductive toxicity and (ii) dermal absorption.

### *(i) Reproduction toxicity*

The obtained NOAEL levels of 2 mg/kg bw/day for Butyl Paraben (Fisher et al. 1999, subcutaneous administration in the rat) and 10 mg/kg bw/day for Propyl Paraben (Oishi 2002, oral administration in the rat) generate MoS levels which are too low to declare the preservatives safe for the intended cosmetic use (up to 0.4% in finished products).

Therefore, industry decided to repeat the studies that led to these values, using the same protocol, but a more robust study design. These studies were performed with Butyl Paraben and Methyl Paraben, since those molecules were considered to bracket the chain lengths of all parabens used and to allow interpolation of the results for the remaining Parabens (Ethyl and Propyl Paraben).

After careful study of these reproductive toxicity repeat tests, the SCCP noticed a number of shortcomings (see also chapter 3.2.2), with the main conclusion that the studies could not be considered scientifically acceptable (SCCP/1017/06). As such, the request from the SCCP for reliable reproduction toxicity data, with emphasis on the male reproductive system, remained unanswered.

### *(ii) In vitro dermal absorption*

Three *in vitro* dermal absorption studies are discussed in detail in the SCCP/1017/06 opinion. They were initiated to show that, although Parabens have the potential to penetrate into human or rat skin, the skin has substantial capability to metabolize these esters, which consequently limits systemic exposure to the parent compounds.

However, none of the studies were considered scientifically acceptable, leading the SCCP to repeat its request for scientifically acceptable *in vitro* dermal absorption data.

In 2007, a publication appeared which dealt with an *in vitro* dermal absorption study of different parabens through human epidermis-dermis (El Hussein et al. 2007). The study, however, suffers many shortcomings (skin compartments not correctly separated, solubility in receptor fluid not documented, etc.) and will therefore not be further discussed in this opinion.

## 3.2 INDUSTRY HEARING (OCTOBER 2007)

As the SCCP was neither accepting the reproduction studies nor the *in vitro* dermal absorption studies presented by the industry and mentioned a number of comments in the most recent opinion on parabens (SCCP/1017/06), a hearing with industry took place in October 2007 in order to see whether the comments made were valid or not.

### 3.2.1 Argumentation in favour of the earlier presented reproduction repeat studies

Industry responded as follows to the individual remarks made by the SCCP:

1) Both so-called "reproduction studies" performed by industry do not follow any well-established scientific protocol (no OECD number, no Annex V EC B. number).
It was the intention to refute the results of Oishi, wherefore the same protocol was used instead of any officially issued OECD guideline.

2) The 64 animals are emanating from the restricted number of 10 dams, expected to generate litters large enough to deliver a F1 generation of 64 males. No further details (which pups are from the same dam) are given in the description of the test.
Cross-fostering at breeder increases diversity. Estimating that a minimum of 13 litters is represented, this is considered a large number for a study with 64 animals.

3) The body weights of the animals are very divergent. In classical toxicity studies, usually a variation of 20% in body weight is accepted, while the assays under consideration display deviations up to 48% within one dosage group.
Body weight variations of the laboratory animals were typical for animals of this species strain and age. The animals were younger than those in traditional toxicity studies. The primary selection criterion for the study was for age, not for body weight.

4) The Methyl Paraben study mentions in its protocol that testosterone, FSH and LH have been measured in the blood, but these values are not discussed in the results section and the raw data cannot be found. Moreover, pages B-45 and B-60 are lacking in the raw data section.
LH and FSH samples were only taken as a back-up in case the main sperm parameters would have shown an effect. Given that no effect was seen, these samples were not further progressed.

5) For Butyl Paraben, the hormone levels are available but they are characterized by large standard deviations which makes interpretation quite difficult. The protocol states that the time of each blood collection will be recorded in the raw data, but these sampling times cannot be found in the information provided. This information is important as measuring hormones at different times of the day is known to generate diverging values.
Standard deviations for hormone levels were typical. Sampling period was within 2-hour interval in the morning.

6) Many animals display unexpected clinical symptoms, such as chromorhinorrhea, chromodacryorrhea, etc., which raises questions about their general health at the start of the study.

These clinical signs were the result of frequent retro-orbital blood sampling for hormone determinations.
The remaining symptoms observed are the typical result of careful, daily, cageside observations that are made in good laboratories. The laboratory had an attending veterinarian on site to assure animal health.

7) Nearly all findings that have statistical significance have been waived due to the lack of dose-dependency, abnormal high values in control animals, etc.
Although sporadic statistical changes were observed in our studies with methyl and butyl paraben, none were dose-responsive, none were consistent over time, and none were corroborated by accompanying effects. One would expect a biologically significant reduction in testosterone concentration to be accompanied by a decrease in weight of testosterone-dependent tissues, or a perturbation in sperm parameters to be accompanied by a change in weight or presence of histopathology in the testis or epididymides.
All effects seen were isolated and not dose dependent. They were simply a sign for the normal variability in the parameters assessed.

8) A full description of a positive control study in the performing laboratory might have given an indication on the validity and scientific value of the results.
Modern protocols of *in vivo* reproductive toxicity studies do not include positive controls. The rat strain used in this study is known to respond to agents affecting reproduction. Historical data were provided by industry to demonstrate that the laboratory can in principle detect an effect, but this should not be considered as a positive control.

9) Additional argumentation
There are some indications that the Oishi laboratory did not have the expertise to appropriately evaluate the parameters being measured. More specifically, (i) the mean values for some parameters fall far outside the accepted historical control ranges and (ii) the standard deviations in the data are far less than the normal biological variability that has been observed by other groups:
(i) Control mean sperm concentration data are given for the three Oishi publications and the two industry studies (labelled "Argus") and compared with the mean sperm concentrations from 25 rat studies conducted by the United States National Toxicology Program (Morrissey et al. 1988) in the following table:

| Data source | Mean control epididymal sperm concentration (million/gram) | SD (million/gram) |
|---|---|---|
| Oishi, methyl/ethyl paraben | 40 | 7.3 |
| Oishi, propyl paraben | 1080 | 436 |
| Oishi, butylparaben | 1698 | 914 |
| Argus, methylparaben | 875 | 379 |
| Argus, butylparaben | 702 | 386 |
| NTP (Morrissey et al. 1988) | 561 | 250 |

The Argus and NTP results show a fairly high variability in epididymal sperm concentration, with a range of 108-1068 million sperm/ gram tissue ($5^{th}$-$95^{th}$ percentiles). Nevertheless, none of the three Oishi control values was within this wide NTP range. Nor were the Oishi data internally consistent, with the control value for one study being substantially below the NTP range, and the other two above the NTP range.

(ii) Data on circulating testosterone concentration provide an example of the variability of the measurement being inordinately low in the Oishi studies. The

following table compares the mean, standard deviation, and coefficient of variation (CV) for the two Oishi studies in which hormones were measured, with studies from US EPA's labs in male rats of similar age.

| Source | Mean control testosterone concentration | SD | CV |
|---|---|---|---|
| US EPA Wistar | 2.118 | 1.27 | 58 |
| US EPA SD | 2.110 | 0.93 | 44 |
| Oishi (PP) | 9.1 | 2.1 | 23 |
| Oishi (MP/EP) | 11.9 | 2.1 | 18 |

Since the EPA data are reported to be compiled from studies conducted to validate a screening system that covers roughly the same developmental period that was used in the Oishi studies, the coefficients of variation are expected to be comparable. These CV's are a measure of experimental and biological variability that compares the standard deviation with the mean, and usually are in the range of 40-60%. Testosterone is secreted in a pulsatile fashion, so even with exquisitely good experimental technique there will be a fair amount of variability in the data that represents the peaks and troughs of concentration that are inherent to pulsatile secretion. Oishi's data are considered by the industry to display abnormally low CVs for this measurement.

Therefore, the industry proposes to have both studies (Oishi and industry-repeat study) reviewed for their robustness, quality and conclusions by a jointly identified, independent outside expert in reproduction toxicity.

### 3.2.2 *In vitro* dermal absorption

Industry responded as follows to the remarks made by the SCCP:

Research from *in vitro* studies indicates significant metabolism of parabens by non-specific esterases at sites of entry (incl. skin). A recently published *in vivo* study in human volunteers indicates that less than 1% of a large dose of Butyl Paraben is absorbed intact and did not affect human reproductive hormones (Janjua et al. 2007). These results suggest that systemic exposure from typical cosmetic use scenarios will be negligible.

Proposal for a pharmacokinetic study:

We propose to evaluate the absorption, distribution, metabolism and elimination of an orally administered dose of methyl, propyl and butyl paraben in rats. Methyl and butyl paraben will be evaluated because they were the parabens tested in the reproductive studies; propyl paraben will be evaluated to provide empirical data on this paraben which will address the assumption that it will be handled comparably to methyl and butyl.

The design of the first pharmacokinetics study will involve oral gavage of a single dose of $^{14}C$ labelled paraben. The use of a radiolabel will allow us to more easily determine mass balance and determine metabolism of the parabens. The radiolabel will be on the aromatic ring. The animals will be cannulated and blood samples will be taken at 0.25, 0.5, 1, 2, 4, 8 and 24 hours after dosing for the purpose of estimating peak concentration, ADC, and elimination half-life. We will analytically determine the chemical identity of the radioactivity (i.e., intact paraben or p-hydroxybenzoic acid).

Animals will be kept in metabolism cages for the duration of the experiment so that urine, faeces, and expired $CO_2$ can be collected and analyzed for radioactivity. The carcass will also be sampled so that mass balance can be estimated.

The second pharmacokinetics study will be by the dermal route and will evaluate only butyl paraben. The design will be similar to that for the oral study, except that dosing will be to the shaved dorsal surface of the rat in an emulsion in which the butyl paraben is solubilized. The animals will be collated to prevent ingestion of the test substance. Collection procedures and times will be comparable to those used in the oral study.

A third pharmacokinetics study will involve subcutaneous dosing of butyl paraben, for the purpose of demonstrating the difference in systemic paraben concentration when dermal metabolism is by-passed.

Our expectation is that the peak concentration and area under the curve for parabens will be low when the route of exposure is a relevant one for consumer product exposure. The results will support the results of the reproductive toxicity studies, and allow us to extrapolate those results to Propyl Paraben.

Proposal for a metabolism study in skin:

We propose to measure the enzymatic hydrolysis of parabens in dermal tissue. The purpose of this study is to provide data on the rate of hydrolysis of all the commonly used n-alkyl and iso-alkyl parabens, for the purpose of determining their relative rate of metabolism. This will complement existing data on the dermal absorption of parabens *in vitro*. The experimental design will use rat dermal S-9 as the source of esterases and determine the enzymological parameters of $K_m$ and $V_{max}$ for methyl, ethyl, propyl, butyl, isopropyl and isobutyl paraben.

## 3.3 DISCUSSION

### 3.3.1 Reproduction toxicity

The majority of industry's arguments in favour of the repeat studies were welcomed by the SCCP. Nevertheless, a number of remarks remain:

- For point 2 (under 3.2.1): the remark was not focused on the number of dams, but mostly on the fact that the test description did not allow to determine which pups could be associated with the same dam. Viewing the suspected illness of the animals, the SCCP is of the opinion that this could have been related with only a restricted number of dams, of which the descendents subsequently could then be systematically excluded from the study.

- For point 3: The fact that the age of the animals (22 days) and not their body weight was the selection criterion for the tests, was understood. Nevertheless, the remark remains that a large variation range in body weights leads to a large variation range in the final dosages received by the animals (factor of at least 2):

| Dose in food (ppm) | Methyl Paraben dosage levels (mg/kg bw/day) | Butyl Paraben dosage levels (mg/kg bw/day) |
|---|---|---|
| 100 | 8.6 - 18.8 | 8.0 - 17.70 |
| 1,000 | 82.9 - 183.1 | 81.8 - 180.7 |
| 10,000 | 874.1 - 1905.2 | 807.2 - 1784.6 |

In the Oishi studies, the animals were aged 19-21 days and showed much lower weight variations. It must be stated, however, that the lack of the raw data in the Oishi studies seriously hampered thorough analysis of the data provided.

- For point 4: That the hormone levels were not measured for Methyl Paraben, as the blood was collected, is a missed opportunity. It also seems quite contradictory to state that the samples were only measured in case of a positive result and therefore not for Methyl Paraben, since the authors also conclude that Butyl Paraben did not show reproductive effects, whereas for this ester, the hormone concentrations were measured.

- For point 6: Looking at some basic publications on blood sampling in experimental animals, retro-orbital bleeding is no longer considered a humane method (Hui et al. 2007). Side effects are mainly noticed in the hands of unskilled operators and typically include blindness, ocular ulcerations, puncture wounds, loss of vitrous humour, infection or keratitis (Hoff 2000). In addition, increases in blood parameters (hormones, glucose, catecholamines) are described to be directly related to stressful methods of blood collection (Hoff 2000, Grouzmann et al. 2003). In case the animals are anesthetized before blood sampling, the interaction with the anesthetic needs to be documented (Hui et al. 2007).
  In view of the above, it seems that the observed chromorhinorrhea and chromodacryorrhea in 17 out of the 64 animals are not explained and additional doubt is casted on the relevance of the obtained hormone levels.

- For point 7: The effects indeed do not show clear dose-response tendencies and are not backed up by concurrent testosterone levels, but viewing their multitude and the high variations in all the parameters (including in the dosage levels within the groups), a reliable conclusion on their relevance is impossible to make.

- For point 9: The doubts casted by industry on the Oishi studies with regard to the unexpectedly low coefficients of variation for the epididymal sperm concentrations and the testosterone levels, are acknowledged and shared by the SCCP. Unfortunately, the request to have the raw data of both sets of studies studied by an independent expert cannot be fulfilled, since full protocols and the raw data of the Oishi publications (as officially requested to the Japanese competent authorities) are no longer available (communication to the European Commission).

Taking all the above together, the SCCP concludes that the quality of the Oishi studies cannot be properly assessed as the full test description and the complete raw data packages are no longer available.

With regard to the industry repeat studies, the full descriptions and raw data are available and the questions raised by the SCCP were all addressed during an industry hearing. The remaining issues stated above, however, hamper their acceptance as unarguable refutation of the Oishi findings.

### 3.3.2 Toxicokinetics

As already concluded in earlier opinions, Methyl Paraben and Ethyl Paraben are not subjects of concern.

Butyl and Propyl Paraben (and also Isopropyl and/or Isobutyl Paraben if further used), however, require further in-depth investigation. In a survey of recent literature, the following was found:

- A newly performed *in vitro* study showed that the parabens mentioned could be detected in rabbit ear dermis and epidermis after application of a cosmetic lotion (Pedersen et al. 2007). What still needs to be shown, however, is the extent to which the individual

esters can be hydrolyzed into p-hydroxybenzoic acid, so that potential systemic exposure to the parent-compounds can be estimated.

- In a recently published *ex vivo* study (Jewell et al. 2007), parabens biotransformation was measured in microsomes and cytosol of human and minipig skin and in short-term cultures, but no data on *in vivo* biotransformation in human skin was present.

- A recent Janjua et al. (2007) publication describes an *in vivo* study in human volunteers exposed for 1 week to a cosmetic formulation containing 2% of Butyl Paraben, 2% of Diethyl Phthalate and 2% of Dibutyl Phthalate. Serum measurements revealed that Butyl Paraben was detected, but that no effect was noticed on a number of relevant hormone levels (TSH, LH, estradiol, Inhibin B, T4, FT4). Although these results are supportive for Butyl Paraben, they do not provide the required information for Propyl Paraben. Also the results were obtained from a combined test of Butyl Paraben with two Phthalates, which does not represent ideal test conditions to investigate the specific parabens concerned.

The proposal by industry to perform additional pharmacokinetic work is welcomed. The toxicokinetic assays proposed by the industry using the rat may deliver useful information. However, preferably human data should be collected on both Butyl and Propyl Paraben (as well as on the other authorised parabens), when applied under different use applications (representative cosmetic product types and different types of formulations). Measurements in plasma and urine seem essential.

## 4. CONCLUSION

As already concluded in earlier opinions, Methyl Paraben and Ethyl Paraben are not subject of concern.

The SCCP is of the opinion that, based upon the available data, the safety assessment of Propyl and Butyl Paraben cannot be finalized yet.

Parabens are important cosmetic preservatives and they have wide use in multiple product types. Since no unequivocal conclusion can be drawn with regards to the contradictory reproductive toxicity studies available, of which none appears to be scientifically acceptable, the SCCP welcomes the proposal made by industry to conduct further work in the field of skin penetration/metabolism and pharmacokinetics to further support existing data. It is, however, recommended to supplement the envisaged studies in the rat with toxicokinetic studies in human volunteers after dermal application of representative cosmetic products containing Propyl and Butyl Paraben, since these may deliver essential information.

In case significant systemic exposure to Propyl and/or Butyl Paraben is measured in the requested human volunteer study, a rodent generation toxicity study may be unavoidable, although it is the opinion of the SCCP that this should only be performed as a last resort.

Safety data need to be provided for all authorised parabens, including iso-alkyl and phenyl parabens.

## 5. MINORITY OPINION

Not applicable

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SCCP/1017/06 - The Scientific Committee on Consumer Products (SCCP) Opinion on Parabens (Colipa n° P82), adopted during the 9th plenary meeting of 10 October 2006.