

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-022

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-022
PRODUCT: Loprox (ciclopirox) Nail Lacquer 8%
SPONSOR: Hoechst Marion Roussel
10236 Marion Park Drive
P.O. Box 9627, Kansas City, MO 64134

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SYNOPSIS

Ciclopirox is a hydroxypyridone antifungal agent. Loprox Nail Lacquer 8% is intended for the topical treatment of mild to moderate onychomycosis in fingernails and toenails without lunula involvement due to *Trichophyton rubrum*.

The lacquer is to be applied once daily to affected fingernails and toenails with the old lacquer coat removed every seven days with isopropyl alcohol. Provided in the human pharmacokinetics are three in vitro penetration studies, two in vivo penetration studies in healthy subjects and three systemic absorption studies in onychomycosis patients. All studies used the to-be-marketed formulation.

Among the three in vitro penetration studies, two studies involved topical applications of the lacquer to nails from human cadavers which showed poor penetration of ciclopirox into deeper layers of healthy nails. However, it is noted that both lacquer application and lacquer removal patterns in these studies were different from the clinical use conditions, which could impact on the results. The findings from the single application suggested that penetration of ciclopirox through sole skin was greater (>10-fold) than through healthy nails. One study involving single application of the nail lacquer to toenails avulsed from onychomycosis. This study showed that ciclopirox concentration 48 hours after application of the lacquer was close to or above $1 \mu\text{g}/\text{cm}^3$ at a nail depth of $400 \mu\text{m}$ in 4 out of the 5 nails studied. However, it is difficult to draw a generalized conclusion from this study. Conceivably, a damaged nail due to mycosis would show better penetration of ciclopirox than a healthy nail and the extent of penetration would vary with the disease condition.

The two in vivo penetration studies had the same lacquer application/removal patterns as proposed for clinical use. These two studies were conducted in healthy subjects and showed penetration might be greater in toenails than in fingernails (possibly due to extrinsic factors). Contrary to in vitro findings, substantial penetration of ciclopirox into deeper nail layers was observed. Because of the way the lacquer was applied and the way the nail samples were collected, however, this observation might be due to the spillover of the lacquer to the ventral side of the distal portion of the nail. The portion of the nail that was farther away from the distal portion might have a very different concentration-nail depth profile.

The three studies that determined the systemic absorption of ciclopirox through nails are described below:

In Protocol 111, the lacquer was applied once daily at bedtime for approximately 6 months to all onychomycotic and healthy toenails and fingernails. Five subjects with distal onychomycosis of fingernails were enrolled and completed the study. The lacquer was removed before each following application. This is different from the clinical use conditions in which the lacquer was removed every seven days. Blood ("trough") and urine samples were collected during and after treatment. The 24-hr renal excretion of ciclopirox and its glucuronide was 2.6 ± 3.9 mg (range: _____). The findings indicate that, in this study, systemic absorption of ciclopirox is 20.2 mg or less (mean: 3.2 mg or 7% of the average daily dose). The highest "trough" serum concentrations observed for each subject ranged from _____ ng/mL (median: 16 ng/mL). Approximately 30 days after treatment, none of the serum samples had detectable ciclopirox concentrations.

Protocols 312 and 313 were two placebo controlled clinical trials of the same design to investigate the safety and efficacy of the nail lacquer. Patients were to apply the lacquer to all toenails and affected fingernails. (Upon our request, the sponsor provided information which revealed that most subjects applied the lacquer to toenails only.) Application and removal of the lacquer was done the same way as proposed for clinical use. In these trials, patients in designated study sites had blood samples taken prior to, during and after treatment with random sampling times. Of the 66 subjects that had post-baseline assessments, 42 had serum concentrations below LOQ during treatment. Twenty-four subjects with detectable levels had maximum levels ranging from _____ ng/mL. Of the 24 subjects with detectable ciclopirox levels, at least 11 took concomitant medication containing ciclopirox (Loprox cream 1%).

COMMENTS

1. The two in vivo penetration studies showed substantial penetration of ciclopirox into deeper layers of healthy nails. However, this observation might be due to the spillover of the lacquer during application to the ventral side of the distal portion of the nail. The portion of the nail that was farther away from the distal portion might have a very different concentration-nail depth profile. Further, the sponsor did not address ciclopirox concentrations in nail bed after application of the lacquer.
2. The systemic absorption study (Protocols 111) did not provide optimal information because of the following reasons:
 - a. The old coat was removed with soap and water and each nail was swabbed with isopropyl alcohol before applying a fresh coat. This removal procedure, which is different from the clinical use conditions, could impact on percutaneous absorption.
 - b. Individual doses on PK sampling days was not determined.
 - c. Only "trough" serum concentration, and not the full concentration-time profile within a dosing interval, was determined.

Nevertheless, the quantity of ciclopirox absorbed into systemic circulation can be derived from urine data. The highest urinary excretion of total ciclopirox over a dosing interval observed in this study was 16.4 mg (Subject #103 at 2-month visit). This value corresponds to a total absorption of 20.2 mg of ciclopirox from one application of the nail lacquer to all toenails and fingernails based on the published literature that elimination of ciclopirox was primarily through renal route (98% of radioactivity in the excreta) and that about 83% of the urinary radioactivity was identified as the free or conjugated drug.

3. Studies 312 and 313 provided some information on serum concentrations at various times after application of the lacquer. However, there is no information on the actual individual dose either on specific days or during the treatment period. (Subjects were to apply the lacquer to all toenails and affected fingernails. It appears that most subjects had no affected fingernails.)
4. According to Dr. Amy Nostrandt, Pharmacologist of HFD-540, cardiac toxicity has not been seen in any of the non-clinical dermal studies but have been observed in oral studies in rats and dogs. For oral doses, the NOAEL in dogs was 10 mg/kg. At an oral dose of 30 mg/kg, all 4 Beagle dogs died. The serum concentration of ciclopirox was 12-13 $\mu\text{g/mL}$ but the sampling time relative to dosing time was not stated. Based on the three human studies, serum ciclopirox concentration from use of the nail lacquer is expected to be much lower ($<0.1 \mu\text{g/mL}$).
5. It should be noted that if patients are allowed to use other Loprox product concomitantly, the systemic exposure can be higher.

RECOMMENDATION

From the biopharmaceutics standpoint, the application is acceptable.

/S/

Sue-Chih Lee, Ph.D.

Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D.

/S/

10/8/99

CC:

NDA 21-022

HFD-540 (Div.File)

HFD-540 (CSO)

HFD-880 (Bashaw)

HFD-880 (Lazor)

HFD-880 (Lee)

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HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

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I. BACKGROUND

Ciclopirox is a broad-spectrum antifungal agent. It is slightly soluble in water, very soluble in chloroform and freely soluble in 96% ethanol. Loprox Cream 1% and Loprox Lotion 1% formulations were approved for the treatment of tinea pedis, tinea corporis, cutaneous (superficial) candidiasis and tinea vesicolor. The active ingredient in the cream and lotion formulations is ciclopirox olamine. The gel formulation containing 0.77% ciclopirox was also approved. The proposed lacquer formulation contains ciclopirox free acid as its active ingredient and is intended for the treatment of onychomycosis.

II. FORMULATION AND DOSAGE ADMINISTRATION

The proposed lacquer formulation (Formulation B) is given below. The lacquer is to be applied evenly over the entire nail plate. If possible, lacquer should be applied to the nail bed, hyponichium, and the ventral surface of the nail plate when it is free of the nail bed (e.g. in onycholysis). The lacquer should not be removed on a daily basis. Daily applications should be made over the previous coat and every seven days the lacquer should be removed.

<u>Ingredient</u>	<u>Quantity (mg/g)</u>
Ciclopirox	
Ethyl acetate NF	
Isopropyl alcohol USP	

III. ANALYTICAL METHOD

IV. SUMMARY OF BIO/PK/PD CHARACTERISTICS

SYSTEMIC ABSORPTION OF CICLOPIROX

Study Title: An open-label study to determine the safety, efficacy and systemic absorption of ciclopirox (Loprox) nail lacquer 8% in patients with dermatophytic onychomycoses of the fingernails (Protocol 111)

This was a single center, open label study involving subjects with distal subungual onychomycosis of the fingernails. Five subjects (4M & 1F; age: 34-74 yrs with a median of 53 yrs.) were enrolled in the study. The median duration of fungal infection was 8 years (range: 2-27 yrs.) and the median duration of the episode that prompted enrollment was 5 years (range: 2-25 yrs.). Ciclopirox nail lacquer 8% was applied once daily at bedtime (with applications approximately 24 hours apart) for approximately 6 months (24-26 weeks) to all onychomycotic and healthy toenails and fingernails. The first application was made under supervision of the investigator or designee. The lacquer was applied evenly over the entire nail plate and the proximal and lateral nail fold areas, approximately 5 mm into the folds. If possible, lacquer also was to be applied to the nail bed, hyponychium and the ventral surface of the nail plate when it

was free of the nail bed. Before applying a fresh coat, the old coat was removed with soap and water and each nail was swabbed with isopropyl alcohol.

Pharmacokinetic variables included measurement of serum and 24-hour urine concentrations of total ciclopirox (i.e. ciclopirox plus its glucuronide metabolite) to assess systemic absorption of the formulation. Serum and urine samples were collected at Baseline (Day 1), and at Months 2, 4, and 6 and at 4 weeks post-treatment. The first two subjects enrolled were to have additional concentration determination at Week 2 and Month 1. Blood samples were collected 16-20 hours after application of test drug product. Twenty-four hour urine collections were started 24 hours before the serum samples were drawn.

Results:

On average, subjects used approximately 127 grams of nail lacquer over the course of the study (range: — g) with a mean daily dose of 566 mg. The systemic exposure was a result of percutaneous and periungual absorption. All subjects had serum and urine concentrations of total ciclopirox above the limit of detection. Three of the five subjects had urine concentrations in excess of 800 ng/mL (highest: 4685 ng/mL). The mean 24-hr renal excretion of ciclopirox and its glucuronide was 2.6 ± 3.9 mg (range: — mg). The highest serum concentrations for each subject ranged from — ng/mL (median: 16 ng/mL). There was considerable variation among subjects. Twenty-three to 35 days after cessation of treatment, ciclopirox was not detectable in the serum or urine of any subject.

Table: Serum Concentrations and Urinary Excretion of Ciclopirox and Its Glucuronide

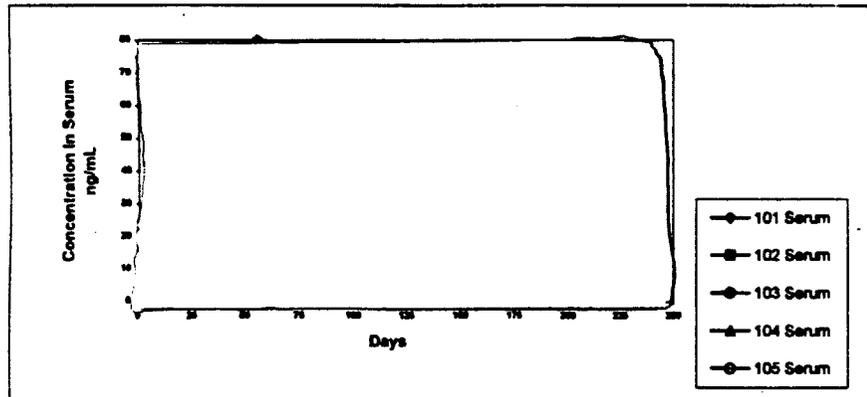
Evaluation/Sampling Time	Subj. #101	Subj. #102	Subj. #103	Subj. #104	Subj. #105
Number of Affected Nails					
During Treatment Period					
Serum Concentration (ng/mL)					
2 Weeks					
1 Month					
2 Months					
4 Months					
6 Month					
1 Month Post- Treatment					
Amount Excreted in Urine 0-24 hrs (mg)					
2 Weeks					
1 Month					
2 Months					
4 Months					
6 Month					

BDL: Below detection limit

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Figure: Individual "Trough" Serum Ciclopirox Concentrations on Various Treatment Days



Four subjects experienced at least one adverse events. Two of these events (gastroenteritis and dehydration) were severe and all others were of moderate intensity. The sponsor stated that none was related to the study drug.

Reviewer's comments:

1. This study does not provide optimal information regarding the systemic absorption for safety assessment because of the following reasons:
 - a. In the study, the old coat was removed with soap and water and each nail was swabbed with isopropyl alcohol before applying a fresh coat. This removal procedure is different from the clinical use conditions.
 - b. Many variables that could affect the results were not documented. For example, the individual dose on PK sampling days was not determined and the time of the blood draw in relation to the time of last application of nail lacquer was not standardized or documented. Besides, it is not clear how closely patients followed the instruction about dosing area. Further, it was indicated that all healthy and onychomycotic toenails and fingernails were treated but data on the conditions (severity and involved surface area) of individual nails on PK sampling days was crude. (Upon our request, the sponsor estimated the average daily dose in this study ranged from 0.36 g to 1.35 g of the lacquer which is equivalent to approximately 1.5-5.4 mg of ciclopirox per nail.)
 - c. Pharmacokinetic variables included measurement of serum concentrations and 24-hour urine concentrations of total ciclopirox (i.e. ciclopirox plus its glucuronide metabolite) to assess systemic absorption of the formulation. However, only "trough" serum concentration (16-20 hrs postdose), and not the full concentration-time profile within a dosing interval, was determined.
2. The sponsor concluded that the highest serum ciclopirox concentration observed was 80 ng/mL (measured in one subject after approximately 2 months of treatment) which was 250 times lower than the lowest concentration measured at a toxic dose in animals (20 $\mu\text{g/mL}$) and 75 times lower than the lowest concentration measured at a nontoxic dose in animals (6 $\mu\text{g/mL}$). It should be noted that the study did not characterize the full concentration-time profile of ciclopirox and the maximum concentration in a dosing interval is unknown.

3. The highest urinary excretion of total ciclopirox (16.4 mg) over a dosing interval was observed with Subject #103 at 2-month visit. However, this high value was not observed in this subject at other visits (1.94 mg at 4 months and 0.94 mg at 6 months). Although serum concentration in this individual was higher at 2 months than at other visits, the difference was only approximately 2-fold. Thus, the accuracy of this high value is not clear. Nevertheless, this suggests that in this study the highest absorption of ciclopirox from the nail lacquer was 20.2 mg. The calculation was made by this reviewer based on the literature report¹ that elimination of ciclopirox was primarily through renal route (98% of radioactivity in the excreta) and that about 83% of the urinary radioactivity was identified as the free or conjugated drug. (Upon our request, the sponsor provided information on the volume of distribution for ciclopirox which was estimated to be 13 L/70 kg body weight. Assuming that all 20.2 mg of ciclopirox was absorbed all at once, the serum concentration would be 1.55 µg/mL. This information does not help with our assessment of systemic toxicity.)

¹Von H.-M. Kellner, et al. *Arzneim.-Forsch./Drug Res.* 31(II), No. 8a (1981) 1337-1353

Study Title: A double-blind study of the safety and efficacy of ciclopirox (HOE 296NL) nail lacquer 8% versus its lacquer vehicle in patients with distal subungual tinea unguium of the toenails (Protocols #312 & 313)

Protocols #312 & 313 were double-blind, vehicle-controlled studies conducted at nine centers each. Subjects with a diagnosis of mild to moderate distal subungual tinea unguium of at least one great toenail with 25-60% involvement were allowed to participate in the study. The nail lacquer was applied once daily for 48 weeks to all toenails and affected fingernails. The nail lacquer was applied evenly over the entire nail plate and the proximal and lateral nail fold areas, approximately 5 mm onto folds. If possible, lacquer also was to be applied to the nail bed, hyponychium and the ventral surface of the nail plate when it was free of the nail bed. Subjects were to wait at least 8 hours after application before washing their feet. Daily applications were made over the previous coat, and every seven days subjects were to completely remove the lacquer with isopropyl alcohol swabs. (Use of acetone based nail lacquer removers were allowed at monthly visits.) Subjects were instructed to file away loose nail material and trim nails as required every seven days (on the day they removed the test material).

Results:

Two study centers in Protocol 312 (total: 54 subjects; 28 on active treatment and 26 on placebo) and three study centers in Protocol 313 (total: 83 subjects; 41 on active treatment and 42 on placebo) collected blood samples from each subject prior to, during, and after treatment for measurement of serum levels of total ciclopirox. The assay method was revalidated following the FDA guidelines and the LOQ was determined as — ng/mL.

Study 312: Out of the 54 subjects who had multiple blood samples collected, 9 (7 on active treatment and 2 on placebo) had detectable serum ciclopirox concentrations ranging from — ng/mL. It is noted that 8 out of these 9 subjects (except Subject #112) had concomitant use of Loprox Cream.

Study 313: Out of the 83 subjects who had post-baseline blood samples collected, 25 (17 on active treatment and 8 on placebo) had detectable serum ciclopirox levels ranging from _____ ng/mL. The highest concentration (24.6 ng/mL) was from a subject not on concomitant use of Loprox cream.

In Studies 312 and 313, a total of 69 subjects on active treatment had post-baseline assessments. Of these subjects, 45 had serum concentrations below LOQ during treatment and 24 subjects had detectable levels (range: _____ ng/mL). The sponsor stated that of these 24 subjects with detectable ciclopirox levels, 11 took concomitant medication containing ciclopirox (Loprox cream 1%) and 13 did not. (Note: From the Sponsor's record, it would appear that 15 had concomitant use of Loprox Cream and 9 did not.)

Reviewer's comments:

1. In these two studies, subjects using Loprox cream for tinea pedis, cruris and corporis were allowed to enroll in the study. However, this would only increase the serum concentrations of total ciclopirox.
2. The amount of lacquer used in Studies 312 and 313 varied from patient to patient and from day to day within a patient and there is no documentation on the amount used on any specific days or during the entire treatment period.
3. Serum concentrations observed in Studies 312 and 313 were generally lower than in Study 111. One important factor that contributed to this difference is the number of nails treated. In study 111, all fingernails and toenails were treated while in Studies 312 and 313, most subjects had only toenails treated. Another possible factor is the frequency of nail lacquer removal. (Note that in Studies 312 and 313, the nail lacquer was removed every 7 days, which is the same as the clinical use conditions. In study 111, however, the lacquer was removed every day.)
4. Subjects who had detectable serum ciclopirox concentrations did not have detectable levels across the study period of 48 weeks. In fact, most of these subjects had only sporadic detectable levels and no apparent correlation between serum level and sampling time could be made. (See individual serum concentrations for Studies 312 and 313 in the Appendix.)
5. One subject in Study 312 had serious adverse event associated with irregular EKG. All adverse events as well as efficacy are being evaluated by the Medical Officer of HFD-540.

B. IN VIVO PENETRATION STUDIES (IN HEALTHY SUBJECTS)

Once daily application to fingernails of healthy volunteers

Study Design and Assay:

Nine healthy volunteers applied ciclopirox nail lacquer 8% once daily to the fingernails; the lacquer was removed once each week. The actual quantity of nail lacquer applied varied among these subjects (from 5 to 15 mg per nail). After 7, 14, 30 and 45 days of treatment, the distal portions of the nails were sampled. In 4 subjects, additional samples were obtained 7 and 14 days after treatment was stopped. Two samples, taken from two different nails were obtained.

One was used to determine the quantity of ciclopirox present in the whole nail. Transverse sections of the other sample were divided into four layers of equal volume to determine the penetration of ciclopirox through the thickness of the nail. A 10% aqueous solution of polyethylene glycol 4000 was used to extract ciclopirox from nails. A _____ method, based on the antifungal activity of ciclopirox against *Candida pseudotropicalis* (MIC: 3.125 $\mu\text{g}/\text{mL}$), was used.

Results:

The mean concentration ($\pm\text{SE}$) of ciclopirox for all subjects after 7, 14 and 30 days of application were 0.89 (0.25), 1.78 (0.41) and 3.35 (0.82) $\mu\text{g}/\text{mg}$ nail, respectively. In four subjects treated for 45 days, the mean concentration of ciclopirox was 2.01 (0.45) $\mu\text{g}/\text{mg}$ nail. (In these four subjects, the mean ciclopirox concentration in the nail was 1.18, 1.84, 2.1 $\mu\text{g}/\text{mg}$ at 7, 14 and 30 days, respectively.) Steady state concentration in nails was reached in 14 days with 4 nail samples but might took more than 30 days in others. After 7 days of applications, mean relative percentage of ciclopirox was highest in layer 1 and decreased with the nail depth as presented in the table below. The relative distribution of ciclopirox in nail layers appeared to stabilize after 14 days of application.

Table 1: Mean ($\pm\text{SE}$) Relative Percentage of Ciclopirox at Various Depths of Fingernails in Healthy Subjects (n=9)

	7 Day Sample	14 Day Sample	30 Day Sample
Layer 1	49.6 (2.8)	32.0 (1.5)	34.7 (1.5)
Layer 2	34.6 (2.4)	24.1 (1.4)	26.4 (2.4)
Layer 3	11.6 (2.8)	21.2 (1.1)	19.7 (1.2)
Layer 4	4.2 (1.3)	22.7 (2.1)	19.2 (1.4)

For the 4 subjects who were also monitored post-treatment, ciclopirox concentrations in the nail decreased substantially 7 days post-treatment. Fourteen days after treatment was stopped, the amount of ciclopirox present in the nail was below the limit of detection — $\mu\text{g}/\text{mg}$ nail).

Table 2: Ciclopirox Concentration ($\mu\text{g}/\text{mg}$ nail) on Last Treatment Day and During Post-treatment

Subject#	Last Treatment Day (Day 45)	7 Days Post-treatment	14 Days Post-treatment
2	1.55	0.05	-
3	3.3	0.32	-
6	1.94	0.13	-
7	1.26	0.04	-

After the treatment with the lacquer was stopped for 2 months, 3 subjects (#2, 3 and 9) received ciclopiroxamine cream once daily for 30 days. Samples of the distal portion of the nail were obtained after 7, 14 and 30 days of treatment and assayed using the same _____ method. The sponsor stated that the amount of ciclopirox present in the nail after 7 to 14 days of treatment with the lacquer was greater than that for Loprox Cream 1% after one month of treatment.

Sponsor's conclusions:

- a. The mean concentration (\pm SE) of ciclopirox in full thickness of nails for all subjects after 7, 14 and 30 days of application were 0.89 (0.25), 1.78 (0.41) and 3.35 (0.82) μ g/mg nail, respectively. These values are well over the MIC values for *Candida pseudotropicalis*. Two weeks after treatment was stopped, the residual concentration of ciclopirox in the nail was below the detection limit.
- b. The mean concentration (\pm SE) of ciclopirox for all subjects increased with treatment days up to 30 days. Steady state concentration in nails was reached in 14 days in 4 subjects but might took more than 30 days in others.
- c. After 7 days of applications, mean relative percentage of ciclopirox was highest in layer 1 and decreased with the nail depth. The relative distribution of ciclopirox was more homogeneous through nail layers and appeared to stabilize after 14 days of application.

Reviewer's comments:

1. Under the study conditions, the mean concentration (\pm SE) of ciclopirox in full thickness of nails for all subjects after 7 days of application were well over the MIC values for *Candida pseudotropicalis* in *in vitro* determinations although the MIC values in nails are not known. It is noted that these values were calculated based on an extraction efficiency of 95% for extracting the drug from nails. It is not clear that the extraction efficiency was appropriately determined. However, if the efficiency was lower, the actual concentrations would be even higher than those given above.
2. Mean (\pm SE) relative percentage of ciclopirox in various fingernail layers on various treatment days is presented in Table 1. However, the sponsor did not provide absolute concentrations which are more meaningful than relative percentage.
3. The sponsor stated that the amount of ciclopirox present in the nail after 7 to 14 days of treatment were greater than those of the Loprox Cream 1% after one month of treatment. However, we will not be able to compare the two formulations if the extraction efficiency was not appropriately determined.
4. The substantial penetration in deeper nail layers might be partly due to the spillover of the lacquer to hyponichium (or the ventral side of the distal portion of the nail). The portion of the nail that was farther away from the distal portion could have a very different concentration profile.

Once daily application to toenails of healthy subjects

Study Title: In vivo toe nails penetration of ciclopirox supplied as an 8% varnish

The design and assay method for this study were similar to those used in the above study. Five healthy subjects applied ciclopirox lacquer 8% once daily to the toenails. The lacquer was removed once each week. The distal portions of the nail were sampled after 7, 14, 30 and 45 days of treatment and seven and 14 days post-treatment.

After 7 days of application, the quantity of ciclopirox in full thickness nails was greater than 0.45 μ g/mg nail in all subjects. The mean (\pm SE) concentrations of ciclopirox after 7, 14, 30 and 45

days of application were 1.39 (0.74), 4.64 (2.25), 5.91 (2.42) and 6.83 (2.76) $\mu\text{g}/\text{mg}$ nail, respectively. The uptake in the nail was significantly different between Days 7 and 14, and Days 14 and 30. Between Days 30 and 45, there was no statistically significant difference in the uptake.

After 7 days of application, ciclopirox was more or less uniformly distributed in all layers of the nail (see Table below). Seven days after the treatment was stopped, the mean ciclopirox concentration in the nails decreased to 1.44 (± 0.71) $\mu\text{g}/\text{mg}$ nail. Fourteen days after the treatment was stopped, residual amounts of ciclopirox remained in the nail (0.81 ± 0.7 $\mu\text{g}/\text{mg}$ nail) although the levels had decreased substantially.

Mean (\pm SE) Relative Percentage of Ciclopirox at Various Depths of Toenail in Healthy Subjects (n=5)

	7 Day Sample	14 Day Sample	30 Day Sample	45 Day Sample
Layer 1	20.4 (2.0)	22.4 (3.3)	25.6 (1.8)	27.8 (1.3)
Layer 2	26.8 (0.4)	24.6 (2.6)	27.2 (1.4)	25.8 (2.8)
Layer 3	25.0 (1.5)	26.8 (1.3)	24.0 (1.2)	21.2 (1.8)
Layer 4	27.6 (2.1)	26.2 (2.8)	23.2 (1.9)	25.2 (2.0)

Mean ciclopirox concentration in toenails was higher than that in fingernails. Possible factors are:

- Toenails were under semi-occlusive condition promoting penetration
- Fingernails were in contact with the external environment and washed more frequently which resulted in removal of some of the drug/lacquer.
- Different keratinization between toenails and fingernails.

Reviewer's comment:

The above two studies were conducted in healthy subjects. The substantial penetration in deeper nail layers may be due to the spillover of the lacquer to the ventral side of the distal portion of the nail during application of the lacquer. The portion of the nail that was farther away from the distal portion could have a very different concentration profile.

IN VITRO STUDIES

Study 999 RA (Penetration of ciclopirox into toenails from human cadavers)

In this study, toenails excised from human cadavers were clamped in the diffusion chamber with openings of 1.0 cm in diameter. Prior to use, toenails were washed in a 1% Pluronic solution and normal saline and scraped with a dull blade to remove excess debris. The nails were soaked in water for 24 hours before mounting onto the apparatus. The receptor chamber was filled with 5 mL of a 40% aqueous propylene glycol solution (at room temperature) so that the fluid was in contact with the ventral surface of the toenails. The lacquer containing ^{14}C -labeled ciclopirox was applied to 5 toenails every third day for 30 days at 0.01 mL (containing 800 μg ciclopirox) per 0.75 cm^2 . No attempt was made to remove previously applied drug. A single application of the lacquer was made to another 5 toenails. Besides, four pieces of sole skin (two with full

thickness and two with epidermis only) was treated with single application of the lacquer. Measurement of levels of radioactivity in the receptor fluid located on the ventral surface of the nail was used to assess penetration.

Results:

Penetration of ciclopirox through full-thickness sole skin after a single application of the 8% lacquer was evidenced by the radioactivity in receptor fluid (after 48 hours: 0.43 and 0.83 μg -equivalent/mL for the 2 samples tested). The results for the two sole epidermis samples differed substantially: one sample behaved more like the full-thickness skin while the other showed much higher penetration of ciclopirox.

The amount of ciclopirox in the receptor fluid of the three thickest nails (thickness: 1.49 to 1.59 mm) after a single application was negligible even after 30 days (—————). For the other 2 thinner toenails (thickness: 0.68 and 1.29 mm), ciclopirox concentrations in the receptor fluid were 0.058 and 0.031 $\mu\text{g}/\text{mL}$, respectively, which is equivalent to less than 0.04% of the applied dose. Ciclopirox appeared to penetrate more readily through sole skin than through toenails.

Following multiple applications, initially relatively little drug penetrated through nail samples. Then, there was a marked increase between 10-20 days (see Figure 1 in the Appendix). After that, the penetration appeared to plateau with the amount of radioactivity in the receptor fluid equivalent to 0.01-0.07% of the applied dose at Day 30 (ciclopirox concentration in receptor fluid: ——— $\mu\text{g}/\text{mL}$) which did not correlate with the thickness of the nail samples.

Reviewer's comments:

1. The radioactivity of receptor fluid was determined for up to 30 days after single application of Loprox lacquer to the sole skin samples. It is doubtful that sole skin could remain intact for 30 days. Therefore, only the 48-hour measurements are discussed above. Ciclopirox appeared to penetrate more readily through sole skin than through toenails unaffected by onychomycosis. However, the sponsor did not demonstrate that the sole skin samples were initially intact and remained so through at least 48 hours into the experiment.
2. In the multiple application study with toenails, the lacquer was applied to toenails every third day for 30 days and no attempt was made to remove previously applied drug. This is different from the proposed clinical use conditions in which the nail lacquer is applied daily and the coat was removed every 7 days. Besides, toenails without onychomycosis were used in both single and multiple application studies. It is conceivable that diseased nails can result in substantially greater penetration of ciclopirox.
3. Following multiple applications, initially relatively little drug penetrated through nail samples. Then, there was a marked increase between 10-20 days. After that, the penetration appeared to plateau. This phenomenon seems peculiar but the sponsor did not explain why a

marked increase occurred after 10-20 days. Besides, data shown in Table 2 (Vol. 1.24, p. 14) do not seem to agree with the results shown in Figure 7 (Vol. 1.24, p. 21).

4. Since each sample for radioactivity determination is about 20% of the volume in the receptor compartment, this loss has to be taken into account when calculating the quantity of ciclopirox in the receptor fluid. It is unclear whether this correction was made.

Study 999

(In vitro penetration of ciclopirox into toenails from human cadavers: a 30 day-study)

Procedures: In this study, excised toenails from human cadavers were clamped in the diffusion chambers each with an exposed area of 1.0 cm in diameter. Prior to use, toenails were washed in distilled water and scraped with a dull blade to remove excess debris. The nails were soaked in water for 24 hours before mounting onto the apparatus. The receptor chamber was filled with 5 mL of distilled water at room temperature, which was in contact with the ventral surface of the toenails. Ciclopirox nail lacquer 8% was applied at 0.01 mL (containing 0.8 mg of ciclopirox) per 0.75 cm² to eight toenails once every third day for 30 days. Previous applications were removed with isopropyl alcohol before application. Controls consisted of two untreated nails and two nails that had the lacquer applied for less than 1 hour and then removed. Nails were measured with calipers and filed with a diamond file. Caliper measurements were used to estimate the amount of material removed by filing. Filings were collected in 4 portions representing approximate nail depth of 25%, 50%, 75% and 100% from dorsal to ventral surface of the nail.

Results:

(A) Inoculation method.

Control nails generally exhibited either moderate or maximum hyphal growth (scores of 3 or 4) at all depths of the nail. Antifungal activity of penetrated ciclopirox was demonstrated in fungal growth inhibition assays to at least 50 to 75% of the way through the nail. The majority of the nail contained enough ciclopirox in filings 25% of the way through the nails to completely inhibit growth of fungal spores. Filings obtained at the depth of 25-50% in 6 out of the eight nails contained enough ciclopirox to markedly inhibit fungal growth (scores of 0 or 1). At the ventral surface of the nails, moderate or maximum fungal growth was noted in the majority of the nails (scores of 3 or 4).

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Table 1: Fungal Growth Scores*

Nail No.	Nail Thickness	Nail Depth (%)				
		Dorsal Surface	0-25%	25-50%	50-75%	75-100%
Nails treated with Ciclopirox nail lacquer 8% for 1 month						
1	1.35	0	4	4	4	4
2	1.35	0	0	0	0	4
3	0.90	0	0	1	3	4
4	0.85	0	0	1	1	3
5	1.15	1	1	1	2	2
6	0.75	0	0	4	4	4
7	0.65	0	0	1	1	2
8	0.90	0	0	1	3	3
Controls: Untreated						
9	1.25	4	4	3	4	4
10	0.65	2	3	3	4	3
Controls: Nails treated with Ciclopirox nail lacquer 8% for ~30 minutes						
11	0.85	3	3	3	3	4
12	0.95	3	4	3	4	4

*Growth scores: 0= no growth; 1= minimal growth; 2= mild growth; 3= moderate growth; 4= maximum growth

(B) Zones of Inhibition Method:

When the zones of inhibition was used to gauge penetration, the dorsal surface of the nails had positive results in most nails (7 out of 8). The nail filings at a depth of 0-25% showed antifungal activity in 6 out of 8 nails (see table below). At a depth of 25-50%, the activity was observed in only 3 out of the 8 nails. Beyond that depth, no anti-fungal activity was observed in any of the 8 samples.

Table 2: Number of Nails with An Observable Zone of Inhibition

Treatment	Number of Nails Treated	Number of Nails with An Observable Zone of Inhibition				
		Nail Depth				
		Dorsal Surface	0-25%	25-50%	50-75%	75-100%
Ciclopirox nail lacquer 8% for 1 month	8	7	6	3	0	0
Untreated	2	0	0	0	0	0
Ciclopirox nail lacquer 8% for ~30 min.	2	1	0	0	0	0

Conclusion: Under the conditions of this in vitro study, penetration of ciclopirox could be demonstrated up to a nail depth of 50% as evidenced from antifungal activities from the nail filings. The antifungal activity at (or the penetration of ciclopirox into) various depths did not appear to correlate with nail thickness. This conclusion was based on the observations that nails of the same thickness did not result in similar penetration (or antifungal activity) at the same nail depths and thinner nails did not necessarily mean better penetration.

Reviewer's comments:

1. Under the study conditions, ciclopirox did not penetrate well into the deeper layer of nails. Further, the two assay methods gave different results.
2. Controls consisted of untreated nails or nails that had the lacquer applied for less than 1 hour and then removed. It would be helpful to include controls that are subjected to the same experimental procedures but are treated with lacquer vehicle so that the antifungal activity of the drug can be separated from the activity due to the vehicle, if any.
3. In this in vitro study, ciclopirox nail lacquer 8% was applied once every third day for 30 days. (The lacquer is recommended to be applied daily in clinical use.) Also, previous applications were removed with isopropyl alcohol before each application. (Again, this is different from the proposed clinical use conditions in which lacquer is removed once every 7 days.) In view of these deviations, this study appears to be more for drug/formulation development purposes.

In vitro penetration of ciclopirox into human toenails avulsed for onychomycosis after single application of Loprox nail lacquer

Study Title: Permeation of Batrafen into Human toenails from nail polish (lot 17084a)

This study evaluated the clinical formulation for in vitro penetration of ^{14}C -labeled ciclopirox into human toenails avulsed for onychomycosis. The experimental procedure was similar to that for single topical application in Study 999RA. Five milligram of the formulation with radiolabeled drug (containing $400\ \mu\text{g}$ of total drug) was applied once in vitro to $1\ \text{cm}^2$ of 15 extracted toenails with different thickness and degree of abnormality. These nails were placed into a diffusion chamber maintained at 32°C for 16, 24 or 48 hours ($n=2, 8$ and 5 , respectively). At the end of experiment, excess nail lacquer was removed with cotton swab moistened with methanol. A circular piece of $0.5\ \text{cm}$ diameter was stamped out of the frozen nail and was cut into $20\ \mu\text{m}$ thick sections using a ~~_____~~. Two sections were combined and their radioactivity was analyzed with a ~~_____~~ after tissue hydrolysis with 0.5N sodium hydroxide.

Results:

Sharp decline of ciclopirox concentration with the increase in nail depth was observed. At the nail depth of $400\ \mu\text{m}$, ciclopirox concentration 48 hours after application of the lacquer was close to or above $1\ \mu\text{g}/\text{cm}^3$ in 4 out of the 5 nails. The surface structure of nail sample #15 was especially damaged by mycosis and this sample showed the greatest penetration among the five samples tested for 48 hours. By comparing the penetration at various times (16, 24 and 48 hours), the sponsor concluded that diffusion beyond a layer depth of $400\ \mu\text{m}$ appears to be independent of time.

Reviewer's Comments:

1. The sponsor did not explain whether the nails were pressed flat before they were cut into $20\ \mu\text{m}$ sections. In addition, penetration of ciclopirox in various nail layers was presented numerically by categorizing the nail layers into superficial layer, upper layer, lower layer and

the remaining layer. For example, the sponsor provided ciclopirox in various layers at 48 hours after application of the lacquer as follows:

surface of the nail: $79.6 \pm 63.9 \mu\text{g}/\text{cm}^2$ ($11734 \pm 6444 \mu\text{g}/\text{mL}$)
upper layer: $39.9 \pm 27.7 \mu\text{g}/\text{cm}^2$ ($1650 \pm 1151 \mu\text{g}/\text{mL}$)
lower layer: $0.8 \pm 0.8 \mu\text{g}/\text{cm}^2$ ($21.2 \pm 33.1 \mu\text{g}/\text{mL}$)

It is noted that the thickness of each category varied from one nail sample to another (see Appendix 1). The sponsor did not explain how these layers were categorized.

2. By comparing the penetration at various times (16, 24 and 48 hours), the sponsor concluded that diffusion beyond a layer depth of $400 \mu\text{m}$ appears to be independent of time. Because the diseased conditions of the nails varied among the 15 samples tested, it is difficult to judge the validity of this statement.
3. It is difficult to draw a generalized conclusion from this study. Conceivably, a damaged nail due to mycosis would show better penetration of ciclopirox than a healthy nail and the extent of penetration would vary with the disease condition.

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APPENDIX 1

(Individual Data)

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Protocol III

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HOE 296NL 8/USA/111A/NM
Ciclopirox (HOE 296NL) Nail Lacquer 8%

Table 1

Listing 1.6
Baseline Evaluation: Disease History

Subject	Visit	Date of Visit	Total Duration of Disease	Duration of Current Episode	Disease Status			Estimated Average Daily Dose (g/day)
					Current Episode	Overall	Status for Target Nail	
0101	BASELINE	05/12/89	27 Years	5 Years	Stable	Severe	Moderate	0.75
0102	BASELINE	05/12/89	4 Years	2 Years	Stable	Severe		0.63
0103	BASELINE	12/08/89	8 Years	8 Years	Stable	Moderate		1.35
0104	BASELINE	12/08/89	20 Months	20 Months	Stable	Moderate		0.73
0105	BASELINE	12/08/89	25 Years	25 Years	Stable	Moderate		0.36

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Protocol III

Table ² Renal excretion of total ciclopirox determined as free acid after glucuronidase treatment

Subj.	Date	Conc. determined [ng/ml]	Urine volume [ml]	Amount excreted [mg/day]
101	26.05.89			
	16.06.89			
	07.07.89			
	01.09.89			
	27.10.89			
102	26.05.89			
	16.06.89			
	07.07.89			
	01.09.89			
	27.10.89			
103	02.02.90			
	30.03.90			
	30.05.90			
104	07.02.90			
	04.04.90			
	08.06.90			
105	02.02.90			
	30.03.90			
	25.05.90			

* - Urine volume not recorded

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Protocol 312: Serum Ciclopirox Concentrations

- Out of 54 subjects who had multiple blood samples collected, 9 (7 on active treatment and 2 on placebo) had detectable serum ciclopirox concentrations.
- Note that all subjects except Subject #112 had concomitant use of Loprox Cream.

Table 3: Serum Ciclopirox Concentrations in the 9 subjects who had detectable levels.

Treatment	Subject#	Visit	Sampling Time (hrs. postdose)	Ciclopirox Serum Conc.
Loprox Nail Lacquer	112*	Baseline Week 12 Week 24		
	126	Baseline Week 12 Week 24 Week 36 Week 48 Week 48		
	130	Baseline Week 12 Week 24 Week 36 Week 48 Week 48		
	806	Baseline Week 12 Week 12 Week 24 Week 36 Week 48 Week 48		
	809	Baseline Week 12 Week 12 Week 24 Week 36 Week 48 Week 48		
	812	Baseline Week 12 Week 12 Week 24 Week 36 Week 48 Week 48		
	828	Baseline Week 12 Week 12 Week 24 Week 36 Week 48		
	Vehicle	115	Baseline Week 12 Week 24 Week 36 Week 48 Week 48	
120		Baseline Week 12 Week 12 Week 24 Week 36 Week 48		

Protocol 313: Serum Ciclopirox Concentrations

Note: Sampling time relative to dosing time varied from patient to patient and from day to day within a patient.

Table 4

Treatment Group	Subject #	Highest Ciclopirox Conc. (ng/mL)	Blood Sampling (Week of Study)	Concomitant Use of Loprox Cream Yes	No
Nail Lacquer	1202				
	1209				
	1213				
	1218				
	1220				
	1221				
	1226				
	1227				
	1309				
	1314				
	1316				
	1321				
	1330				
	1405				
	1412				
	1417				
1426					
Placebo	1204				
	1223				
	1225				
	1319				
	1404				
	1413				
	1419				
1421					

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In Vivo Penetration of Ciclopirox into Finger nails

Subject	7 days	14 days	30 days	45 days
1				
2				
3				
4				
5				
6				
7				
8				
9				
Mean	0.892	1.783	3.35	2.01
+/-	+/-	+/-	+/-	+/-
S.E.	0.252	0.413	0.822	0.45

5
Table X:

Concentrations of ciclopirox in nail (as µg/mg nail)

ND: not determined

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In Vivo Penetration of Ciclopriox into Finger Nails

Table 6: Relative percentages of ciclopriox in the 4 nail layers

Subject	7-day sample				14-day sample				30-day sample			
	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
Mean	49.6	34.6	11.6	4.2	32	24.1	21.2	22.7	34.7	26.4	19.7	19.2
+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
s.e.	2.0	2.4	2.0	1.3	1.5	1.4	1.1	2.1	1.5	2.4	1.2	1.4

In Vivo Penetration of Ciclopirox into Fingernails

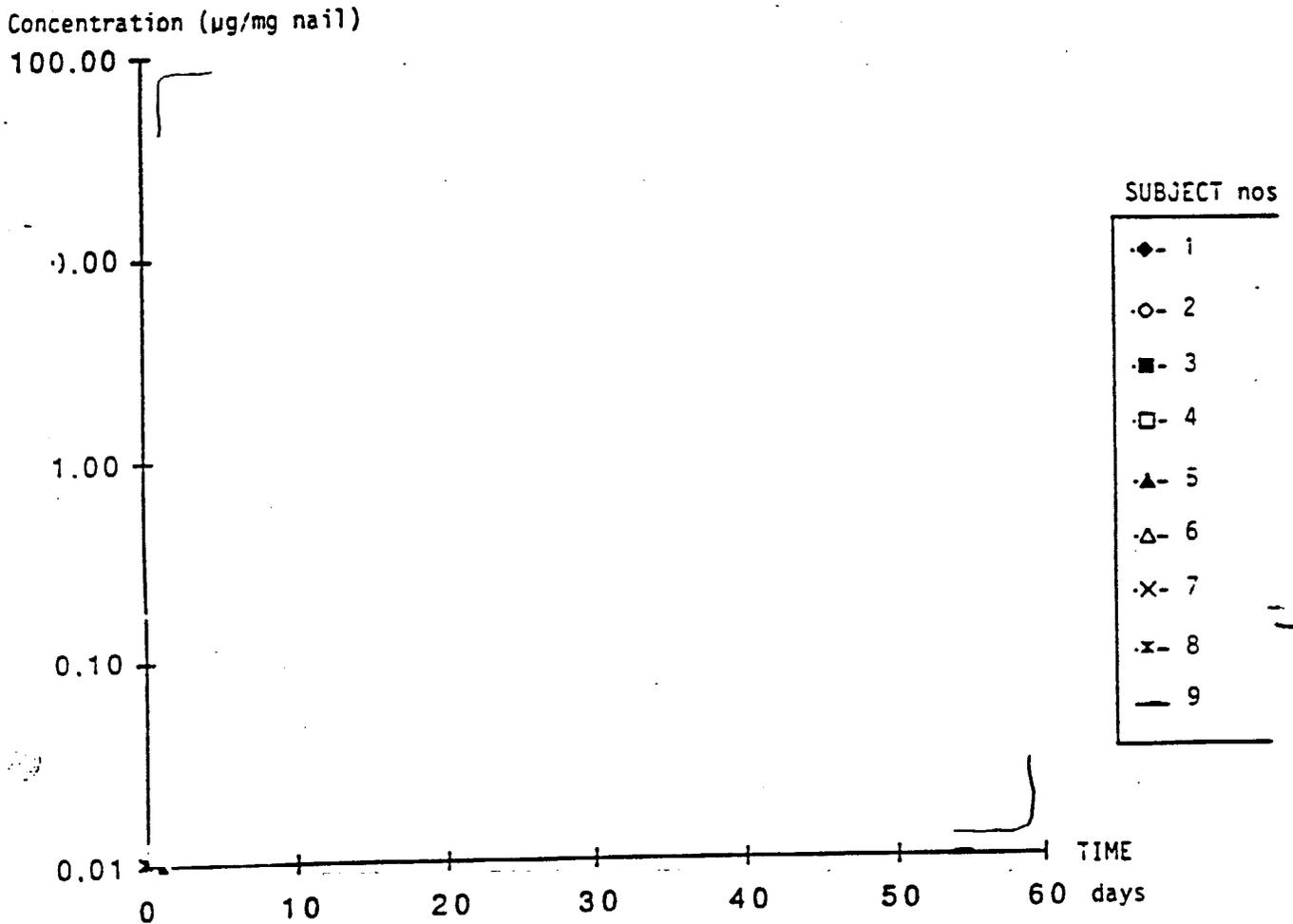


Figure 1:
Ungueal penetration of ciclopirox in fingernails

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In Vivo Penetration of Cyclopirox into Toenails

Table 7: Relative percentages of cyclopirox in the 4 nail layers

Subjects	Sample at time 7 days				Sample at time 14 days				Sample at time 30 days				Sample at time 45 days			
	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4
1																
2																
3																
4																
5																
Mean	20.4	26.8	25	27.6	22.4	24.6	26.8	26.2	25.6	27.2	24	25.2	27.8	25.8	21.2	25.2
±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
Stand. error	1.99	0.57	1.52	2.09	3.31	2.38	1.32	2.85	1.78	1.36	1.18	1.85	1.20	2.75	1.85	1.98

In Vivo Penetration of Ciclopirox into Toenails

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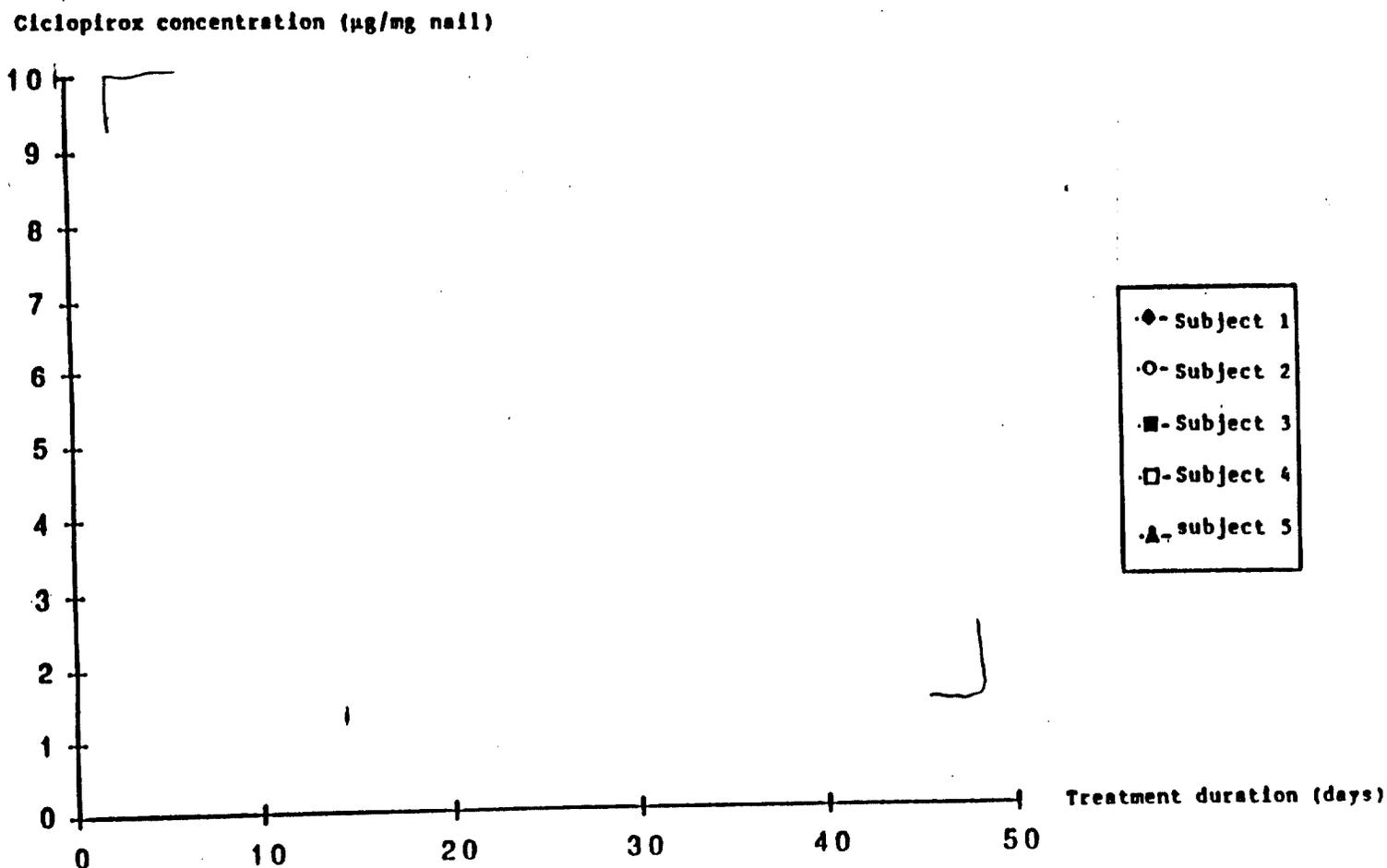


Figure 2: Individual ciclopirox concentrations in the toe nails (µg/mg nail), as a function of treatment duration

79

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Study 999-RA

CICLOPIROX In Vitro NAIL PENETRATION

background- 20
conversion factor- 1.8700001E-05 mg/l/count

TABLE 8:

PENETRATION IN MG/L: SINGLE APPLICATION

day	sample1	sample2	sample3	sample4	sample5
1	0.0002	-0.0005	-0.0002	0.0017	-0.0006
4	-0.0002	-0.0006	0.0010	0.0086	0.0011
7	-0.0002	0.0006	-0.0002	0.0126	0.0037
10	0.0002	-0.0004	0.0010	0.0164	0.0087
13	0.0001	-0.0004	0.0009	0.0146	0.0139
16	-0.0006	-0.0004	-0.0002	0.0186	0.0162
19	0.0004	0.0003	0.0002	0.0195	0.0258
22	0.0002	0.0004	0.0009	0.0219	0.0293
25	0.0018	0.0007	0.0015	0.0235	0.0356
28	0.0018	0.0025	0.0011	0.0289	0.0495
31	0.0028	0.0019	0.0033	0.0308	0.0584
Nail Thickness (mm)	1.59	1.51	1.49	1.29	0.68

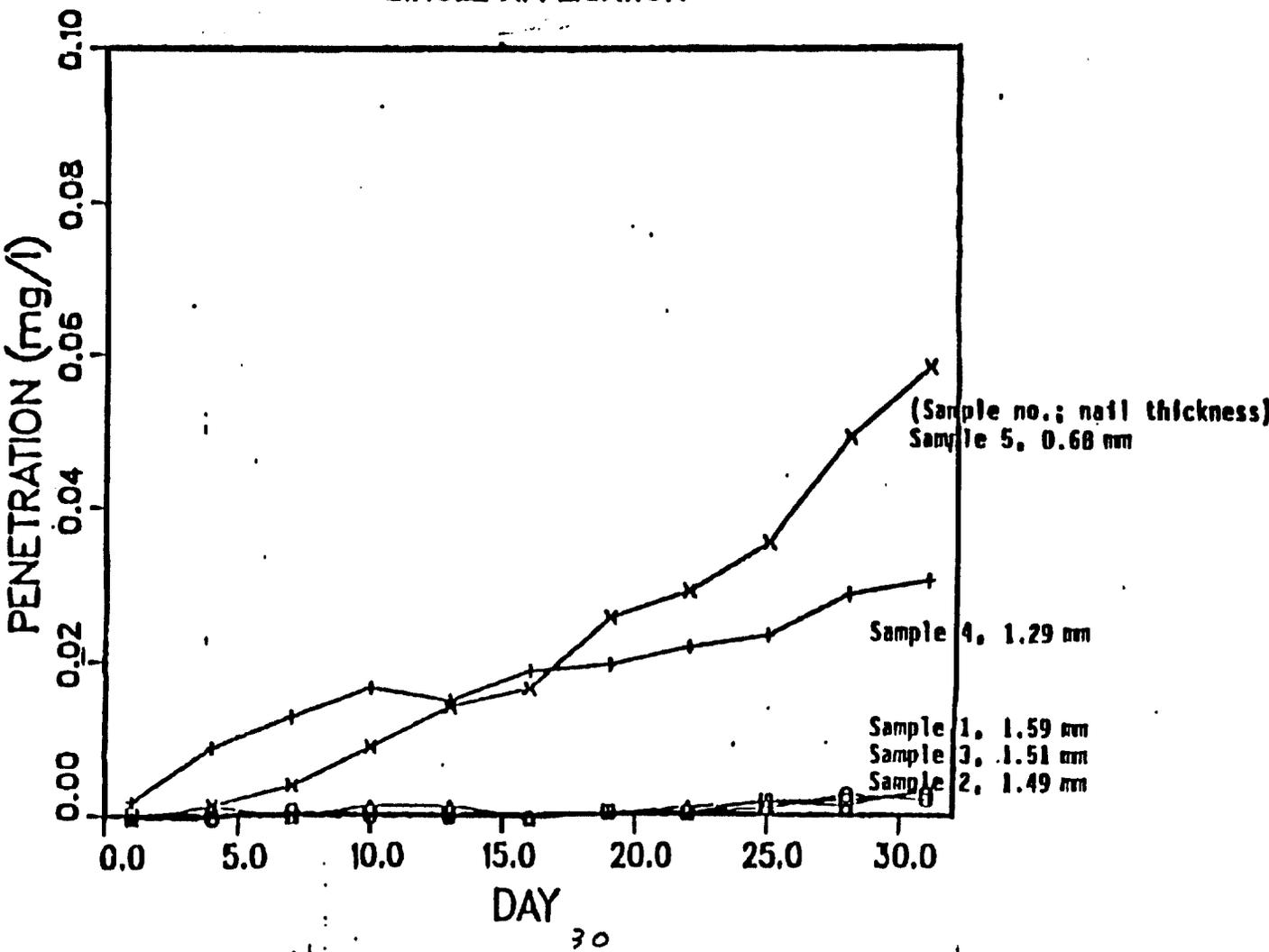
PENETRATION IN MG/L: MULTIPLE APPLICATIONS

day	sample1	sample2	sample3	sample4	sample5
1	-0.0001	-0.0002	0.0023	0.0124	-0.0007
4	0.0000	0.2171	0.0076	0.0304	0.0003
7	0.0006	0.1781	0.0108	0.0445	0.0012
10	0.0993	0.1406	0.0155	0.0502	0.0025
13	0.3404	0.1428	0.0193	0.0675	0.0036
16	0.2940	0.1376	0.0208	1.2940	0.0064
19	0.2683	0.1407	0.0262	1.6141	0.0092
22	0.2639	0.8180	0.0268	1.3580	0.0141
25	0.2554	0.7838	0.0301	1.1622	0.0195
28	0.2612	0.7502	0.0345	1.3975	0.0338
31	0.2563	0.6944	0.0534	1.3307	0.0464
Nail Thickness (mm)	1.75	1.58	1.30	1.05	0.98

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Study 999 RA

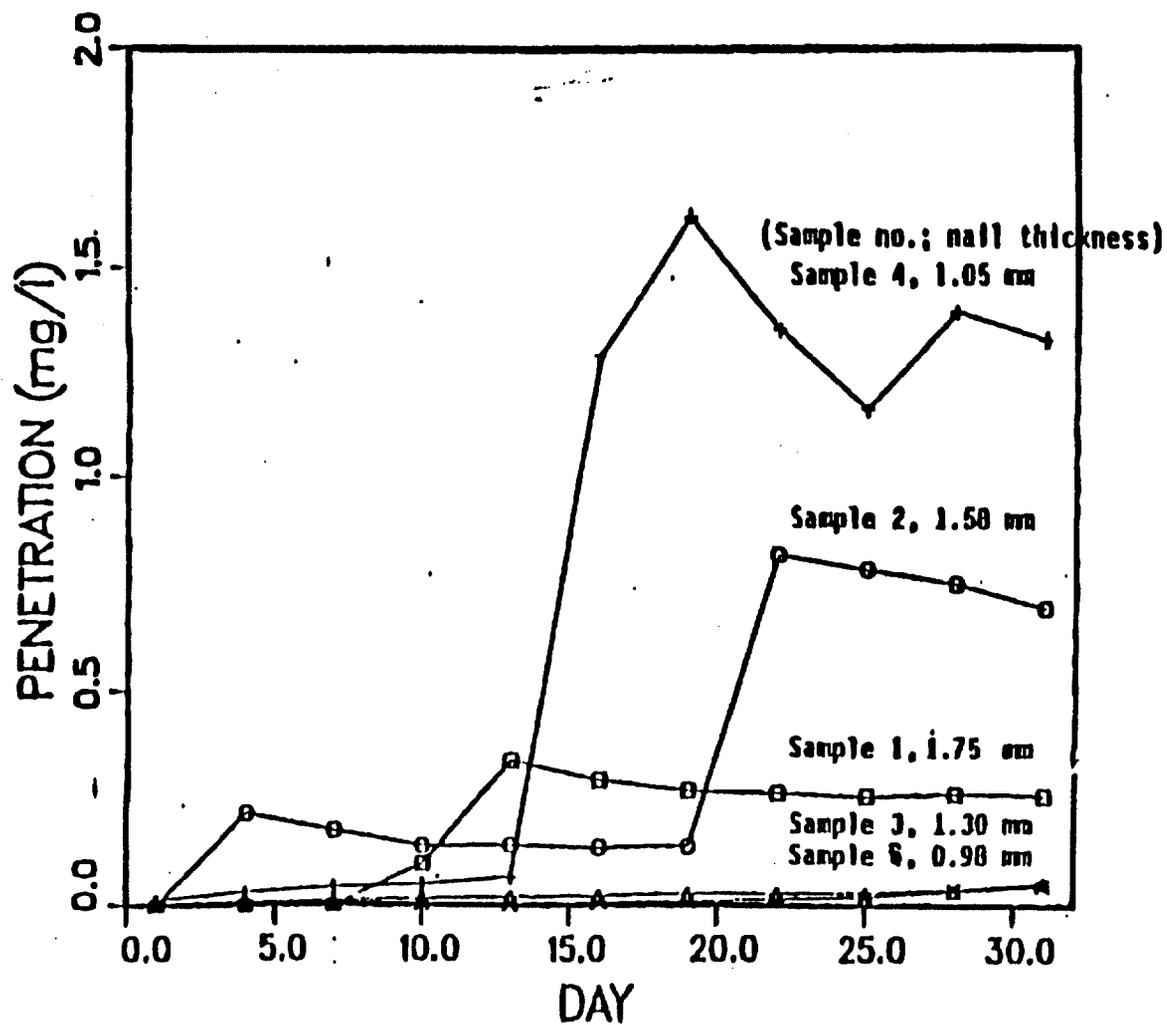
FIGURE 3
CICLOPIROX In Vitro NAIL PENETRATION
SINGLE APPLICATION



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Study 999 RA

FIGURE 4
CICLOPIROX In Vitro NAIL PENETRATION
MULTIPLE APPLICATIONS



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Table 9 In Vitro penetration of cecropinox into diseased Terails

superfical part of the nail		upper part of the nail		lower part of the nail	
$\mu\text{g.cm}^{-2}.\text{d}^{-1}$	$\mu\text{g.ml}^{-1}$	$\mu\text{g.cm}^{-2}.\text{d}^{-1}$	$\mu\text{g.ml}^{-1}$	$\mu\text{g.cm}^{-2}.\text{d}^{-1}$	$\mu\text{g.ml}^{-1}$
16 h					
			n = 2		
67.2	16791	29.0	1209	3.8	104.8
37.4	3598	37.4	1559	14.1	124.2

52.3	10198	33.7	1384	9.0	114.5
(± 21.1)	(± 9334)	(± 6.7)	(± 248)	(± 7.3)	(± 13.7)
 24 h					
			n = 8		
45.3	8716	12.0	501	2.4	46.6
39.7	5512	38.6	1610	3.3	55.6
35.9	2991	9.2	382	0.8	9.8
46.2	6331	19.4	807	1.5	23.3
72.9	7008	34.2	1426	6.3	105.4
26.1	4353	16.6	525	0.2	2.2
79.8	10933	23.7	986	1.1	23.0
66.6	16647	55.3	2309	0.4	5.8

51.6	7811	26.1	1068	2.0	34.0
(± 19.2)	(± 4342)	(± 15.6)	(± 668)	(± 2.0)	(± 34.5)
 48 h					
			n = 5		
39.7	6620	25.0	1044	0.4	5.7
80.2	16045	32.5	1356	0.4	13.7
30.9	7713	16.3	680	0.1	1.7
188.9	20987	87.1	3625	2.2	79.9
58.5	7307	38.4	1598	0.7	5.2

79.6	11734	39.9	1660	0.8	21.2
(± 63.9)	(± 8444)	(± 27.7)	(± 1151)	(± 0.8)	(± 33.1)

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Table 10: In vitro Penetration of Cycloproprax into Diseased Toenails

		superficial part of the nail	upper part of the nail	lower part of the nail
data in $\mu\text{g. ml}^{-1}$				
16 h				
—	16008a n = 3	3536 (\pm 1534)	684 (\pm 495)	9.8 (\pm 14.6)
—	17084a n = 2	10198 (\pm 9334)	1384 (\pm 243)	114.5 (\pm 13.7)
24 h				
—	16008a n = 4	5782 (\pm 3002)	433 (\pm 250)	7.8 (\pm 4.1)
—	17084a n = 8	7811 (\pm 4342)	1068 (\pm 668)	34.0 (\pm 34.5)
48 h				
—	16008a n = 5	11391 (\pm 3592)	1648 (\pm 933)	40.0 (\pm 44.8)
—	17084a n = 5	11734 (\pm 6444)	1661 (\pm 1151)	21.2 (\pm 33.1)

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Figure 5 : Cichpinox Concentration at various nail depths

T = 24 hrs.

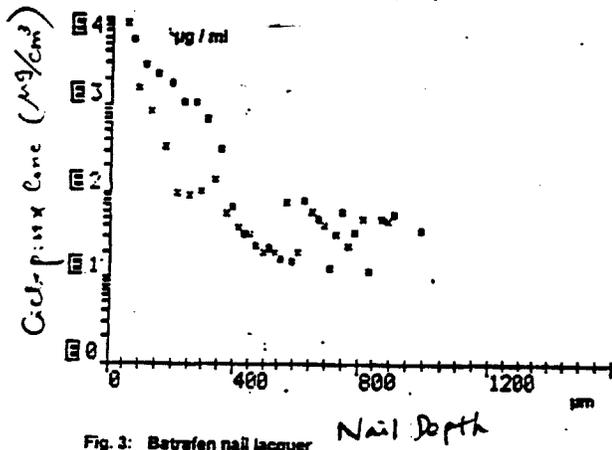


Fig. 3: Batrafen nail lacquer 24 h

□ nail 3
● nail 4

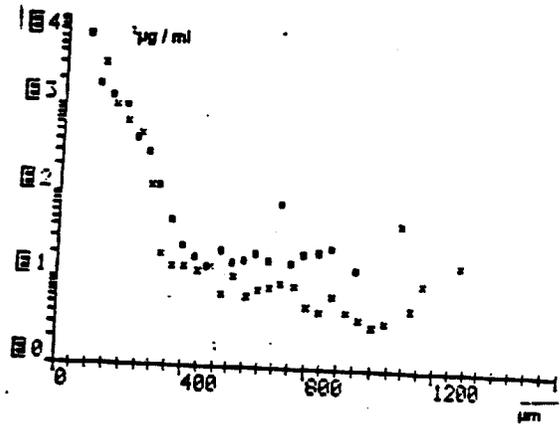


Fig. 4: Batrafen nail lacquer 24 h

□ nail 5
● nail 6

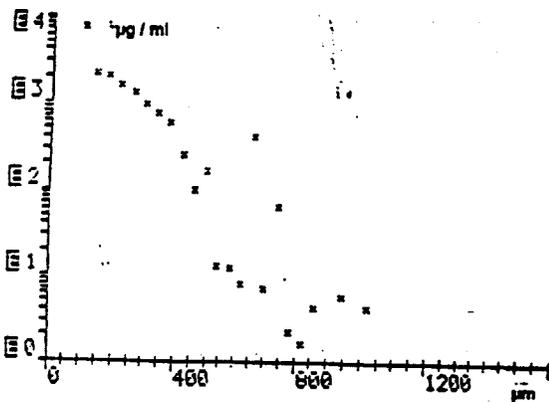


Fig. 5: Batrafen nail lacquer 24 h

□ nail 7

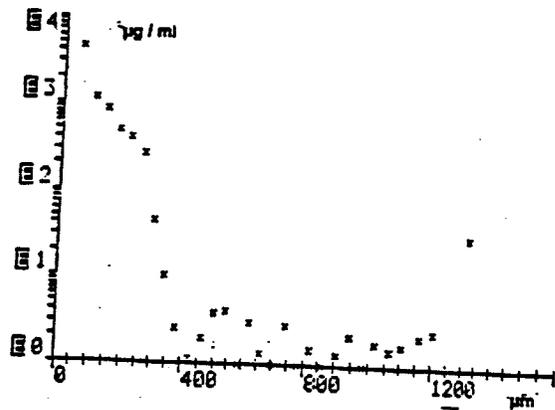


Fig. 8: Batrafen nail lacquer 24 h

□ nail 12

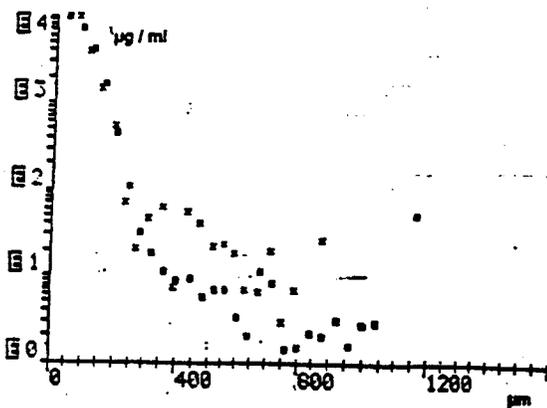


Fig. 9: Batrafen nail lacquer 24 h

□ nail 13
● nail 14

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Figure 5 (continued)

T = 16 hrs.

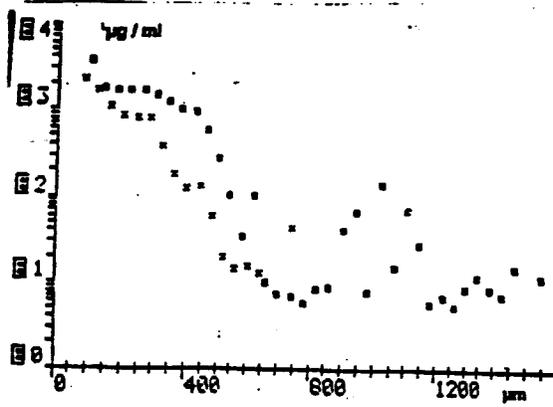


Fig. 2: Batrafen nail lacquer

16 h

- nail 1
- nail 2

T = 48 hrs

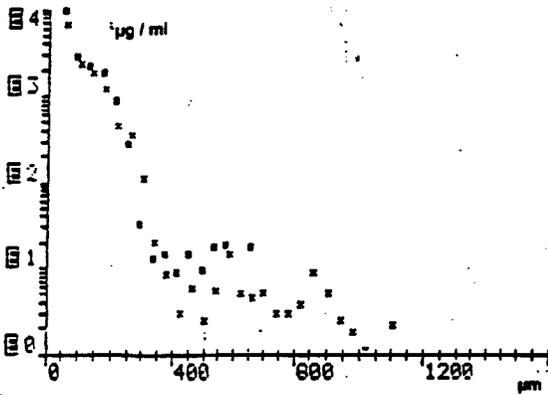


Fig. 6: Batrafen nail lacquer

48 h

- nail 9
- nail 10

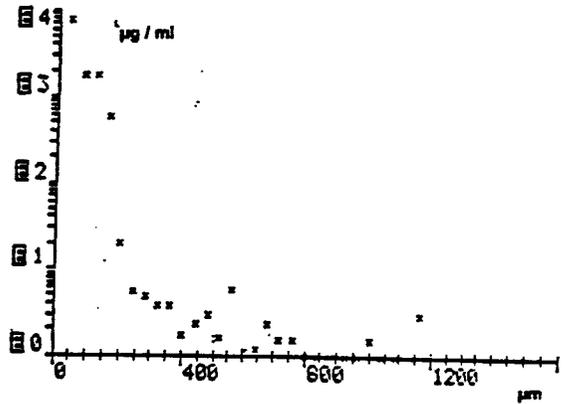


Fig. 7: Batrafen nail lacquer

48 h

- nail 11

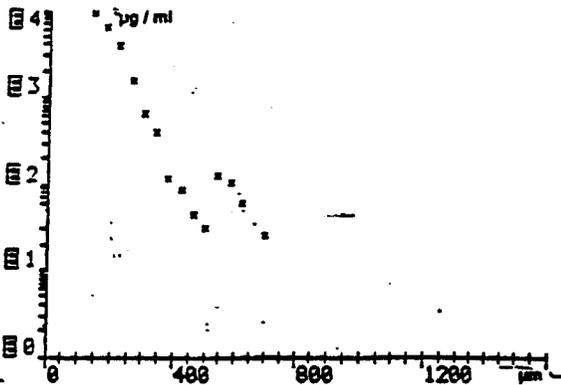


Fig. 10: Batrafen nail lacquer

48 h

- nail 15

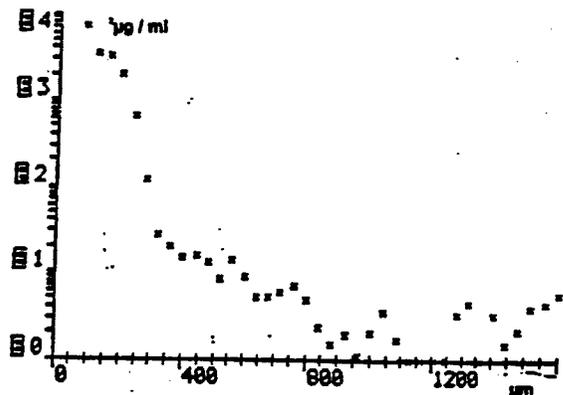


Fig. 11: Batrafen nail lacquer

48 h

- nail 16

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