p-Chloro-m-Cresol is a substituted phenol that functions as a cosmetic biocide preservative in skin care and suntan cosmetic formulations. While p-Chloro-m-Cresol is approved for preservative use by the European Union at concentrations of up to 0.2%, it can be used at other concentrations when not intended as a preservative, and it is prohibited from use in products intended to contact mucous membranes. p-Chloro-m-Cresol is approved for use as an indirect food additive in the United States. Acute, short-term, and subchronic tests in animals indicate no dose-related toxicity other than reduced body weight gain. A chronic feeding study in rats identified kidney damage in high-dose males and an increase in pituitary adenomas in mid- and high-dose females. No evidence of mutagenicity was seen in Ames tests, but there was an increase in SOS-DNA repair synthesis in Escherichia coli. A solution of p-Chloro-m-Cresol at concentrations as low as 0.05% produced ocular irritation in rabbits. Some evidence of dermal irritation and sensitization was found in animal studies. In clinical studies, 2% p-Chloro-m-Cresol seems to be a skin irritant. Predictive patch tests using 5% p-Chloro-m-Cresol as the challenge were negative, but provocative patch tests yielded positive responses in a few individuals. Other data pertinent to the safety assessment of this ingredient are not available, including the concentration of use in cosmetics, UV absorption data (photosensitization data also are needed if the ingredient absorbs in the UVA or UVB region), dermal developmental toxicity data and a mutagenicity study using a mammalian system (a 2-year dermal carcinogenicity study is also needed if the mutagenesis study is positive). Based on the presently available data, the safety of this ingredient in cosmetic formulations cannot be supported.

p-Chloro-m-Cresol (PCMC) is a substituted phenol that functions as a cosmetic biocide and as a preservative (Wenninger and McEwen, 1995a). This review assesses the safety of this ingredient as used in cosmetic formulations.

1 Reviewed by the Cosmetic Ingredient Review Expert Panel.
Monice Zondlo Fiume, Scientific Analyst/Report Management Coordinator, prepared this report.
Address correspondence to Dr. F. A. Andersen, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.
CHEMISTRY
Definition and Structure
PCMC (CAS No. 59-50-7) generally conforms to the formula shown in Figure 1 (Wenninger and McEwen, 1995b). Other names for PCMC are listed in Table 1.

Physical and Chemical Properties
The physical and chemical properties of PCMC are summarized in Table 2.

Manufacture and Production
PCMC is prepared by the chlorination of m-cresol (Budavari, 1989).

Analytical Methods
PCMC had been assayed by high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS) (Andersen and Hamann, 1984a). A saturated solution of PCMC can be identified by adding one drop of ferric chloride test solution to the solution and shaking; a light blue-purple color develops (Yakuji Nippo Ltd., 1985).

Ultraviolet Absorbance
Published data on the ultraviolet absorbance of PCMC were not found.

Impurities
PCMC contains less than 0.1% 3-methylphenol (m-cresol) as measured by HPLC and GC-MS (Andersen and Hamann, 1984a).

\[
\text{Figure 1. Formula for } p\text{-Chloro-}m\text{-Cresol.}
\]
Table 1. Synonyms for p-Chloro-m-Cresol

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Chloro-m-Cresol</td>
<td>Budavari, 1989; Lewis, 1993; and RTECS, 1993</td>
</tr>
<tr>
<td>6-Chloro-m-Cresol</td>
<td>Budavari, 1989; and RTECS, 1993</td>
</tr>
<tr>
<td>p-Chloro-m-Cresol</td>
<td>RTECS, 1993</td>
</tr>
<tr>
<td>4-Chloro-1-Hydroxy-3-Methylbenzene</td>
<td>Lewis, 1993</td>
</tr>
<tr>
<td>2-Chloro-Hydroxytoluene</td>
<td>RTECS, 1993</td>
</tr>
<tr>
<td>2-Chloro-5-Hydroxytoluene</td>
<td>Budavari, 1989</td>
</tr>
<tr>
<td>4-Chloro-3-Hydroxytoluene</td>
<td>Greenberg and Lester, 1954</td>
</tr>
<tr>
<td>6-Chloro-3-Hydroxytoluene</td>
<td>Budavari, 1989; Lewis, 1993; and RTECS, 1993</td>
</tr>
<tr>
<td>2-Chloro-5-Methylphenol</td>
<td>RTECS, 1993</td>
</tr>
<tr>
<td>4-Chloro-3-Methyl Phenol</td>
<td>Budavari, 1989; and Wenninger and McEwen, 1995b</td>
</tr>
<tr>
<td>Chlorocresol</td>
<td>Greenberg and Lester, 1954; Budavari, 1989; and RTECS, 1993</td>
</tr>
<tr>
<td>p-Chlorocresol</td>
<td>RTECS, 1993</td>
</tr>
<tr>
<td>3-Hydroxy-4-Chlorotoluene</td>
<td>Greenberg and Lester, 1954</td>
</tr>
<tr>
<td>3-Methyl-4-Chlorophenol</td>
<td>Budavari, 1989; and RTECS, 1993</td>
</tr>
<tr>
<td>Parachlorometacresol</td>
<td>Budavari, 1989; and Wenninger and McEwen, 1995b</td>
</tr>
<tr>
<td>PCMC</td>
<td>RTECS, 1993; and Wenninger and McEwen, 1995b</td>
</tr>
</tbody>
</table>

**USE**

**Cosmetic**

PCMC functions as a cosmetic biocide and as a preservative in cosmetic formulations (Wenninger and McEwen, 1995a). The product formulation data submitted to the Food and Drug Administration (FDA) in 1995 stated that PCMC was contained in a total of 16 cosmetic product formulations (Table 3). PCMC was used in cleansing, body and hand (excluding shaving), moisturizing, night, paste masks, and other skin-care preparations and miscellaneous suntan preparations. The greatest reported use of PCMC in any one category (four formulations) was in the moisturizing category (FDA, 1995).

Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992), and the product formulation data submitted to the FDA in 1984 stated that PCMC was used at an unknown concentration in bath oils, tablets, and salts (FDA, 1984).

Cosmetic chemists may avoid using PCMC in their formulations because it may interfere with the perfumes (Cronin, 1980).
Table 2. Physical and chemical properties of \( p \)-Chloro-\( m \)-Cresol

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical characteristics</td>
<td>Colorless or white crystals or crystalline powder</td>
<td>Yakuji Nippo Ltd., 1985</td>
</tr>
<tr>
<td></td>
<td>Dimorphous crystals</td>
<td>Budavari, 1989</td>
</tr>
<tr>
<td></td>
<td>White or slightly pink crystals</td>
<td>Lewis, 1993</td>
</tr>
<tr>
<td>Odor</td>
<td>Odorless when very pure, but usually phenolic</td>
<td>Budavari, 1989</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lewis, 1993</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>( \text{C}_2\text{H}_6\text{ClO} )</td>
<td>Wenninger and McEwen, 1995b</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>142.58</td>
<td>Budavari, 1989</td>
</tr>
<tr>
<td>Melting point</td>
<td>66°C</td>
<td>Sax, 1979</td>
</tr>
<tr>
<td></td>
<td>55.5°C and 66°C (ligroin)</td>
<td>Budavari, 1989</td>
</tr>
<tr>
<td></td>
<td>64–66°C</td>
<td>Lewis, 1993</td>
</tr>
<tr>
<td>Boiling point</td>
<td>235°C</td>
<td>Sax, 1979; Budavari, 1989; Lewis, 1993</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>6.67 mbar (at 100°C)</td>
<td>Paulus and Genth, 1983</td>
</tr>
<tr>
<td>( pK_a ) Value</td>
<td>10.7</td>
<td>Paulus and Genth, 1983</td>
</tr>
<tr>
<td>Solubility</td>
<td>Somewhat soluble in water;</td>
<td>Sax, 1979</td>
</tr>
<tr>
<td></td>
<td>very soluble in organic solvents</td>
<td>Paulus and Genth, 1983</td>
</tr>
<tr>
<td></td>
<td>Solubility in water is 4.0 g/L</td>
<td>Budavari, 1989</td>
</tr>
<tr>
<td></td>
<td>Freely soluble in alcohol, ( \text{benzene, chloroform, ether, acetone, petroleum ether, fixed oils, terpenes, aq. alkaline solutions; 1 g dissolves in 260 mL water (20°C), more soluble in hot water} )</td>
<td>Lewis, 1993</td>
</tr>
<tr>
<td></td>
<td>Soluble in alkalies, organic solvents, fats, oils; soluble 1:250 in water at 25°C</td>
<td>Budavari, 1989; Lewis, 1993</td>
</tr>
<tr>
<td>Stability</td>
<td>Volatile with steam</td>
<td>Budavari, 1989</td>
</tr>
<tr>
<td>Optimum ( \text{pH} )</td>
<td>( \text{aq soln turns yellow on exposure to air or light} )</td>
<td>Budavari, 1989</td>
</tr>
</tbody>
</table>
Table 3. Product formulation data for p-Chloro-m-Cresol

<table>
<thead>
<tr>
<th>Product category</th>
<th>Total no. of formulations in category</th>
<th>Total no. containing ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleansing</td>
<td>771</td>
<td>2</td>
</tr>
<tr>
<td>Body and hand (excl. shaving)</td>
<td>987</td>
<td>3</td>
</tr>
<tr>
<td>Moisturizing</td>
<td>873</td>
<td>4</td>
</tr>
<tr>
<td>Night</td>
<td>220</td>
<td>1</td>
</tr>
<tr>
<td>Paste masks (mud packs)</td>
<td>276</td>
<td>1</td>
</tr>
<tr>
<td>Other skin-care preparations</td>
<td>782</td>
<td>2</td>
</tr>
<tr>
<td>Other suntan preparations</td>
<td>62</td>
<td>3</td>
</tr>
<tr>
<td><strong>1995 Totals</strong></td>
<td></td>
<td><strong>16</strong></td>
</tr>
</tbody>
</table>


International

On the basis of available information (which is summarized in this report), PCMC is approved for use by members of the European Union as a preservative at a maximum authorized concentration of 0.2% and is prohibited for use in products intended to come in contact with mucous membranes; PCMC “may also be added to cosmetic products in concentration[s] other than those laid down in this Annex [Annex VI; Dir. 76/768/EEC, June 1986] for other specific purposes apparent from the presentation of the products, e.g. as deodorants in soaps or as anti-dandruff agents in shampoos” (EEC Cosmetics Directive, 1993).

PCMC is listed in the Japanese Standards of Cosmetics Ingredients (Rempe and Santucci, 1992). Products containing this ingredient must declare it on the label.

Noncosmetic

PCMC has applications as a topical antiseptic, disinfectant, and preservative in pharmaceutical products (Kabara, 1984). Because of its antiseptic properties, it is commonly used in heparin solutions, in electrode paste, and in various creams used in dermatology and general skin care (Dossing et al., 1986). It is an efficient bactericide that is more effective in acid than in alkaline solutions (Cronin, 1980). PCMC also can be used in veterinary topical medicaments and in veterinary intrauterine lubricants as an antiseptic and preservative at concentrations of 0.1% to 0.2% (Rossoff, 1974).

PCMC is approved for use as an indirect food additive (Rothschild, 1990). Nonfood or medical uses of PCMC include packaging materials, adhesives, glues, inks, paints and varnishes, textile finishes, leather
and tanning agents, and industrial oils and emulsions (Dooms-
Goossens et al., 1981).

The use concentration for most noncosmetic applications of PCMC
ranges from 0.05% to 0.5% (Andersen and Hamann, 1984b); aqueous
drugs for parenteral use are sometimes preserved with 0.05% to 0.1%
PCMC (Cronin, 1980).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

A pharmacokinetic study was performed in which rats were dosed
orally with 300 mg/kg PCMC. PCMC reportedly was eliminated rapidly
through the kidneys. In addition, there is no likelihood of cumulation
effects. A corresponding examination of fatty and hepatic tissues from
rats that were fed 150 to 1500-ppm PCMC for up to 13 wk reported no
indication of an accumulation of PCMC in these tissues (Paulus and
Genth, 1983).

Four groups of conventional female albino guinea pigs, three per
group, were used to determine the bioavailability of PCMC (Andersen
et al., 1985). Occlusive patches of 0.2 mL of a 5% PCMC aqueous sus-
pension stabilized with Carbomer 941, a saturated aqueous solution of
0.38% PCMC, 5.0% PCMC in olive oil/acetone (4/1), or 5.0% PCMC in
propylene glycol were applied for 24 h. After 96 h, the animals were
killed and the skin at the site of patch testing was removed for analysis
(the patches were kept for analysis to determine the amount of PCMC
remaining in the patch material). Fractional sampling of the urine and
feces was performed to determine the rate of absorption of PCMC. An
additional three animals had been injected with PCMC intraperi-
toneally to determine the excretion rate; however, no free PCMC was
found, indicating rapid metabolism. The investigators stated that fur-
ther analysis would be required before PCMC absorption can be esti-
mated by this method (14C-PCMC was not available).

In determining bioavailability, the calculations were based on the
assumption that the saturated PCMC solution is 0.4% (w/v), corre-
spanding to 0.8 mg in 0.2 mL, and that 0.2 mL of the 5% PCMC prepa-
rations contained 10 mg of the chemical. The results indicated that 25%
of the aqueous PCMC (stabilized with carbomer 941) and 46% of the
saturated aqueous PCMC solution remained in the patches. Only 0.2%
of the aqueous PCMC (stabilized with carbomer 941) and 0.5% of the
saturated aqueous PCMC solution were found in the skin at the patch
site. These findings were compared with 65% of the PCMC in propylene
glycol and 66% of the PCMC in olive oil/acetone solutions remaining in
the patch; 0.7% and 1.6%, respectively, were found in the skin at the patch site. The investigators concluded that PCMC was more bioavailable from the aqueous preparations. After 96 h, 0.2% and 0.5% PCMC was detected at the patch test site in the animals dosed with 5.0% and saturated aqueous PCMC, respectively, and 0.7% and 1.6% PCMC were found in the skin of the animals patch-tested with 5% PCMC in olive oil/acetone and propylene glycol, respectively.

Abdominal skin from SKH-hr-1 mice was used to determine the permeability of PCMC (Huq et al., 1986). The permeability was evaluated, both through whole skin and skin that was stripped repeatedly (20 times) with cellophane tape to remove the stratum corneum, by mounting the excised samples in a two-compartment diffusion cell, with the two half-cells being filled with normal saline. Samples were withdrawn and assayed spectrophotometrically; the absorbance was measured at 245 nm. Permeability coefficients were assessed for both stripped and whole skin under conditions that kept ionization to a minimum.

In assessing the permeability of PCMC through whole skin, the concentration used was 0.05 g/100 mL, the pKa of PCMC was 9.56, the donor pH was 6.18, and the receiver pH was 6.2. Under these conditions, the apparent permeability coefficient for whole skin was 119 ± 1.8 × 10⁻³ cm/h, and the average lag time was 35.8 min. For stripped skin, 0.055 g/100 mL PCMC was used, and the donor and receiver pH was 6.2. The permeability coefficient of stripped skin was 241 ± 22 × 10⁻³ cm/h, and the lag time was 14.6 min. The estimated permeability coefficients of PCMC for viable tissue and stratum corneum were 302 × 10⁻³ and 235 × 10⁻³, respectively.

**Hepatic Effects**

Male Wistar rats were dosed orally with 400 mg/kg PCMC to determine the effect on the development of hepatocellular vacuoles (Meiss et al., 1981). Hepatic tissue taken from the left lobe of the liver 7 days after dosing was examined by electron microscopy. Markedly widened intracellular spaces, intracytoplasmic vacuoles of different sizes, and alterations of the cell organelles and nuclei were observed. Cells from older animals contained more invaginations and vacuoles than those of younger animals. When younger animals were fasted prior to being killed, the vacuolic formation was similar to that of older animals.

The investigators considered the origin of the hepatic cell vacuoles to be the intracellular space. They observed the following stages of vacuolar formation: dilated cell surface, often limited to a restricted region; the plasmalemma-formed vesicular invaginations; and the invaginations extended to form large vacuoles with an open connection to inter-
cellular space. The investigators theorized that increasing blood pressure caused by PCMC intoxication of the liver was the reason for the pathologic invaginations in the region of the contacts between the hepatocytes.

**Neurologic Effects**

A single dose of 0.2% PCMC (to correspond with 0.25 mg/kg and 0.5 mg/kg) was injected into the cisterna magna of three rabbits per dose after withdrawal of an appropriate amount of cerebrospinal fluid; two animals were used as controls (Gray and Naim, 1972). One animal from each dose group was killed after 24 h, 48 h, and 5 days. All animals survived. None of the animals developed any functional disability suggestive of neurologic damage. No evidence of pathologic lesions caused by PCMC was present, and the brains had no evidence of meningeal parenchymatous damage.

**Antimicrobial Activity**

A study was conducted to determine whether PCMC affected the enzymatic activity or the use of amino acids in the inhibition of germination of *Bacillus subtilis* spores (Sierra, 1970). The initiation of germination of *B. subtilis* in complete medium and in phosphate buffer plus the enzyme subtilopeptidase is inhibited by PCMC, but the activity of the enzyme is not, which suggests that the proteolytic enzyme is not the primary site of inhibition. Amino acid-initiated germination was reversibly inhibited by PCMC, suggesting that the inhibitor prevents the initiation of germination of bacterial spores at the level of amino acid use, in both complete medium and with subtilopeptidase.

The antimicrobial spectrum of 0.02% PCMC included gram-positive and gram-negative bacteria, including tubercle bacilli, and also yeasts and fungi (Paulus and Genth, 1983).

The effectiveness of PCMC as a preservative in aqueous cream was examined using the Test for Efficacy of Preservatives (British Pharmacopoeia, 1982) modified to include membrane filtration (Brown et al., 1986). Ten-gram samples of the cream were inoculated with 0.1 mL of a suspension containing either *Candida albicans* or *Aspergillus niger* to give concentrations of approximately $10^6$ organisms/g. PCMC did meet the British Pharmacopoeia requirements for the efficacy of antimicrobial preservatives [the number of molds or yeasts recovered per gram is reduced by a factor of not less than 100 within 14 days of challenge and there is no increase thereafter] when tested against *A. niger*, but not when tested against *C. albicans*, using membrane filtration to isolate the microorganisms.
ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Five groups of male Wistar II rats were dosed with 1.0 to 5.0 g/kg PCMC by stomach tube (BAYER AG, 1978). Intensified diuresis, sedation, disturbed respiration, trembling, and convulsions were observed (specific doses not identified). The oral LD$_{50}$ of PCMC for Wistar II rats was 1830 mg/kg.

Groups of male Wistar rats were given a single oral dose of 400 mg/kg PCMC in peanut oil; controls were dosed with an equivalent amount of peanut oil only (Robenek et al., 1980). All animals were killed 60 h after dosing, and hepatic tissue was removed from the center of the right lobe of the liver for examination by electron microscopy.

After dosing, the animals’ behavior changed: after 30 min, the animals were uneasy and had “ruffled-up” coats. These signs diminished after 1 h but were replaced by long “apathetic motions.” After 24 h until study termination, the haircoats were altered again. At necropsy, the liver appeared slightly enlarged and was a pale red color with pale gray spots.

Light microscopy findings included a distinct dilation of the sinusoids with an activation of the Kupffer cells. The intercellular spaces were enlarged, and there were numerous vacuoles found in the cytoplasm.

In electron micrographs, outpouchings of cell membranes were observed. A greater-than-normal number of lysosomes were found around the bile canaliculi after dosing. Also, there was an increase in the number of mitochondria, many membrane-surrounded vacuoles, alterations in the intercellular space and in the rough endoplasmic reticulum, and an increase in the number and size of gap junctions. In addition, the bile canaliculi were dilated and had irregularities and side branches that extended into the cytoplasm of adjacent hepatocytes.

Five groups of Sprague-Dawley rats, 10 per sex per group, were dosed orally with PCMC in carbowax; males were dosed with 2000 to 7683 mg/kg and females with 1500 to 5762 mg/kg (Mobay Chemical Corporation, 1981). Ataxia, wheezing, muscle fasciculations, tremors, convulsions, and salivation were observed in all dosed animals. The oral LD$_{50}$ of PCMC was 5129 mg/kg for male Sprague-Dawley rats and 3636 mg/kg for female Sprague-Dawley rats. These values are higher than those reported for Wistar II rats, but no explanation for this strain difference was available.

Percutaneous

The percutaneous LD$_{50}$ of PCMC for rats was more than 500 mg/kg (Paulus and Genth, 1983).
Subcutaneous

Five groups of 10 or 20 mice (sex not specified) were dosed subcutaneously with 100 to 500 mg/kg PCMC as a 0.4% aqueous solution (Wein, 1939). Toxic signs appeared within 5 min and included severe muscular tremors, especially in the fore and hind limbs. Death from respiratory failure usually occurred within 3 h, with some animals dying within 30 min. The calculated subcutaneous LD$_{50}$ of PCMC for mice was 360 mg/kg.

Three groups of 10 albino rats per group (sex not specified) were injected subcutaneously with a 0.4% aqueous solution of 30, 400, or 500 mg/kg PCMC (Wein, 1939). Observations included tremors followed by death in approximately 15 min. The calculated subcutaneous LD$_{50}$ was 400 mg/kg PCMC.

The Robenek et al. (1980) acute toxicity study described in the “Oral” section also included testing in which a single subcutaneous dose of 400 mg/kg PCMC in peanut oil was administered to rats; the same procedures were followed. The same general behavioral and macroscopic hepatic changes and light microscopy findings were observed. In electron microscopic examination of the liver, the reported findings included enlarged sinusoids, an increase in detritus in the Kupffer cells, enlarged intercellular spaces, and an increased number of cytoplasmic vacuoles. An increase also occurred in the number of lysosomes, some of which were comparable in size to mitochondria. The rough endoplasmic reticulum appeared disorganized, often surrounded by mitochondria and with an increase in the loss of ribosomes. In addition, an increase occurred in mitochondria, which often appeared pleomorphic. Some of the mitochondria had a long shape and showed a tear in the outer membrane. Also, a translucent matrix accompanied by a decrease in mitochondrial cristae was observed.

Inhalation

Upon a 4-h exposure, the inhalation LC$_{50}$ for rats was more than 583 mg PCMC-NA/m$^3$ air (Paulus and Genth, 1983).

Intravenous

Five groups of 10 or 20 mice (sex not specified) were injected intravenously with 100 to 500 mg/kg PCMC as a 0.4% aqueous solution (Wein, 1939). The calculated intravenous LD$_{50}$ of PCMC for mice was 70 mg/kg.
Short-Term Toxicity

Dermal

New Zealand White rabbits, 50 per sex, received cutaneous applications of 0, 10, 40, and 160 mg/kg/day PCMC 5 days per week for 3 wk on a shaved area of the back (Mobay Chemical Co., 1980). Irritation and erythema were observed, but no PCMC-related systemic effects were present compared with controls.

Oral

Groups of 20 Wistar SPF rats, 10 males and 10 females per group, were dosed with 50, 200, or 400 mg/kg/day PCMC in food-grade soybean oil by gavage at a volume of 5 ml/kg/day for 28 days (Madsen et al., 1986). A control group was dosed with soybean oil only. The animals were examined twice daily, and body weights and feed consumption were determined weekly. Blood samples were taken from eight males and eight females in each group for hematologic and clinical chemistry analysis after 21 days of dosing. All rats were necropsied at study termination. The only toxicologic sign observed was a statistically significant decrease in body weight gain for the males and females dosed with 400 mg/kg PCMC. Relative organ weights were comparable for all groups, and the hematologic and clinical chemistry parameters were normal. No dose-related pathologic changes were observed. The no-effect level (NOEL) was 200 mg/kg/day PCMC.

Rats were fed 2500, 5000, or 10,000 ppm PCMC, and controls were fed untreated feed (number per group, sex, and dose duration not stated) (BAYER AG, 1992). Male rats of the 10,000-ppm dose group had reduced body-weight gains. Dose-related effects were not observed for males of the 2500-ppm and 5000-ppm dose groups or for any of the female rats.

Subcutaneous

Five albino rats were injected subcutaneously with 72 mg/kg PCMC as a 0.4% solution daily for 2 wk, and five rats were used as controls (Wein, 1939). All animals survived until study termination. The only observation was that of a mild inflammatory reaction, with some leucocyte infiltration, at the site of injection.

Three rabbits were injected subcutaneously with 5 ml/day of 0.25% PCMC in saline for 4 wk (Wein, 1939). Survival was 100% and pathology was noted.
Subchronic Toxicity

Oral

SPF rats, 20 per sex per group, were fed 150, 500, or 1500 ppm PCMC in feed, and controls were fed untreated feed daily for 13 wk (BAYER AG, 1980a). Body weights of the animals of the 500-ppm and 1500-ppm dose groups were retarded, independent of dose. No dose-related changes were observed at necropsy or on microscopic examination; survival was 100%. The no-toxic effect concentration was 150 ppm.

Chronic Toxicity

Oral

Bor:WISW(SPF Cpb) Wistar rats, 60 animals per sex per group, were fed 400, 2000, or 10,000 ppm PCMC for 2 yr, with the exception of 10 animals per sex per group that were necropsied after 53 wk (BAYER AG, 1992). A control group of 60 animals per sex was fed a diet that did not contain PCMC for 2 yr, again with the exception of 10 animals per sex that were necropsied after 53 wk (dosages were determined based on results of previous short-term and subchronic studies summarized previously in this report).

The animals were observed at least twice daily, with detailed weekly evaluations; body weights also were measured weekly. Feed consumption was determined weekly for 13 wk, after which it was determined at 4-wk intervals. Water intake was determined at 4-wk intervals over the entire study. Ophthalmologic evaluations were performed on 20 animals per sex per group prior to study initiation and then on 20 animals per sex of the control and 10,000-ppm groups after 52 and 104 wk of dosing. Blood samples were obtained for examination from 10 animals per sex per group after 27, 52, 79, and 104 wk of dosing. Urinalyses were performed during weeks 26/27, 51/52, 78/79, and 103/104.

Averaged over 2 yr, the males and females of each dose group ate the following quantities (per day) of PCMC: 400-ppm group, 21 and 27.7 mg, respectively; 2000-ppm group, 103.1 and 134.3 mg, respectively; and 10,000-ppm group, 558.9 and 743.5 mg, respectively. Body weights of female rats of all dose groups and of male rats of the 10,000-ppm dose group were significantly lower compared with controls throughout the study. Body weights of the males of the 400-ppm and 2000-ppm dose groups were comparable with control values. Mean feed intake per animal per day was comparable between males of all dose groups and controls but was slightly lower for females of all dose groups compared with controls. When related to body weight, the mean feed intake of males and females of the 10,000-ppm dose groups was increased compared with controls. Males rats of the 10,000-ppm group had increased
mean water intake per animal per day, and the water intake per kg body weight for females of the 10,000-ppm group also was increased compared with controls.

The incidence of an increased abdominal circumference was significantly reduced for female animals of the 2000-ppm and 10,000-ppm dose groups, and the frequency of a poor general condition was statistically increased for females of the 10,000-ppm dose group. Ophthalmologic examination did not indicate any ocular toxicity. No significant difference existed in mortality between animals of the test and control groups.

PCMC-related clinical chemistry or hematologic changes were limited to reduced serum potassium and phosphate concentrations (compared with control values) for males and females of the 10,000-ppm group. Urinalysis results included a decrease in total protein excretion for males and females fed 10,000-ppm PCMC; males of this group also had a reduced urinary density, often in conjunction with a slightly enhanced urinary volume.

No significant findings were reported in the rats at the interim necropsy after 52 wk; absolute and relative organ weights did not differ significantly between test and control groups. At study termination, necropsy findings included deformation of the kidneys of 6 of 44 surviving males of the 10,000-ppm group. Relative kidney weights of males of the 2000-ppm group and males and females of the 10,000-ppm group were slightly increased compared with control values.

No microscopic lesions were observed at interim necropsy. Females of the 2000-ppm dose group that died during the study had dilated ducts of the mammary gland. At study termination, an increased incidence of papillary necrosis, cortical tubular dilations, and cortical fibrosis of the kidneys was observed in male rats of the 10,000-ppm group. Females of the 2000-ppm and 10,000-ppm groups that died on study had a greater incidence of pituitary adenoma, a finding that was not observed at interim necropsy (only preliminary microscopic information is available from rats of the final necropsy). The NOEL was 2000 ppm PCMC.

Ocular Irritation

PCMC, 0.05% or 0.1% in 0.9% saline, was instilled into the conjunctival sac of the eyes of rabbits (number of animals not stated) by applying 20 drops/min for 10 min; the eyes were rinsed with saline after 15 min (Fiebig et al., 1972). Fluorescein staining was used. In the animal(s) dosed with 0.05% PCMC, the “cornea” [sic] was reddened for 15 min–4 h after application, and the eye was normal after 24 h. In the animal(s) dosed with 0.1% PCMC, the eye was inflamed after 48 h and clear after 106 h.
Soft lenses that were stored in bactericidal-strength solution were applied to the eyes of 13 rabbits for 6 h/day and the eyes were not rinsed; the isotonic solution, pH 7.0, contained 0.1% PCMC (Davies, 1973). PCMC produced severe irritation after a few days.

**Dermal Irritation**

The trypan blue method of Hoppe was used to determine the dermal irritation potential of PCMC (Baichwal and Phadnis, 1968). Groups of rabbits, two per group (sex not specified), were given a single application of 0.2% PCMC in normal saline or 0.4% or 0.8% PCMC in 1% Tween in normal saline. The site of application was four areas in the abdominal region and the duration of contact was 0.4 mL injected intradermally within 10 to 15 min. Twenty min after dosing, 1 mL/kg of 1% trypan blue was injected intravenously and the color at the injection sites was observed for 3 h. The maximal irritation score (scale not stated) was 4 for 0.2% and 0.4% and 8 for 0.8% PCMC.

**Sensitization**

The sensitization studies reported here are summarized in Table 4.

Groups of 20 female outbred albino guinea pigs were used in a guinea-pig maximization test (GPMT) (Magnusson and Kligman, 1970) to determine the sensitization potential of two commercial biocides that contained PCMC; one biocide contained pentachlorophenol and PCMC (percentage of each not stated), whereas the other was more than 99.9% PCMC (Andersen and Hamann, 1984a). A control group that was dosed with vehicle only (induction and challenge dose concentrations were determined in a one-application skin irritancy test using at least four guinea pigs) also was used. The challenge reactions were scored on a scale of 0 to 3 after 48 h and 72 h. A grade 1 reaction was not regarded as evidence of sensitization.

The induction doses of the pentachlorophenol–PCMC formulation consisted of intradermal administration of 5% of the biocide in propylene glycol and a patch containing 0.5 mL of 25% biocide formulation in yellow petrolatum. Animals were challenged using Finn chambers containing 0.5 mL of 5.0% of the biocide on day 21, 1.0% pentachlorophenol or 1.0% PCMC on day 35, and 0.5% of the biocide (all in yellow petrolatum) on day 42.

For the pure-PCMC formulation, the induction doses consisted of intradermal administration of a 5% solution in propylene glycol and a patch of 0.5 mL of 10% PCMC in yellow petrolatum. The animals were challenged with an occlusive patch with 0.5 mL of 1% PCMC in petrolatum on days 21 and 35.
### Table 4. Animal sensitization studies

<table>
<thead>
<tr>
<th>Group size, sex, species</th>
<th>Test</th>
<th>Induction/challenge doses</th>
<th>Results and comments</th>
<th>Reference</th>
</tr>
</thead>
</table>
| 20 female outbred albino guinea pigs | GPMT | **Induction:** 5% PCMC intraderm. and 10% PCMC top.  
**Challenge:** Occlusive patch with 1% PCMC on days 21 and 35  
**Induction:** 5% of a pentachlorophenol/PCMC biocide intraderm. and 25% biocide top  
**Challenge:** Finn chambers with 5% biocide on day 21, 1% PCMC or pentachlorophenol on day 35, and 0.5% biocide on day 42 | 16/19 animals had reacted upon challenge on day 21; only 4/19 reacted upon challenge on day 35  
Positive upon challenge with the biocide and PCMC, but not with pentachlorophenol.  
Frequency of positive reactions decreased between days 21 and 42; 17/19 reacted to biocide challenge on day 21; 12/19 reacted to PCMC challenge on day 35; 6/19 reacted to biocide challenge on day 42 | Andersen and Hamann, 1984a |
| 20 female outbred albino guinea pigs | GPMT | **Induction:** 0.2, 1, or 5% PCMC intraderm. and 10% PCMC top.; 0.2% PCMC intraderm. and 2% PCMC top.; or 0.2% PCMC intraderm. and 0.4% PCMC top.  
**Challenge:** Finn chambers with 0.1, 0.5, and 1% PCMC on day 21 (also on day 35 for some groups) | Positive reactions frequencies of 75, 70, 65, and 84% for animals induced with 0.2, 1, 1, and 5% intraderm./10% top.; 30 and 15% for animals induced with 0.2% intraderm./0.4 and 0.2% top.; the 72-h, but not the 48 h, readings were sig. increased with increased challenge concentrations, reactivity decreased from day 21 to 35 | Andersen and Hamann, 1984b |

(Table continued on next page.)
Table 4. Animal sensitization studies (continued)

<table>
<thead>
<tr>
<th>Group size, sex, species</th>
<th>Test</th>
<th>Induction/challenge doses</th>
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<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 female outbred albino guinea pigs</td>
<td>GPMT</td>
<td><em>Induction:</em> 1% PCMC intraderm. and 10% PCMC top.; three types of FCA emulsions were used</td>
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<td></td>
<td></td>
<td><em>Challenge:</em> Finn chambers with 0.1 and 1% PCMC on day 21; patch placements were inter- changed and were also placed near the abdomen</td>
<td>No sig. difference in response due to different FCA emulsions. After 48 h, 19, 15, and 14 animals of the three groups reacted upon challenge to 1% PCMC; after 72 h, 18, 18, and 17 reacted; reactions were significantly weaker near the abdomen than those higher on the flank</td>
<td>Andersen, 1985a</td>
</tr>
<tr>
<td>36 guinea pigs</td>
<td>GPMT</td>
<td><em>Induction:</em> 1% PCMC intraderm. and 10% PCMC top.</td>
<td>28/36 animals reacted after 48 h</td>
<td>Andersen and Staberg, 1985</td>
</tr>
<tr>
<td>20 outbred albino guinea pigs</td>
<td>GPMT</td>
<td><em>Induction:</em> 1% PCMC intraderm. and 10% PCMC top. Two groups were dosed i.p. with 250 mg/kg CY on day 18 or 32</td>
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<tr>
<td></td>
<td></td>
<td><em>Challenge:</em> Finn chambers with 0.2, 0.5, and 1.0% PCMC on days 21 and 35</td>
<td>Most test animals not dosed with CY prior to day 21 reacted upon challenge; the number reacting upon challenge on day 35 was reduced, especially in the group dosed with CY on day 32; dosing with CY on day 18 reduced the number reacting to day 21, but not day 35, challenge</td>
<td>Andersen, 1985b</td>
</tr>
<tr>
<td>60 Stamm Pirbright White guinea pigs (30/sex)</td>
<td>Magnusson-Kligman</td>
<td><em>Induction:</em> 1x3 intraderm. injections (2 w/PCMC and 1 w/Freund's adjuvant); top. application of 1 and 25% PCMC 1 wk later</td>
<td>The 25% solution was strongly sensitizing while the 1% solution was weakly sensitizing</td>
<td>BAYER AG, no date</td>
</tr>
<tr>
<td>Guinea Pig Description</td>
<td>Induction</td>
<td>Challenge</td>
<td>Sensitization Result</td>
<td>References</td>
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<tr>
<td>------------------------</td>
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<tr>
<td>35 female Stamm Pirbright White guinea pigs</td>
<td>Epicutaneous</td>
<td><strong>Induction:</strong> 2 open applications of 1, 3, 10, or 30% PCMC</td>
<td>No sensitization reaction</td>
<td>BAYER AG, 1980b</td>
</tr>
<tr>
<td>8 female outbred albino guinea pigs</td>
<td>OET</td>
<td><strong>Induction:</strong> Daily open applications of 1, 3, 10, or 30% PCMC</td>
<td>PCMC was a “doubtful” sensitizer; doses ≥3% produced irritation</td>
<td>Andersen and Hamann, 1984b</td>
</tr>
<tr>
<td>20 conventional female albino guinea pigs</td>
<td>CCET</td>
<td><strong>Induction:</strong> Patches with a suspension of 5% PCMC, a saturated aq. solution of 0.38% PCMC, or 5% PCMC in various vehicles on days 0, 3, 7, and 9</td>
<td>Frequency of sensitization was vehicle-related</td>
<td>Andersen et al., 1985</td>
</tr>
</tbody>
</table>
For the animals injected with the pentachlorophenol/PCMC biocide, positive reactions were obtained upon challenge with the biocide and with PCMC but not with pentachlorophenol. The frequency of positive reactions upon challenge decreased between days 21 and 42; on day 21, 17 of 19 animals reacted to challenge with 5% of the biocide; on day 35, 12 of 19 animals reacted to 1% PCMC; on day 42, 6 of 19 animals reacted to challenge with 0.5% of the biocide.

Of the animals induced with PCMC, 16 of 19 had a positive reaction at day 21 of challenge, but only four of 19 animals reacted on day 35. Of the control animals used in determining the sensitizing potential of PCMC, three had slight erythema and one had moderate erythema upon challenge; none of the positive results in controls were clinically explainable.

Six groups of 20 female outbred albino guinea pigs were used in a GPMT to determine the sensitization potential of PCMC (Andersen and Hamann, 1984). Induction consisted of intradermal administration of 0.2%, 1.0%, or 5.0% PCMC and topical administration of 10.0% PCMC, intradermal administration of 0.2% PCMC and topical administration of 2.0% PCMC, and intradermal injection of 0.2% PCMC and topical administration of 0.4% PCMC. The vehicles used for intradermal administration and topical administration were propylene glycol and petrolatum, respectively. A group of 40 negative control animals was dosed with vehicle only. The challenge performed on day 21 (and day 35 for some groups), used Finn chambers with 0.1%, 0.5%, and 1.0% PCMC in yellow petrolatum. The challenge reactions were scored on a scale of 0 to 3 after 48 and 72 h. A grade 1 reaction was not regarded as evidence of sensitization.

The frequencies of positive reactions were 75%, 70%, 65%, and 84% for the animals induced with intradermal administration of 0.2%, 1.0%, and 5.0% PCMC and topical administration of 10.0% PCMC, respectively, and 30% and 15% for animals induced with intradermal administration of 0.2% PCMC and topical application of 0.4% or 2.0% PCMC, respectively. The 72-h, but not the 48-h, readings were significantly increased with increased challenge concentrations. Reactivity to PCMC at challenge decreased from day 21 to day 35.

As a follow-up to the study described previously (Andersen and Hamann, 1984), another GPMT was performed using female outbred albino guinea pigs to determine whether the sensitization rate that was observed could be caused by minor changes in the type of Freund's complete adjuvant (FCA) used or to the sites of the challenge patch applications (Andersen, 1985). Three groups of 20 animals were dosed intradermally with 1% PCMC in propylene glycol on day 0 and topically with 10% PCMC in yellow petrolatum on day 10. The animals were challenged on day 21 with 0.1% and 1.0% PCMC in petrolatum using Finn chambers that were placed horizontally on the flanks of the ani-
mals; the 0.1% patch was placed in front on half the animals and in back on the other half. A parallel pair of patches were placed 2 cm lower on the flank to determine whether the responses near the abdomen were similar to the challenge responses nearer the back. The challenge sites were scored 48 h and 72 h after challenge, and the reactions were scored on a scale of 0 to 3. A grade 1 reaction was not regarded as evidence of sensitization.

Three types of FCA emulsions were used: (1) 50% FCA (v/v) and 50% propylene glycol, with (for the test groups) and without (for the control group) 2% PCMC (w/w); (2) 50% FCA (v/v) and 50% saline-ethanol (7+3) (v/v) with and without 2% PCMC (w/w); and (3) 50% saline and 50% FCA (v/v) that contained 2% PCMC (w/w) that was partly dissolved, partly suspended in the FCA prior to mixing with saline.

After 48 h, 19 animals of the FCA-propylene glycol group, 15 animals of the FCA-saline-ethanol group, and 14 animals of the FCA-saline group reacted to challenge with 1% PCMC; after 72 h, the number of animals that reacted was 18, 18, and 17, respectively. Based on the frequency of reaction to PCMC upon challenge, no significant difference was shown between the three FCA emulsions; however, the reactions to challenge patches placed nearer to the abdomen were significantly weaker than those placed 2 cm higher on the flank.

Skin blood flow determined by laser Doppler flowmetry (LDF) and skin-fold thickness (SFT) were used to quantitate allergic contact dermatitis in a GPMT examining PCMC (Andersen and Staberg, 1985). Thirty-six guinea pigs were induced by intradermal administration of 1% PCMC in propylene glycol on day 0 and topical administration of 10% PCMC in petrolatum on day 7. The animals were challenged on day 21 using occlusive patches of 0.1% and 1.0% PCMC in petrolatum. The patches were placed anteroposterior on the mid-flank, with 10 mm of skin between the chambers. The challenge sites were examined visually and scored for reactions on a scale of 0 to 3. A grade 1 reaction was not regarded as evidence of sensitization. LDF was performed daily on the animals used to evaluate daily variation and was measured twice to determine the influence of the closed challenge. SFT, measured using calipers, was determined within seconds to avoid the effect of compression.

Upon visual examination 48 h after challenge, 28 of the 36 test animals were sensitized to PCMC. Upon examination of the control animals, it was determined that the occlusive patch test procedure influenced LDF and SFT measurements; LDF and SFT were maximal after 24 and 48 h, respectively.

Five groups of 20 female outbred albino guinea pigs were used in a GPMT to determine the sensitization potential of PCMC (Andersen, 1985b). Three groups were given induction doses consisting of 1% PCMC in propylene glycol administered intradermally and 10% PCMC
in yellow petrolatum administered topically. Two of the test groups were given an intraperitoneal injection of 250 mg/kg cyclophosphamide (CY) on days 18 and 32, respectively. A negative control group was treated in a manner similar to the test group that was not given CY, with the exception that vehicle only was used during induction. A positive control group was induced with 1% sodium lauryl sulfate (SLS) in saline given intradermally and 5% SLS in petrolatum administered topically. The positive control animals also were dosed with CY by intraperitoneal injection on day 18. The animals of all groups were challenged using Finn chambers on days 21 and 35. The test animals were challenged with 0.2%, 0.5%, and 1.0% PCMC in yellow petrolatum, the positive control animals were challenged with 0.1%, 0.2%, and 0.5% SLS in yellow petrolatum, and the negative control animals were challenged with PCMC and SLS. Challenge reactions were scored on a scale of 0 to 3 after 48 h and 72 h. A grade 1 reaction was not regarded as evidence of sensitization.

Most animals of the test groups that were either not given CY or were dosed with CY on day 32 reacted upon challenge with PCMC on day 21; the number of these animals reacting at challenge on day 35 was reduced, especially in the group dosed with CY on day 32. Administration of CY on day 18 caused a decrease in the number of animals reacting to challenge with PCMC on day 21; however, upon challenge at day 35, almost all animals reacted. CY administration had no effect on reaction to SLS, indicating that the influence of CY was specific. One of the control animals reacted strongly at the day 35 challenge to PCMC; all of the others were negative. It was stated that the decrease in reactions to PCMC at the day-35 challenge "suggests that a chemical may induce effector and suppressor cells which have a different time course of development." The investigators proposed that PCMC, "besides being a potential sensitizer[,] significantly induced suppressor cells and, with less probability, antibodies which are responsible for the 'down regulation' of sensitivity."

Sixty Stamm Pirbright White guinea pigs, 30 per sex, were used in a sensitization study performed according to the method of Magnusson and Kligman (BAYER AG, no date). Induction consisted of intradermal injections, two with PCMC and one with FCA, followed 1 wk later with a topical application of 0.1 mL of 1% and 25% PCMC in Lutrol (site of application not stated). The challenge, performed after 2 wk, consisted of cutaneous application of 12.5%, 22.0%, and 50.0% PCMC in Lutrol and 100.0% PCMC to the flank of the animals. A 25% solution of PCMC was "strongly sensitizing," whereas a 1% solution was "weakly sensitizing."

An epicutaneous test using 35 female Stamm Pirbright White guinea pigs and performed according to the methods of Klecak et al. (1977) was
used to determine the sensitization potential of PCMC (BAYER AG, 1980b). Induction consisted of two 0.1-mL open applications of 1%, 3%, 10%, and 30% PCMC in Lutrol applied to the left flank, with a negative control group being dosed with vehicle only. Challenge consisted of 3%, 10%, and 30% PCMC in Lutrol and 100% PCMC applied to the right flank (length of time in between induction and challenge was not specified). No sensitization reaction was observed.

The sensitization potential of PCMC was examined in an open epicutaneous test (OET) using five groups of eight female outbred albino guinea pigs (Andersen and Hamann, 1984b). The induction, performed according to the methods of Kleckak et al. (1977), consisted of daily open applications of 1%, 3%, 10%, or 30% PCMC in petrolatum; a negative control group was dosed with vehicle only. The animals were challenged using occlusive patches (with a procedure modified from the original method) on the contralateral flank with vehicle, 0.5%, 1.0%, and 2.0% PCMC on day 21 and with vehicle, 0.5%, and 1.0% PCMC on day 35. In addition, on day 28, the animals were challenged with open applications of 0.1%, 2.0%, and 5.0% PCMC.

PCMC was a “doubtful” sensitizer in the OET (which is regarded as a less sensitive test because it does not use FCA); varying responses were recorded during the successive challenges of the test and control groups. Successive applications of 3% and 10% PCMC in petrolatum resulted in strong irritancy reactions. An irritant reaction was observed in five of eight animals dosed with 30% PCMC after one open application; induction using 30% PCMC was discontinued after 2 wk because of severe reaction to the test substance. The animals of this group were challenged with the other test groups.

A cumulative contact enhancement test (CCET) was performed according to the methods of Tsuchiya et al. (1982) using groups of 20 conventional female albino guinea pigs to examine the sensitization potential of PCMC (Andersen et al., 1985). Five test groups were induced on days 0, 3, 7, and 9 using patches containing a suspension of 5% PCMC partly dissolved, mainly suspended in water containing Carbomer 941 as a gelling agent, a saturated aqueous solution of 0.38% PCMC, 5.0% PCMC in olive oil/acetone (4/1), 5.0% PCMC in propylene glycol, or 5.0% PCMC in propylene glycol containing 0.15% Carbomer 941. Prior to the third induction patch application, 2 × 0.1 mL of an FCA water-in-oil emulsion (50/50) was injected intradermally at the lateral borders of the induction area in the postnuchal region. A negative control group also was used. The animals were challenged using horizontally placed Finn chambers on day 21 with 0.1% and 1.0% PCMC in petrolatum. Challenge reactions were scored 48 h ad 72 h after patch application on a scale of 0 to 3. A grade 1 reaction was not regarded as evidence of sensitization.
During induction, the animals treated with the saturated PCMC aqueous solution had marked erythematous and edematous reactions at the patch-test site. A significant difference was observed between the sensitizing capacity of the preparations. The 5% PCMC suspensions in water and olive oil/acetone solution were the most sensitizing, with 12 of 19 and 11 of 20 animals reacting to 1% PCMC after 48 h, respectively; the 5% PCMC in propylene glycol solution had the least sensitizing potential, with only 4 of 20 animals reacting to challenge with 1% after 48 h. Carbomer 941 had no effect on the sensitization rate.

**MUTAGENICITY**

The mutagenic potential of 500 µg/plate or less PCMC was evaluated in an Ames test that was performed using *Salmonella typhimurium* strains TA1535, TA100, TA1537, and TA98 in the presence of metabolic activation (BAYER AG, 1980c). Two positive controls, endoxan and trypanflavin, were used. PCMC was not mutagenic.

A single Ames test was performed using *S. typhimurium* strain TA100 (Rapson et al., 1980). PCMC, tested at $10^{-1}$ to $10^7$ µg/plate, was not mutagenic.

The mutagenic potential of PCMC was evaluated in a *Salmonella*/mammalian microsome test performed according to the methods of Ames et al. (1975), using *S. typhimurium* strains TA100, TA1535, TA1537, and TA98 (Madsen et al., 1986). Doses of 1.28, 6.4, 32.0, 160.0, and 800.0 µg PCMC per plate were tested with and without metabolic activation; each dose was tested in five parallel plates and two runs were performed. The vehicle, dimethylsulfoxide (DMSO), served as the negative control. Without metabolic activation, the positive controls were sodium azide (TA1535 and TA100) and 2-nitroflourene (TA1537 and TA98). With metabolic activation, 2-antramine served as the positive control for all strains.

PCMC did not have mutagenic potential in *S. typhimurium* strains TA1535, TA100, TA1537, or TA98, with or without metabolic activation. The number of His* revertants observed per plate using 1.28 to 32 µg/plate PCMC was similar to the value for the negative control; however, concentrations of 160 and 800 µg/plate generally produced an increasing toxic effect on the tester strains; metabolic activation seemed to decrease this effect.

The mutagenic potential of PCMC in DMSO, 3.3 to 666 µg/plate, was examined using *S. typhimurium* strains TA100, TA1535, TA1537, TA97, and TA98, with and without metabolic activation (Zeiger et al., 1992). The vehicle was used as a negative control. Without metabolic activation, the positive controls were sodium azide (TA100 and
TA1535), 9-aminoacridine (TA1537 and TA97), and 4-nitro-o-
phenylenediamine (TA98); with metabolic activation, 2-amino-
anthracene served as the positive control for all strains. PCMC was not
mutagenic.

A modified SOS chromotest was performed using *Escherichia coli*
strain PQ37 to measure the genotoxic potential of PCMC (Malaveille et
al., 1991). At concentrations of 0.1 to 4 mM, PCMC induced SOS-DNA
repair synthesis without metabolic activation. The addition of a meta-
bolic activation system decreased the genotoxicity of PCMC. Also, the
addition of a radical scavenger, Trolox C (a hydrosoluble form of vita-
min E), inhibited the genotoxicity of PCMC at 0.3 mM.

**CLINICAL ASSESSMENT OF SAFETY**

**Irritation**

Patch testing with 2% PCMC in petrolatum may produce irritant reac-
tions, particularly in people with multiple patch-test reactions that are
misinterpreted as allergic responses (Lewis and Emmett, 1987). Often
retesting several months after the dermatitis had cleared did not result
in positive results.

**Sensitization**

*Predictive*

In a modified human Draize study using 31 male subjects, 5% PCMC
in petrolatum was used for both induction and challenge (Marzulli
and Maibach, 1973). Induction consisted of 10 successive applications
of 5% PCMC in petrolatum under occlusive patches being applied to
the upper lateral portion of the arm; the patches were removed after
48 h or 72 h. After a 2-wk nontreatment period, a challenge patch of
5% PCMC in petrolatum was applied for 72 h. None of the 31 subjects
was sensitized.

In another Draize test performed using male subjects, groups of 98,
88, and 66 subjects were induced with 5%, 10%, and 20% PCMC in
petrolatum, respectively, for 3 to 5 wk (Marzulli and Maibach, 1974).
Ten 48- to 72-h applications of 0.5 g of the test material were made
under an occlusive patch to the upper lateral portion of each subject's
arm. Following an approximately 2-wk nontreatment period, subjects
of all three groups were challenged with a 72-h patch containing 5%
PCMC in petrolatum. None of the subjects in the three test groups
responded to the challenge patch.
Provocative

A single occlusive patch of a below-irritation dose of PCMC (concentration not specified) was applied for 48 h to 363 patients with allergic contact dermatitis (Burry, 1969). Upon scoring after 96 h, three patients had positive reactions to PCMC.

Two percent PCMC in petrolatum was added to the standard patch series in 1972 (Cronin, 1980). During the time period of 1973 to 1976, the incidence of PCMC sensitivity varied between 0.2% to 1.0%, 0.3% to 0.6%, and 0.3% to 0.6% for men, women, and overall, respectively. The total incidence for this time period was 0.5% (17/3189), 0.4% (13/3630), and 0.4% (30/6819) for men, women, and overall, respectively.

Patch tests were performed on patients in two regions of England using allergens, one of which was PCMC, included in a Standard Patch Test Battery because of concern regarding medicament sensitivity (Wilkinson et al., 1980). A total of 651 patients, 267 men and 384 women, were tested in one region and 1029 patients, 373 men and 656 women, were tested in the other region. The occlusive patches were removed after 2 days, and the test sites were scored again after 4 days (the dose concentration was not given). Of the 651 patients in the first region, a total of 0.8% had positive patch-test results to PCMC; 0.5% and 1.1% of the men and women, respectively, reacted to PCMC. In the second region, 0.7% of the patients had positive reactions; 1.3% and 0.3% of the men and women, respectively, reacted to patch testing with PCMC.

An additional 45 patients, 11 men and 34 women, and 128 patients, 36 men and 92 women, with leg ulcers and stasis eczema were patch tested in the two regions. Of the 45 patients tested in the first region, 4.4% had positive reactions to patch testing with PCMC; 9% and 2.9% of men and women, respectively, reacted positively to PCMC. In the second region, 0.8% of 128 patients reacted positively to PCMC; 0.0% and 1.1% of the men and women, respectively, reacted to patch testing with PCMC.

Consecutive eczema patients were tested with the International Contact Dermatitis Research Group (ICDRG) standard patch test series, which included PCMC-containing biocides (Andersen and Hamann, 1984a). Reactions were scored according to the recommendations of the ICDRG (Wilkinson et al., 1970). Of 1462 patients tested with 2% PCMC in petrolatum, only five had positive patch-test results and six had irritant reactions; none of the positive results were clinically explainable.

Another study was conducted in which consecutive eczema patients were tested with the ICDRG standard series (Andersen and Veien, 1985). PCMC, 1% in petrolatum, was tested on 671 patients and no pos-
Positive reactions were observed. PCMC was withdrawn from the patch-test battery after 3 mo because of the lack of reactions observed.

Case Reports

PCMC is a strong sensitizer in guinea pig maximization tests, but human sensitization has been reported to be fairly rare (Lewis and Emmett, 1987); however, several case studies were reported in the published literature and are summarized in Table 5.

Cross-Reactivity

Cross-reactivity has been observed between PCMC and chloroxylenol (Hjorth and Trolle-Lassen, 1963); however, the cross-reactivity has only occurred where the initial sensitization was to chloroxylenol, not to PCMC (Lewis and Emmett, 1987).

SUMMARY

PCMC is a substituted phenol that functions as a cosmetic biocide and a preservative in skin-care and suntan preparations. It is soluble in alkalies, organic solvents, fats, oils, and somewhat in water.

In 1995, data submitted to the FDA reported that PCMC was used in 16 cosmetic product formulations. Internationally, PCMC is approved for use by members of the European Union as a preservative at a maximum authorized concentration of 0.2%; however, it also may be added to cosmetic products at a concentration other than that specified for a preservative for other specific purposes apparent from the presentation of the product. PCMC is prohibited for use in products intended to come in contact with mucous membranes. In Japan, PCMC is listed in the Japanese Standard of Cosmetic Ingredients; products containing this ingredient must declare it on the label. PCMC is approved for use as an indirect food additive. Many of the noncosmetic uses of PCMC use its antiseptic properties. The use concentrations for most noncosmetic applications of PCMC range from 0.05% to 0.5%.

In a pharmacokinetic study in which rats were dosed orally with PCMC, rapid elimination through the kidneys occurred, and no indication of accumulation of PCMC in fatty or hepatic tissues was present. In a study assessing the permeability of PCMC using whole and stripped abdominal skin from mice, the estimated permeability coefficients of PCMC for viable tissue and stratum corneum were $302 \times 10^{-3}$ and $235 \times 10^{-3}$, respectively.

The antimicrobial spectrum of 0.02% PCMC included gram-positive and gram-negative bacteria, yeast, and fungi. In aqueous cream,
Table 5. Case reports concerning PCMC-containing substances

<table>
<thead>
<tr>
<th>Test material</th>
<th>Patient</th>
<th>Case</th>
<th>Testing/results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid cream containing PCMC</td>
<td>39-yr-old man</td>
<td>Dermatitis recurred on previously affected sites on the ankle and feet due to treatment with the steroid cream; an erythematous reaction with fine vesiculation was observed on the legs</td>
<td>Patch testing with 1% PCMC resulted in ++ reactions after 48, 72, and 96 h; subsequent testing several months later resulted in +++ reactions with 1 and 5%, ++ reaction to 0.1%, and + reaction to 0.01% PCMC after 96 h</td>
<td>Lewis and Emmett, 1987</td>
</tr>
<tr>
<td>Steroid cream containing PCMC</td>
<td>24-yr-old man</td>
<td>Application of the steroid cream exacerbated existing dermatitis</td>
<td>Patch testing with 2% PCMC resulted in ++ and +++ reactions after 48 and 96 h, respectively</td>
<td>Oleffe et al., 1979</td>
</tr>
<tr>
<td>Steroid cream containing PCMC</td>
<td>40-yr-old woman</td>
<td>Application of the steroid cream caused existing eczema to deteriorate</td>
<td>Patch testing with 2% PCMC (from two sources) resulted in + and ++ reactions and in – and ++ reactions after 48 and 96 h, respectively</td>
<td>Oleffe et al., 1979</td>
</tr>
<tr>
<td>Glue and steroid cream containing PCMC</td>
<td>27-yr-old woman</td>
<td>Handling of the glue caused severe contact eczema; treatment with the steroid cream did not relieve the condition</td>
<td>Patch testing with 2% PCMC was positive</td>
<td>Dooms-Goossens et al., 1981</td>
</tr>
<tr>
<td>Steroid cream containing PCMC</td>
<td>18-yr-old woman</td>
<td>An eczematous eruption was treated with the cream for 6 mo; the condition worsened and spread</td>
<td>Initial patch testing with 2% PCMC was negative; patch testing after the condition worsened resulted in + reactions to 2% PCMC after 48 and 96 h</td>
<td>Archer and MacDonald, 1984</td>
</tr>
<tr>
<td>Steroid cream containing PCMC</td>
<td>35-yr-old woman</td>
<td>Treatment with the steroid cream for acute dermatitis initially resulted in transient improvement but then caused it to spread</td>
<td>Patch testing with 2% PCMC resulted in ++ reactions after 48 and 96 h</td>
<td>Goncalo et al., 1987</td>
</tr>
<tr>
<td>PCMC as a preservative in betamethasone cream</td>
<td>56-yr-old woman</td>
<td>Daily applications of dilute cream were being used to treat widespread dermatitis; application was stopped and the dermatitis cleared</td>
<td>A patch test with PCMC was positive; (previous testing gave positive reactions to chloroxylenol)</td>
<td>Burry et al., 1975</td>
</tr>
</tbody>
</table>
PCMC as a preservative in betamethasone cream
35-yr-old woman
An acute contact dermatitis was treated with the cream; itching and mild dermatitis continued and mild contact dermatitis appeared elsewhere; this cleared with cessation of cream usage
Patch tests with PCMC was positive (previous testing gave positive reactions to chloroxylenol)
Burry et al., 1975

PCMC as a preservative in betamethasone cream
32-yr-old man
The cream was used to treat dermatitis; the dermatitis cleared when treatment was stopped
A patch test reaction to 5% PCMC in soft paraffin was greater than the reaction to 1% PCMC in soft paraffin (positive reaction to chloroxylenol was slight)
Burry et al., 1975

PCMC as a preservative in betamethasone cream
43-yr-old woman
The cream was used to treat dermatitis; mild contact dermatitis appeared elsewhere; the dermatitis cleared once treatment was stopped
Upon patch testing, there was no reaction to 1% or 5% PCMC in soft paraffin (a strong positive reaction to chloroxylenol was observed)
Burry et al., 1975

PCMC, 0.15%, as a preservative in mucous heparin
35-yr-old woman
The patient was given 10,000 units of the heparin i.v. and immediately collapsed after the second dose with pallor, sweating, hypotension, and tachycardia; she recovered spontaneously after 30 min.
Intradermal skin tests gave positive reactions to both PCMC-preserved and preservative-free heparin
Hancock and Naysmith, 1975

PCMC, 0.15%, as a preservative in mucous heparin
55-yr-old man
The patient was given 10,000 U of the heparin i.v. and over the next hr developed nasal congestion, profuse sweating, and a generalized urticarial rash
Intradermal skin testing with preservative-free heparin did not produce a reaction
Hancock and Naysmith, 1975

PCMC, 0.15%, as a preservative in mucous heparin
Seven patients (sex unspecified)
The patients were given 10,000 U prophylactic subcutaneous heparin twice daily; within a few hr after the first and subsequent injections, an indurated erythematous reaction developed at the injection site
Intradermal skin testing with preservative-free heparin in four of these patients produced no response
Hancock and Naysmith, 1975

(Table continued on next page.)
Table 5. Case reports concerning PCMC-containing substances (continued)

<table>
<thead>
<tr>
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<th>Patient</th>
<th>Case</th>
<th>Testing/results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCMC, 0.15%, as a preservative in mucous heparin</td>
<td>21-yr-old woman</td>
<td>The patient was given 5000 U heparin 6-hourly; administration of the first two doses resulted in severe burning pain at the injection site, radiating along the veins and up the forearm into the arm, nausea, light-headedness, and drowsiness with pallor and sweating</td>
<td>A dose of PCMC-free heparin did not result in pain of a systemic reaction; formal intradermal skin testing produced a reaction to the mucous heparin but none to preservative-free heparin</td>
<td>Ainley et al., 1977</td>
</tr>
<tr>
<td>Cleaning detergent and disinfectant containing PCMC</td>
<td>28-yr-old woman</td>
<td>The patient complained of red swollen eyelids each time she used the detergent disinfectant [of which the two active principles are PCMC and ( \alpha )-benzyl-( p )-chlorophenol (OBPCP)]</td>
<td>PCMC was diluted to 1 and 10% in water: ethanol (1:1) and tested with open and prick tests; the results of the open test were negative and +++ for 1 and 10%, respectively, and of the prick test were +? and +++ for 1 and 10%, respectively; open tests for 30 min with the detergent at 20% in water elicited a urticarial wheal; after the wheal, tests with PCMC produced superficial necrosis, which could be observed on the eyelids at the same time; testing with the detergent at 10% in water and of OBPCP were negative</td>
<td>Freitas and Brandao, 1986</td>
</tr>
</tbody>
</table>
PCMC met the British Pharmacopoeia requirements for the efficacy of antimicrobial preservatives when tested against *A. niger* but not when tested against *C. albicans*.

The oral LD₅₀ of PCMC was 1830 mg/kg for Wistar rats and 5129 and 3636 mg/kg for male and female Sprague-Dawley rats, respectively. The percutaneous LD₅₀ of PCMC was more than 500 mg/kg for rats, and the subcutaneous LD₅₀ was 400 mg/kg for rats and 360 mg/kg for mice. The inhalation LC₅₀ for rats, following a 4-h exposure, was more than 583 mg PCMC-NA/m³ air.

In a short-term dermal toxicity study, 160 mg/kg or less PCMC produced irritation and erythema but had no systemic effects on rabbits. In two short-term oral toxicity studies, no significant dose-related toxicity (excluding body weight parameters) was observed when rats were given 400 mg/kg/day or less PCMC by gavage or 10,000 ppm or less PCMC in feed. In short-term subcutaneous toxicity studies, 72 mg/kg and 0.25% PCMC did not have an effect on rats and rabbits, respectively. In a subchronic study in which rats were fed 1500 ppm or less PCMC, the only observations made were retardation of body weight.

In a chronic study in which rats were fed 10,000 ppm or less PCMC for 2 yr; the NOEL was 2000 ppm PCMC. No PCMC-related changes in clinical chemistry and hematologic parameters were observed, and no significant difference in mortality was observed between test and control animals. At study termination, necropsy findings included kidney deformation and, microscopically, an increase in papillary necroses and cortical tubular dilations and fibrosis of the kidneys for some of the high-dose male rats. Female rats of the mid-dose and high-dose groups that died on study had a greater incidence of pituitary adenoma.

PCMC, as low as 0.05%, produced ocular irritation in the eyes of rabbits, and soft lenses that were stored in solution containing 0.1% PCMC produced severe irritation after a few days.

In a dermal irritation study using the trypan blue method, 0.2%, 0.4%, and 0.8% PCMC resulted in maximum irritation scores of 4, 4, and 8, respectively.

Numerous sensitization studies were performed with PCMC. Generally, some type of reaction was seen upon challenge; however, the reactivity to PCMC decreased with time. In an epicutaneous test, 30% or less PCMC did not produce a sensitization reaction, and in an OET, PCMC was a "doubtful" sensitizer. In a CCET, the frequency of sensitization was vehicle-dependent.

PCMC produced no evidence of mutagenic potential in Ames tests. PCMC, 0.1 to 4.0 mM, induced SOS-DNA repair synthesis without metabolic activation; the addition of metabolic activation or a radical scavenger decreased or inhibited the genotoxicity of PCMC, respectively.
In clinical studies, patch testing with 2% PCMC in petrolatum may produce irritant reactions, particularly in people with multiple patch-test reactions, that are misinterpreted as allergic responses. In two predictive patch tests, initiation with 20% or less PCMC followed by challenge with 5% PCMC did not produce a sensitization reaction in 31 of 252 subjects. In several provocative patch tests, some reactions to PCMC usually were observed. Cross-reactivity between PCMC and chloroxylenol has been observed, but only when the initial sensitization was to chloroxylenol.

**DISCUSSION**

Section 1, paragraph (p), of the Cosmetic Ingredient Review (CIR) Procedures states that “a lack of information about an ingredient shall not be enough to justify a determination of safety.” In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on PCMC were insufficient to determine whether PCMC, for possible purposes of cosmetic use, is either safe or unsafe. The Expert Panel released a “Notice of Insufficient Data” announcement on September 13, 1994 outlining the data needed to assess the safety of PCMC. The types of data required included:

1. Concentration of use in cosmetics
2. UV absorption data; if absorbed in the UVA or UVB range, photosensitization data are needed
3. Dermal developmental toxicity data
4. At least one genotoxicity study using a mammalian system; if positive, dermal carcinogenicity data performed according to National Toxicology Program methods are required

No offer to supply the necessary data was received. In accordance with Section 45 of the CIR Procedures, the Expert Panel will issue a Final Report—Insufficient Data. When the requested data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

**CONCLUSION**

The Expert Panel concludes that the available data are insufficient to support the safety of p-Chloro-m-Cresol for use in cosmetic products.
REFERENCES


BAYER AG. 1978. Acute oral toxicity study using rats. Unpublished data submitted by COLIPA (1 page).*

BAYER AG. 1980a. Thirteen wk study using rats. Unpublished data submitted by COLIPA (1 page).*

BAYER AG. 1980b. Epicutaneous sensitization study using guinea pigs. Unpublished data submitted by COLIPA (1 page).*

BAYER AG. 1980c. *Salmonella/microsome* test with PCMC. Unpublished data (Report No. 9122) submitted by COLIPA (1 page).*


BAYER AG. No date. Sensitization study performed according to Magnusson-Kligman using guinea pigs. Unpublished data submitted by COLIPA (1 page).*


Mobay Chemical Corporation. 1980. Subchronic dermal study in rabbits. Unpublished data submitted by COLIPA. (1 page).*


* Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036.