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To whom it may concern

Re: English translation of

RADIOMETRIC STUDIES INTO THE SUBSTANTIVITY OF THE ANTI-DANDRUFF AGENT PIROCTONE OLAMINE ON HUMAN HAIR

from the German into the English language

The English translation of
RADIOMETRIC STUDIES INTO THE SUBSTANTIVITY OF THE ANTI-DANDRUFF AGENT PIROCTONE OLAMINE ON HUMAN HAIR
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On behalf of Sprachen-Service GbR

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Ermächtigte Übersetzerin der englischen und französischen Sprache für die Gerichte und Notare im Lande Hessen
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RADIOMETRIC STUDIES INTO THE SUBSTANTIVITY OF THE ANTI-DANDRUFF AGENT PIROCTONE OLAMINE ON HUMAN HAIR

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1. Introduction

Piroctone olamine is the generic name for the new anti-dandruff agent 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H) pyridone, monoethanolamine salt (for structural formula see Fig. 1). Clinical trials have shown the preparation to be highly effective against the formation of dandruff (pityriasis simplex capillitii). In comparative tests under simulated practical conditions, e.g. by the "half-side method", very good results were obtained with concentrations of 0.5 to 1.0% piroctone olamine in shampoo (1). Piroctone olamine differs from other known anti-dandruff agents in having relatively low toxicological values as well as formulation advantages (2). Adequate solubility in water and very good solubility in water/alcohol mixtures guarantee a wide spectrum of application for this preparation in cosmetic products.

For use in shampoos, the substantivity of the agent on hair and skin is of particular importance. By determining the non-adsorbed piroctone olamine present in washing and rinsing solutions by UV spectroscopy after a single hairwash (shampoo with 1.0% active ingredient), the substantivity on hair plus scalp was found by Futterer, E. in exploratory tests (3) to be of the order of 20 mg. In these studies carried out on individual subjects, only difference measurements were possible for methodological reasons.

In the present work, model tests with isolated human hair to determine the adsorption of piroctone olamine on keratin are presented. The radiometric tests carried out with a ^{14}C-labeled preparation permit direct determination of active ingredient adsorbed on human hair with high accuracy and sensitivity of detection. As individual determinations are simple and inexpensive to conduct, it was possible to carry out extensive, statistically validated test series. In these, the influence of various parameters on adsorption and the effects of repeated application under simulated practical conditions were studied.

2. Material and methods

2.1 ^{14}C-labeled preparation

The piroctone labeled with carbon 14 in the pyridone ring was produced by the following method (for reaction diagram, please see Fig. 2):- From ^{14}C barium carbonate, ^{14}C carbon dioxide is eliminated with concentrated sulfuric acid. The ^{14}C carbon dioxide is then reacted with 1-bromo-2,4,4-trimethyl pentane in a Grignard reaction to yield 3,5,5-trimethyl caproic

acid (1-^{14}C). Reaction of this substance with thionyl chloride at the boil produces 3,5,5-trimethylhexanoyl chloride (1-^{14}C). Further reaction with dimethylacrylic acid methyl ester in methylene chloride in the presence of anhydrous aluminum chloride results in 3-methyl-4-(3',5',5'-trimethyl hexanoyl) crotonic acid methyl ester (1'-^{14}C), from which 4-methyl-6-(2',4',4'-trimethyl pentyl) pyran-2-one-(6-^{14}C) is obtained by cyclization. By treating this product under heat with hydroxylamine hydrochloride, it is possible to produce 1-hydroxy-4-methyl-6-(2',4',4'-trimethyl pentyl) pyridin-2-one (6-^{14}C). On addition of an equimolar amount of 2-aminoethanol to a solution of this product in acetic acid ethyl ester, the required piroctone olamine (6-^{14}C) is precipitated as colorless crystals at the flash point of 134-135°C. The yield is approx. 20% of the theoretical yield, based on barium carbonate-^{14}C.

In this way, approx. 1 g piroctone olamine with a specific activity of 109 mCi/g (= 4.03 GBq/g) was obtained.

The identity of the compound was validated by comparing the melting points and IR spectra with those of authentic material. Chemical and radiochemical purity (>99%) were determined by thin-layer chromatography on polyamide 11 F_{254} (Merck) with methanol/ethanolamine (99:1) as the mobile phase.

Before the start of each test series, a 1% stock solution of the ^{14}C-labeled piroctone olamine (solvent: ethanol/water 50:50) was prepared. Thin-layer chromatographic tests showed that the preparation was stable in this solution until used in the test (see Fig. 3).

2.2 <u>Hair types and pretreatment</u>

The following human hair mixtures were available for the test:

- Human hair, Asian (China), brown, untreated;
  Origin: Fischbach u. Müller, Laupheim

- Human hair, European, not chemically pretreated, dark blonde, continuous tresses;
  Origin: Kerling, Backnang

  Mixture I
  Mixture II

- Human hair, European, dark blonde, bleached twice (with 6% H_2O_2 solution at pH 9, 120 min)

Hair tresses, 5 cm in length and weighing approx. 200 mg, were conditioned in a climatic chamber (50% relative humidity, 23°C) and weighed. Before the adsorption operation, the hair strands were prewashed with 1% ®Genapol CRO solution (sodium $C_{12/14}$ alkyl triglycol ether sulfate) and rinsed with deionized water.

2.3 Adsorption tests

To simulate hair washing, the standard shampoo formulation used (% w/w):

®Genapol LRO liquid (28%)		53.6%
(= 15.0% sodium $C_{12/14}$ alkyl diglycol ether sulfate)		
Piroctone olamine		0.5%
Citric acid (approx. 0.1%)	to pH	7.0
Water	to	100.0%

was diluted in a ratio of 1:10 with tap water. Labeling was carried out by adding 100 µl of the stock solution containing the ^{14}C-labeled preparation with a specific activity of 109 mCi/g to 50 ml of dilute shampoo. This brought only an insignificant increase in active ingredient concentration; the specific activity of the active ingredient was on average 4.5 ± 0.3 mCi/g.

The standard operation for adsorption comprised the following steps:

- Dipping the hair tresses with tweezers into 30 ml of the 1:10 dilute shampoo under the selected conditions.
- Rinsing by dipping several times in 3 x 30 ml tap water.
- Drying the hair tresses on absorbent paper.

The standard conditions were:

- Concentration in the shampoo	0.5% piroctone olamine
- Application concentration	10.0% shampoo in tap water
- pH	7
- Duration	3 min
- Temperature	40°C

In each test series, one parameter was varied (concentration, time, temperature, pH, number of treatments).

To determine substantivity as a function of the shampoo composition, tests were conducted with the surfactants listed in Table 3. The concentration of active detergent ingredient in the shampoo was 15%, as with the standard formulation. The pH was correspondingly adjusted to 7.0.

In a further series of tests, the effect of the quaternary ammonium compounds listed in Table 4 on adsorption of the anti-dandruff agent was tested. In these tests, standard formulations containing 1.0% of the cationic substance were used.

2.4 Desorption tests

Desorption tests were carried out using a cream rinse and a plain shampoo (no active ingredient) with the following compositions:

Cream rinse:	®Genamin KDM (80%) (= $C_{20/22}$ alkyltrimethyl ammonium chloride)		3.75%
	Cetyl alcohol		3.0%
	Water	to	100.0%
Plain shampoo:	Genapol LRO liquid (28%) (= 15.0% sodium $C_{12/14}$ alkyldiglycol ether sulfate)		53.57%
	Water	to	100.0%

To simulate practical conditions as closely as possible, the cream rinse and plain shampoo were again diluted in a ratio of 1:10. The temperature was 40°C and the treatment time 3 min and 5 min. Rinsing with tap water was carried out as in the adsorption tests.

2.5 Radioactivity measurement and evaluation

The hair tresses, weighing approx. 200 mg, were combusted in the Tri-Carb sample oxidizer from Packard Instrument Comp. The $^{14}CO_2$ collected in ethanolamine and the resulting aqueous desorption solutions were measured by liquid scintillation counting in a mixture (suitable for colloid formation) of xylene, a polyethoxyethanol and ethanol with 1.1% PPO and 0.1% dimethyl POPOP. The measurements were carried out in the Tri-Carb analyzer 3385 (Packard Instrument Comp.).

1 ml of the rinse solutions was measured directly in each case.

In each case triple determinations were carried out. The results are generally quoted as arithmetic averages ± standard deviation. To standardize to standard conditions, standard values were also measured in each test series. Standardization (μg piroctone olamine/g hair on single adsorption $\triangleq$1.00) allows better comparison of the results from different test series.

3. Results and discussion

3.1 Adsorption under standard conditions

As Table 1 shows, with the standard formulation, only slightly differing adsorption values were obtained for the 4 hair groups tested. A European hair mixture (I), which had a value of 140.0 ± 18.1 μg piroctone olamine/g hair, did not differ from an Asian hair mixture (140.2 ± 8.5 μg/g). Another untreated European hair mixture (II), which had a value of 180.4 ± 10.5 μg/g, was of the same order of magnitude as bleached hair (173.7 ± 6.5 μg/g). Individual deviations within a group can, however, be considerable. Figure 4 shows the distribution of 18 standard values for the most frequently used hair type (European I). The values show an approximately symmetrical distribution around the average value.

3.2 Adsorption as a function of temperature, time, pH and concentration

Table 2 shows the results of a typical test series, in which one parameter – in this case temperature – was varied, while all other parameters were held constant to the standard conditions. At the standard temperature of 40°C, a typical value is obtained (142 µg/g) for the first mixture of European hair. The single values of 130.8, 142.3 and 152.9 give rise to a standard deviation of ± 11.1 µg/g. At 18°C, on the other hand, adsorption reaches only 92.7 ± 3.0 µg/g, with single values of 89.5, 93.8 and 95.1. As Fig. 5 makes clear, the increase in adsorption values between 20 and 40°C is approximately linear.

As can be seen from Fig. 6, the pH of the shampoo has no significant effect on adsorption within the range tested (pH 5 to pH 8).

The kinetics of the adsorption process are demonstrated in Fig. 7 with the aid of a typical example (European hair mixture II). As the graph shows, the adsorption process is not completed after a 3-minute application under standard conditions. Saturation is only reached after 10 – 15 minutes. Up until that point, a further 30%, based on the value for adsorbed active ingredient under standard conditions, is adsorbed. The low adsorption observed at temperatures < 40°C (see Fig. 5) must therefore be a consequence of a lower adsorption rate at lower temperatures.

The effect of active ingredient concentration in the shampoo on the adsorption of piroctone olamine on human hair was studied at concentrations ranging from 0.25 to 2.0%. As can be seen in Fig. 8, after an initial linear increase, the curve flattened in the concentration range between 1 and 2% without saturation being reached.

3.3 Accumulation on repeated application

On repeated application of piroctone olamine-containing shampoo on European hair (I) under standard conditions, the adsorption curve plotted in Fig. 9 is observed. After a short linear section, the curve starts to flatten after only a few applications and reaches saturation on about the 15th application. The quantity adsorbed (528 ± 134 µg/g) is nearly four times as much as after a single treatment. The scatter of the results was relatively wide, as the high standard deviation shows; another measuring point at n = 20 confirms the limited accumulation on hair with repeated application under simulated practical conditions.

3.4 Adsorption as a function of shampoo composition and shampoo additives

When piroctone olamine was used in shampoos containing different surfactants from the one specified in the standard formulation, the same or slightly higher substantivity on European hair (I) was observed. The average values were between 135.9 and 208.2 µg/g hair (see Table 3).

By adding low-molecular-weight and polymeric cationic substances and products with pseudo-cationic properties to the shampoo, the substantivity of piroctone is generally increased. At a cationic product concentration of 1.0%, average values of 177.4 to 262.5 µg/g were determined (see Table 4). In the case of formulations with only 0.5% addition, the same or somewhat lower effects were usually recorded.

3.5 Adsorption and desorption in aftertreatment with a cream rinse

Combined adsorption/desorption tests were conducted to examine the effect of cream rinse aftertreatment on the adhesion behavior of piroctone olamine.

Fig. 10 shows a graph of the desorption process after a single application of piroctone olamine, including the water rinses. With the cream rinse used here, only about 15% of the quantity of piroctone olamine adsorbed in a single application (≙ 100%) was removed from bleached hair. With other hair samples, the proportion removed was less than 10% on average.

The adsorption curve for repeated use of piroctone olamine-containing shampoo and cream rinse is plotted in Fig. 11. Graph a shows the values measured on the hair after n operations; graph b plots the amounts determined in the desorption solutions after 10 applications of piroctone olamine over this curve.

The curve measured here for the cumulative process shows practically no difference from the curve in Fig. 9 for cream-rinse-free treatment. After the 10^{th} alternating application, only some 5% of the total amount of piroctone olamine adsorbed on the hair is desorbed. The cationic surfactant, whose substantivity on hair had been demonstrated in earlier radiometric studies (4), therefore has practically no influence on the adhesion of piroctone olamine when used as a cream rinse.

3.6 Desorption on alternating use of plain shampoo (active-ingredient-free) and cream rinse

In comparison to hair aftertreatment with cationic products (cream rinse), piroctone olamine is better desorbed by plain shampoo based on sodium alkyl diglycol ether sulfate. Figure 12 shows the desorption curve for repeated use of plain shampoo and cream rinse. After three treatments over 50% of the adsorbed piroctone olamine had been removed from the hair. The desorption curve, however, decreased after this so that, even when treatment with piroctone olamine is stopped, a continuing anti-dandruff effect can be deduced from these results.

Summary:

Tests to determine the substantivity of the anti-dandruff agent piroctone olamine on human hair using a ^{14}C-labeled preparation yielded the following results:

- Under standard conditions (3 min, 40°C, 0.5%, pH = 7), the preparation, used in shampoos, showed excellent substantivity. The deviations noted with different types of hair and different shampoos were slight.

- The adsorbed quantity is dependent on time, temperature and concentration; it is independent of pH in the range pH 5 to 8.

- On repeated application under standard conditions with and without alternating cream rinse treatment, further piroctone olamine is adsorbed. Saturation is achieved after 10 to 15 applications.

- By adding cationic and pseudo-cationic substances to the shampoo, substantivity is increased, as was demonstrated in a number of examples. Aftertreatment with cream rinse has practically no influence on adhesion to human hair.

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+) Data can be supplied on request

Table 1: Adsorption of ^{14}C-labeled piroctone olamine on human hair under standard conditions (shampoo, 0.5%, 3 min, 40°C, pH 7)

Hair type	Piroctone olamine adsorbed on hair ($\mu g/g$)
Asian, brown	140.2 ± 8.5 (n = 6)
European, dark blonde (I)	140.8 ± 18.1 (n = 18)
European, dark blonde (II)	180.4 ± 10.5 (n = 9)
European, dark blonde, 2 x bleached	173.7 ± 6.5 (n = 6)

Table 2: Adsorption of ^{14}C-labeled piroctone olamine on human hair as a function of temperature
European hair, dark blonde (I)
shampoo, 0.5%, 3 min, pH 7

Temperature °C	Adsorbed quantity ($\mu g/g$ hair)	
	x_i	$\bar{x} \pm s$
18	89.3 93.8 95.1	92.7 ± 3.0
23	104.9 106.9 114.7	108.8 ± 5.2
30	114.7 117.6 129.4	120.6 ± 7.8
40	130.8 142.3 152.9	142.0 ± 11.1

Table 3: Adsorption of ^{14}C-labeled piroctone olamine on human hair when used in different shampoos

Hair: European, dark blonde (I)
Adsorption conditions: 40°C, 3 min, 0.5%, pH 7
Concentration of active detergent ingredient: 15%

Serial no.	Active detergent ingredient of the shampoo		Piroctone olamine adsorbed on hair (µg/g)
	Chemical name	Trade name (manufacturer)	
1	Sodium lauryl sulfate	Texapon K 12 (Henkel)	157.9 ± 16.4 (n=3)
2	Sodium acyl amino triglycol ether sulfate	Genapol AMS (Hoechst)	147.2 ± 23.3 (n=6)
3	Fatty alkyl dimethyl amino oxide	Genaminox KC (Hoechst)	162.9 ± 27.4 (n=6)
4	Fatty acid amido alkyl betaine	Tego-Betain L7 (Goldschmidt)	208.2 ± 19.0 (n=3)
5	Coconut fatty alkyl polyglycol ether	Genapol C 100 (Hoechst)	135.9 ± 13.1 (n=3)

Table 4: Effect of shampoo additives on the adsorption of ^{14}C-labeled piroctone olamine on human hair

Hair: European, dark blonde I
Shampoo: standard formulation
Adsorption conditions: 40°C, 3 min, 0.5%, pH 7
Concentration of shampoo additive: 1.0%

Serial no.	Shampoo additive		Piroctone olamine adsorbed on hair (µg/g)
	Chemical name	Trade name, abbreviation (manufacturer)	
1	Cetyltrimethyl ammonium chloride	Genamin KS 5 (Hoechst)	177.4 ± 22.1 (n=3)
2	Etheramine	Hoe S 2650 (Hoechst)	198.8 ± 21.4 (n=3)
3	Stearamido ethyl diethylamine	Chemical Base 6352 (Sandoz)	220.9 ± 16.7 (n=3)
4	Polyethylene glycol (15) tallow polyamine condensation resin	®Polyquart H (Henkel)	224.8 ± 21.0 (n=3)
5	Polymeric quaternary ammonium salt from monomers of acrylamide and dimethyl diallyl ammonium chloride	Merquat 550 (Mobil Oil, Merck/USA)	262.5 ± 30.9 (n=3)
6	Polymeric quaternary ammonium salt from dimethyl sulfate and copolymer of polyvinyl pyrrolidone and dimethyl aminoethyl methacrylate	®Gafquat 734 (GAF)	237.1 ± 19.0 (n=3)
7	Cationic polymers obtained by reaction of trimethylamine with the reaction product of hydroxyethyl cellulose and epichlorohydrin	Polymer IR-30M (UCC)	231.5 ± 38.3 (n=6)
8	- " -	Polymer IR 400 (UCC)	252.3 ± 46.9 (n=3)

Fig. 1: Structural formula, designations

Piroctone olamine

(anti-dandruff agent)

Monoethanolamine salt of 1-hydroxy-4-methyl
-6-(2,4,4-trimethylpentyl)-2(1H) pyridone;

Octopirox® (registered trademark of Hoechst AG)
*^{14}C labeling

Fig. 2: Synthesis of the ^{14}C-labeled preparation

Pirocton olamin = Piroctone olamine

14C-markiert = ^{14}C-labeled

Fig. 3: Radio thin-layer chromatogram;
purity and stability testing of piroctone olamine
(6-^{14}C) in 1% solution;
Solvent: water/ethanol (50:50)

Hoechst	**RADIOCHEMICAL LABORATORY**			
	Radio thin-layer chromatogram no.			
Preparation: *Octopirox – [6 – ^{14}C]*				
Batch no.:	*9027 I*		**Specific activity:** *109*	**mCl/g**
Quantity:	*200*	**µg**	**Solvent:** *H_2O:C_2H_5OH 1:1*	
Static phase: *Polyamide 11 F254*			*Merck*	
Mobile phase: *methanol:ethanolamine (99:1)*				
Scanner: *Berthold LB 2722*				
Pulse rate:	*1 x 10^4*	**pps**	**Time constant:** *1*	**sec**
Slit width:	*1 x 16*	**mm**	**Paper feed rate:** *600*	**mm/h**
Date:	*18.5.70*		**Initials:** *(signed)*	

Fig. 4: Adsorption of ^{14}C-labeled piroctone olamine on human hair[+)]
Distribution of 18 standard test values (3 min; 40°C; pH 7; 0.5%)

Anzahl der Standardwerte = Number of standard values

Adsorbierte Menge (μg/g Haar) = Adsorbed quantity (μg/g hair)

[+)] Gemisch/Endlostressen (I) europäisch, dunkelblond (Kerling Backnang) = [+)]Mixture/continuous tresses (I) European, dark blonde (Kerling Backnang)

Figs 5, 6, 7: Adsorption of ^{14}C-labeled piroctone olamine on human hair as a function of temperature, pH and time

Adsorbierte Menge pro g Haar unter Standardbedingungen = 1.00	=	Adsorbed quantity per g hair under standard conditions = 1.00

rel. adsorbierte Menge pro g Haar = Relative adsorbed quantity per g hair

Temperatur = Temperature

pH-Wert = pH

Zeit (min) = Time (min)

Europ.Haar = European hair

Fig. 8: Adsorption of ^{14}C-labeled piroctone olamine on human hair as a function of concentration in the shampoo

Adsorbed quantity under standard conditions / g hair (European hair I, 3 min, 40°C, pH 7, 0.5%) $\triangleq$ 1.00

rel. adsorbierte Menge / g Haar = Relative adsorbed quantity / g hair

Konzentration im Shampoo = Concentration in the shampoo

Fig. 9: Accumulation on repeated adsorption of ^{14}C-labeled piroctone olamine on human hair under standard conditions (European hair I, 3 min, 40°C, pH 7, 0.5%)

Adsorbed quantity / g hair on single application $\triangleq$ 1.00

rel. adsorbierte Menge / g Haar = Relative adsorbed quantity / g hair

Anzahl der Adsorptionsvorgänge n = Number of adsorption operations n

Fig. 10: Desorption of ^{14}C-labeled piroctone olamine with cream rinse after single adsorption on human hair

European hair, 2 x bleached
Adsorption conditions: shampoo, 0.5%, 40°C, 3 min,
pH 7
3 x rinses with water
Desorption conditions: cream rinse, 40°C, 5 min,
3 x rinses with water
Adsorbed quantity / g hair $\triangleq$ 100%

restliches Pirocton olamin am Haar = Residual piroctone olamine on the hair

Desorption = Desorption

ohne Cream rinse = without cream rinse

mit Cream rinse = with cream rinse

Behandlung	=	Treatment
mit H_2O		with H_2O
nach		after
Adsorption		adsorption

Behandlung	=	Treatment
mit H_2O		with H_2O
nach		after
Desorption		desorption

Cream rinse = cream rinse

Fig. 11: Accumulation on repeated absorption of ^{14}C-labeled piroctone olamine on human hair and desorption with cream rinse

Hair: European, dark brown (II)
Adsorption conditions: shampoo, 0.5%, 40°C, 3 min, pH 7
Desorption conditions: cream rinse, 40°C, 5 min
a) Quantity of adsorbed piroctone olamine on the hair after n treatments (adsorption and desorption)
b) Adsorbable and desorbable content after 10 treatments
Adsorbed quantity/g hair on single adsorption
$\triangleq$ 1.00

rel. adsorbierte Menge pro g Haar = Relative adsorbed quantity per g hair

Anzahl der Adsorptions- und Desorptionsvorgänge n	=	Number of adsorption and desorption operations n

Fig. 12: Desorption of ^{14}C-labeled piroctone olamine adsorbed on human hair with plain shampoo and cream rinse.

Top: Residual quantity on the hair after three treatments
Bottom: Distribution between cream rinse, shampoo and hair

restliches Pirocton olamin am Haar (%) = Residual piroctone olamine on the hair (%)

Anteil Pirocton olamin (%) = Percentage of piroctone olamine (%)

Anzahl der Behandlungen (n) mit Cream rinse und Shampoo = Number of treatments (n) with cream rinse and shampoo

Cream rinse = cream rinse

Shampoo = shampoo

Haar = hair