Central University of Technology, Free State

QUIT® AND NICORETTE®: A COMPARISON OF NICOTINE PHARMACOKINETICS IN CIGARETTE SMOKERS

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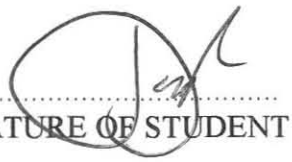
DECLARATION OF INDEPENDENT WORK

I, JAN BASTIAAN DU PLESSIS, do hereby declare that this research project submitted for the degree DOCTOR TECHNOLOGIAE: BIOMEDICAL TECHNOLOGY, is my own independent work that has not been submitted before to any institution by me or anyone else as part of any qualification.



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SUMMARY

Introduction

Nicotine medications make it easier to abstain from tobacco by partially replacing the nicotine formerly obtained from tobacco. They are referred to as "replacement medications". Considering the many shortcomings of known nicotine delivery systems, a product called Quit® was developed. The aim was to provide an effective, user-friendly and affordable replacement product in support of tobacco withdrawal programmes.

Objectives

Primary

- To compare the relative bioavailability of nicotine and its major metabolite, cotinine, in cigarette smokers after application of nicotine by means of, chewing nicotine resin chew pieces (Nicorette®), and buccal application from a novel metered-dose applicator (Quit®).

- To compare descriptively the pharmacokinetics of nicotine and its major metabolite, cotinine, in cigarette smokers after application of nicotine by means of cigarette smoking, chewing nicotine resin chew pieces (Nicorette®), and buccal application from a novel metered-dose applicator (Quit®).

Secondary

- Comparison of Nicorette® and Quit® with regard to suppression of cigarette craving.

- Comparison of Nicorette® and Quit® with regard to the occurrence and severity of adverse events.

Study design

This was an open, laboratory-blind, multiple-dose, randomised, 2-way cross-over design.

Healthy male and female volunteers, aged 18 to 54 years, and who had smoked cigarettes for at least one year participated. Thirty-six volunteers entered the study, and 2 were withdrawn due to intercurrent illness which required treatment.

Regimen 1

One cigarette was smoked hourly from 7:30 until 22:30 for 3 days. The tar content per cigarette was 14 - 15 mg and nicotine delivered per cigarette smoked was stated to be 1.2 - 1.4 mg.

Regimen 2 (Reference)

One Nicorette® chew piece was chewed for 30 minutes every 2 hours from 7:30 until 22:30 for 3 days. Chew pieces delivered 2 mg nicotine.

Regimen 3 (Test)

One Quit® spray was applied to the buccal mucosa every hour from 7:30 until 22:30 for 3 days. Each spray delivered 1 mg nicotine per 70µl.

Regimen 1 was applied from Day 1 to Day 3 (all volunteers). Regimens 2 and 3 were applied in randomised, cross-over fashion from Day 4 to Day 9.

Variables analysed

- Plasma pharmacokinetics: C_{max}, C_{min}, T_{max}, AUD_{ss}, %PTF and $T75\%C_{max}$.
- Urine pharmacokinetics: fractional and cumulative excretion of nicotine and cotinine over 24 hours at steady state.
- Preference with regard to suppression of cigarette craving.
- Safety as assessed by adverse event summary, haematology and biochemistry profiles.

Statistical evaluation included analysis of variance, calculation of point estimates and confidence intervals and descriptive statistics in respect of preference and safety.

Results

The 90% confidence intervals for the "test/reference" mean ratios of the pharmacokinetic variables AUD_{ss} (as primary characteristic of the extent of absorption of nicotine) and C_{min} fall within the conventional bioequivalence range of 80% to 125% for nicotine and cotinine. The 90% confidence interval for the "test/reference" mean ratio of the pharmacokinetic variable C_{max} and urinary excretion fall within the bioequivalence range of 70% to 143% for nicotine and cotinine.

Twenty-nine (29) out of 34 volunteers rated Quit® higher than Nicorette® with regard to suppression of the craving to smoke. Four were undecided whilst one preferred Nicorette®. The incidence of adverse events was low and similar for the two products.

Conclusion

The test and reference products are bioequivalent with respect to both the rate and extent of nicotine absorption and the rate and extent of cotinine formation. The test product should be as effective and safe as the reference product with respect to nicotine replacement in smoking cessation programmes.

OPSOMMING

Inleiding

Nikotienmedikasie vergemaklik tabakweerhouding deur gedeeltelike vervanging van die nikotien wat voorheen deur tabak verskaf is. Hierdie tipe medikasie staan bekend as "vervangingsmedikasie". Met inagneming van die vele tekortkominge van bekende sisteme vir die lewering van nikotien, is 'n produk, Quit®, ontwikkel. Die strewe was 'n effektiewe, bekostigbare en gebruikersvriendelike nikotienvervangingsproduk ter ondersteuning van tabak-onttrekkingsprogramme.

Doelwitte

Primêr

- Die vergelyking van die relatiewe biobeskikbaarheid van nikotien en kotinien (hoofmetaboliet), in sigaretrokers na toediening van nikotien deur middel van sigaretrook, die kou van nikotienhars kougomstukke (Nicorette®), en bukkale toediening deur 'n afgemete doseringstoestel (Quit®).

- Die beskrywende vergelyking van plasma-, en urienfarmakokinetika van nikotien en kotinien (hoofmetaboliet), in sigaretrokers na die toediening van nikotien deur middel van sigaretrook, die kou van nikotienhars kougomstukke (Nicorette®), en bukkale toediening deur 'n afgemete doseringstoestel (Quit®).

Sekondêr

- Die vergelyking van Nicorette® en Quit® ten opsigte van die onderdrukking van rooklus en algemene aanvaarbaarheid.

- Die vergelyking van Nicorette® en Quit® ten opsigte van die frekwensie en erns van ongewenste newe-effekte.

Studie-ontwerp

Dit was 'n laboratoriumblinde, meervoudige dosis, gerandomiseerde, 2-rigting oorkruis studie.

Gesonde manlike en vroulike vrywilligers, 18 tot 54 jaar, wat vir minstens die afgelope jaar sigarette gerook het, het deelgeneem aan die studie. Ses-en-dertig vrywilligers het aan die studie deelgeneem, waarvan 2 onttrek is weens siekte wat behandeling vereis het.

Behandeling 1

Een sigaret is uurliks gerook van 7:30 tot 22:30 vir 3 dae. Die teerinhoud per sigaret was 14 - 15 mg en nikotien gelewer per gerookte sigaret was veronderstel om 1.2 - 1.4 mg te wees.

Behandeling 2 (Verwysing)

Een Nicorette® kougomstuk is elke 2 ure gekou van 7:30 tot 22:30 vir 3 dae. Elke kougomstuk het 2 mg nikotien gelewer.

Behandeling 3 (Toets)

Een Quit® sproei op die bukkale slymvlies elke uur van 7:30 tot 22:30 vir 3 dae. Elke sproei moes 1 mg nikotien per 70µl lewer.

Behandeling 1 is toegedien van Dag 1 tot Dag 3 (alle vrywilligers). Behandelings 2 en 3 is in gerandomiseerde volgorde toegedien vanaf Dag 4 tot Dag 9.

Veranderlikes ontleed

- Plasma farmakokinetika: C_{max}, C_{min}, T_{max}, AUD_{ss}, %PTF and T75%C_{max}.
- Urien farmakokinetika: fraksionele en kumulatiewe uitskeiding van nikotien en kotinien oor 24 uur by gelykvlak.
- Effektiwiteitsvoorkeur ten opsigte van die onderdrukking van die lus vir sigarette.
- Veiligheid soos geëvalueer volgens 'n opsomming van newe-effekte en hematologiese en biochemiese profiele.

Statistiese ontleding het ingesluit variansie analise, puntberaming en vertrouensintervalle. Voorkeur en veiligheid is beskrywend ontleed.

Resultate

Die 90% vertrouensintervalle vir die "toets/verwysing" gemiddelde waardes van die farmakokinetika veranderlikes AUD_{ss} (as 'n primêre veranderlike van die omvang van absorpsie van nikotien) en C_{min} val binne die konvensionele bio-ekwivalensie reikwydte van 80% tot 125% vir beide nikotien en kotinien. The 90% vertrouensinterval vir die "toets/verwysing" van die farmakokinetiese veranderlike C_{max} en urinêre uitskeiding val binne die bio-ekwivalensie reikwydte van 70% tot 143% vir beide nikotien en kotinien.

Nege-en twintig (29) uit 34 vrywilligers het Quit® bo Nicorette® verkies ten opsigte van die onderdrukking van die lus om te rook. Vier vrywilligers was besluiteloos, terwyl een vrywilliger Nicorette® verkies het. Die voorkoms van ongewenste newe-effekte was laag en vergelykbaar vir die twee produkte.

Gevolgtrekking

Die toets-en verwysingsprodukte is bio-ekwivalent ten opsigte van die tempo en omvang van nikotienabsorpsie sowel as die tempo en omvang van kotinienvorming. Quit® behoort net so effektief en veilig te wees as Nicorette® ten opsigte van nikotienvervanging in rookstaakprogramme.

LEGEND OF ABBREVIATIONS USED

AE	Adverse event
AUDC	Area under the plasma concentration *vs* time data pairs, with extrapolation to infinity (also indicated as AUC)
AUD_{ss}	Area under the plasma concentration *vs* time data pairs at steady state
BLQ	Below the lower limit of quantification
BP	Blood pressure (mm Hg)
C_{av}	Average steady state concentrations
CFCs	Chlorofluorocarbons
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CRF	Case report form
CV%	Coefficient of variation
ECG	Electrocardiogram
FARMOVS	FARMOVS Research Centre for Clinical Pharmacology and Drug Development
FDA	Food and Drug Administration
GC	Gas-chromatography
GI	Gastro-intestinal

LLOQ	Lower limit of quantitation (ng/ml)
MCC	South African Medicines Control Council
NNA	Nicotine nasal aerosol
NNS	Nicotine nasal spray
%PTF	Percentage peak - trough fluctuation
RSA	Republic of South Africa
SACT	South Africa Clinical Trials (Pty) Ltd
SAE	Serious adverse event
SD	Standard deviation from mean
$T75\%C_{max}$	Plateau time during which the concentration remains above 75% of the C_{max} concentration
T_{max}	Time to maximum concentration
UOFS	University of the Orange Free State

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1. Introduction

1.1 Nicotine

The use of tobacco products is a pastime enjoyed by a large number of people world-wide. Alkaloids are important ingredients of the *Nicotiana tabacum* leaf because they are a major factor in determining the quality of cigarette smoke, and provide a physiological stimulus which makes the use of tobacco products pleasurable. Nicotine is the major alkaloid in commercial tobacco.

Cigarettes are among the most addictive products known and the majority of people who stop smoking relapse within days (Henningfield *et al.*, 1991; Hughes *et al.*, 1992). The number and proportion of smokers in some Western countries is declining, but in spite of many regulatory and medical interventions the percentage of heavy smokers (i.e. people who smoke twenty or more cigarettes per day) did not change between 1974 and 1985 (Bartecchi *et al.*, 1994). In the United States less than 10 percent of the nearly twenty million people who stopped smoking remained abstinent one year later (Fiore, 1992). Thus, only 2 to 3 percent of smokers become non-smokers each year (Fiore, 1992). Nicotine containing medications enable health care providers to markedly increase the ability of their patients to achieve and sustain tobacco abstinence (Henningfield, 1995).

Nicotine is a water-soluble and lipid-soluble base (Lide, 1991). Nicotine delivered in alkaline cigar and pipe smoke, smokeless tobacco, and some European cigarettes is readily absorbed across the mucosal membranes of the mouth and nose. This explains the rapid absorption associated with smokeless tobacco (Henningfield, 1995). Cigarette smoke is acidic and must

be inhaled to be absorbed into alveolar capillary blood and carried to the heart and hence to the brain and other organs. Peak arterial plasma nicotine concentrations may therefore be 10 times greater than venous concentrations (Henningfield *et al.*, 1993).

Cigarettes contain 6 to 11 mg nicotine, of which the smoker typically absorbs 1 to 3 mg (Benowitz *et al.*, 1991a), irrespective of the nicotine-yield ratings provided by the tobacco companies (Henningfield *et al.*, 1994; Benowitz *et al.*, 1983b). The typical pack-per-day smoker absorbs 20 to 40 mg of nicotine each day, achieving plasma concentrations of 25 to 35 ng/ml by the afternoon (Department of Health and Human Services, 1988).

The first nicotine medication was a transmucosally delivered product, nicotine polacrilex ("nicotine gum"), that was approved in a 2 mg form by the Food and Drug Administration (FDA) of the United States of America in 1984. The 4 mg form, approved by the FDA in 1992, enables patients to achieve higher plasma nicotine concentrations with less effort. Four transdermal-delivery systems ("via a nicotine-patch") were approved by the FDA in late 1991 and 1992 (Palmer *et al.*, 1992; Gorsline, 1993; Fagerström *et al.*, 1993). The development of new nicotine formulations, including a nasal spray, vapour inhaler, and lozenge, has been encouraged by the proven utility, as well as the limitations, of nicotine polacrilex and transdermal medications (Russell, 1991). Although nicotine alone is less harmful than nicotine plus tar plus noxious gases, decisions about policies for opening the market to cleaner nicotine replacement products and gradually phasing out tobacco will depend crucially on the health risks of nicotine. Unlike many other addictive drugs, nicotine does not disturb consciousness, nor does it impair judgement or social behaviour. In fact, it enhances rather than impairs cognitive and psychomotor performance and the capacity to work (Russell, 1991). Nicotine appears to have no part in tobacco-related premature deaths (Russell, 1991). There is, however, some evidence that it contributes to the overall cardiovascular risk of smoking. This would appear to be most evident when nicotine is rapidly absorbed through the lungs (Froggatt and Wald, 1989).

Russell (1991) advanced a case for promoting nicotine replacement based on what it seeks to replace, namely tobacco, not as a good in itself, but rather as something less harmful than tobacco. He further made a plea that selected nicotine replacement products be made as palatable and acceptable as possible and actively promoted to enable them to compete with

tobacco products. There should be health authority endorsement to enable exploitation of their health advantages.

Nicotine medications make it easier to abstain from tobacco by replacing at least partially the nicotine formerly obtained from tobacco. These medications are often referred to as "replacement medications". This term is a misnomer, however, since the formulations available are not capable of producing the high arterial plasma concentrations produced by smoked tobacco (Henningfield, 1995). It is only by absorption through the lung alveoli that the efficiency of smoke inhalation can be fully matched to give the intermittent high-nicotine boluses that follow each inhalation (Russell, 1991). On the premise that some smokers might find it more helpful to receive nicotine that is absorbed more rapidly, the development of a nasal nicotine spray was initiated which produces a blood nicotine peak approximately 5 minutes after dosage. This product delivers 0.5 mg of nicotine per pulse and can be used repeatedly to deliver higher doses quickly (Sutherland *et al.*, 1992). An oral inhaler that provides approximately 0.01 mg of nicotine to the buccal mucosa and throat when a 35 ml puff is inhaled through its mouthpiece, has been tested but cannot easily be used to achieve the systemic doses produced by tobacco or most other nicotine preparations (Tønnesen *et al.*, 1993). Another product which may be a potential competitor of nicotine gum is a nicotine lozenge which dissolves slowly in the cheek (Russell, 1991).

Nicotine chewing gum (Nicorette®) is marketed in 2 mg and 4 mg strengths. The nicotine is attached in a loose bond with the ionic bonding agent polacrilex, and intermittent chewing releases approximately 90 percent of the available nicotine after 20 minutes (Ferno *et al.*, 1973). Most of the nicotine is absorbed through the buccal mucosa; on average approximately a quarter is swallowed in saliva and metabolised, but there is much variation between individuals (Benowitz *et al.*, 1987a). Correct chewing technique is important - many people chew the gum too quickly (Tang *et al.*, 1994). Nicotine skin patches release nicotine into the blood at a slow constant rate. Three brands are licensed in Britain and are available over the counter. Two (Nicotinell® and Nicabate®) are worn constantly for 24 hours, with three strengths corresponding to patch areas of 30, 20 and 10 cm^2, respectively delivering 21, 14 and 7 mg of nicotine into the circulation over 24 hours.

Steady state nicotine concentrations are higher with 4 mg gum than with 2 mg gum or the dermal patch, but no form of replacement therapy achieves levels as high as those achieved by smoking 20 cigarettes a day. The rate of increase to steady state concentrations is slow with the patch. The 24 hour patch maintains a constant plasma concentration of approximately 10 ng/ml, which at night is comparatively high (Tang *et al.*, 1994). The immediate effect of smoking is poorly reproduced by gum and patch replacement therapy. One cigarette produces a rapid "surge" of plasma nicotine; the level rises by approximately 25 ng/ml within minutes, but rapidly declines (Benowitz *et al.*, 1987b; Russell *et al.*, 1976; Russell *et al.*, 1983). Nicotine gum produces a smaller rise over 30 minutes (Russell *et al.*, 1983) and the patch produces no immediate effect (Tang *et al.*, 1994). Nicotine nasal spray (not commercially available in South Africa as yet) is absorbed through the nasal mucosa. It might satisfy craving more effectively as it causes a rapid surge of plasma nicotine, over half of that attained from smoking a cigarette (Sutherland *et al.*, 1992; Russell *et al.*, 1983). A nicotine inhaler has been tested; the nicotine is supposedly absorbed through the alveoli as with cigarette smoking, but plasma nicotine levels are lower than with the nasal spray (Tønnesen *et al.*, 1993).

In a cross-over study done by Benowitz *et al.* (1989), in which cigarette smokers in a balanced order used cigarettes, oral snuff, chewing tobacco and abstained from tobacco, the exposure to nicotine was similar in peak levels and circadian pattern while smoking cigarettes, consuming nasal snuff or chewing tobacco, although the average exposure measured as area under the plasma concentration *vs* time curve (AUC) tended to be less with the use of smokeless tobacco.

When the steady state levels of nicotine and cotinine (the major metabolite of nicotine) were measured in different body fluids of snuff users, it was found that the average levels of nicotine and cotinine in plasma were 20.8 and 304 ng/ml, respectively (Curvall and Vala, 1993).

Cotinine has a longer elimination half-life than nicotine (15 hours compared with 2 hours) and is therefore more suitable for estimating nicotine exposure during the preceding few days (Benowitz *et al.*, 1983a). No correlations were found between the consumption parameters (intake per day, number of times per day or habit duration) and the nicotine and cotinine concentrations in any of the body fluids. The best estimate of the nicotine intake appeared to be obtained by measuring the amount of nicotine and all metabolites excreted in urine after

nicotine exposure. At steady state, the rate of excretion reflects the generation rate. In a study comprising 94 tobacco users (45 moist snuff users, 9 chewers, 40 smokers) it was found that the average doses of nicotine estimated from the total amount of nicotine and metabolites excreted during 24 hours were 40, 60 and 33 mg per day, respectively (Curvall and Vala, 1993). Together, nicotine and six metabolites in urine account for up to 85 percent of nicotine absorbed during cigarette smoking, with nicotine at 9 percent, cotinine at 12 percent and trans-3-hydroxycotinine at 37 percent (Jacob and Benowitz, 1993).

To date, no effective and user friendly nicotine buccal spray has been researched. The subject of this thesis is the evaluation of such a product, namely Quit® with respect to the study objectives outlined in section 1.2

1.2 Study Objectives

1.2.1 Primary Objectives

1) To compare the relative bioavailability of nicotine and its major metabolite, cotinine, in cigarette smokers after application of nicotine by means of, chewing nicotine resin chew pieces (Nicorette®), and buccal application from a novel metered-dose applicator (Quit®).

2) To compare descriptively the pharmacokinetics of nicotine and its major metabolite, cotinine, in cigarette smokers after application of nicotine by means of cigarette smoking, chewing nicotine resin chew pieces (Nicorette®), and buccal application from a novel metered-dose applicator (Quit®).

1.2.2 Secondary Objectives

1) To compare the various modes of application with respect to the occurrence and severity of adverse events.

2) To compare Nicorette® and Quit® with respect to volunteer preference.

2. Literature Survey

2.1 Physical and Chemical Properties

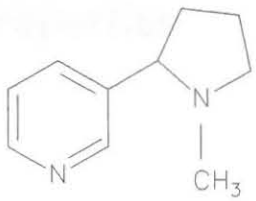
Nicotine is a liquid alkaloid which is present, together with a number of minor alkaloids, in tobacco leaf and a wide variety of other plants.

2.1.1 Physical Characteristics of Nicotine

Chemical name: 3-(1-Methyl-2-pyrrolidinyl)pyridine.

Chemical composition: $C_{10}H_{14}N_2$

Molecular weight: 162.2



Taste: Sharp burning taste.

Odour: Slightly fishy odour when warm.

Colour: Nicotine is a colourless liquid that browns on contact with air and with ageing.

pH: pKa of nicotine is 8.5.

Snuff: The pH of 4 brands of moist snuff was 7.8 to 8.2.

Nicotine Gum: Is buffered to a pH of 8.5.

Cigarettes: Nicotine in cigarettes is highly ionised in cigarette smoke, which is acidic (pH=5). Chewing tobacco contains added alkali, and is relatively basic.

Specific gravity: 1.0097 at 2°C.

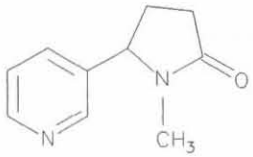
Density: 1.00924 (liquid).

2.1.2 Physical Characteristics of Cotinine

Chemical name: (1 Methyl-5-[3-pyridyl]-2-pyrrolidinone)

Chemical composition: $C_{10}H_{12}N_2O$

Molecular Weight: 176.2



2.2 Pharmacokinetic Properties

2.2.1 Absorption

The variety of ways in which nicotine-containing products is administered and the pH dependency of nicotine absorption markedly influence the amount of nicotine which enters the systemic circulation. With the exception of the intravenous route, nicotine administration involves absorption through a cell membrane. In the form of undissociated base, highly lipid soluble nicotine readily permeates cell membranes, however differences in pH throughout the body determine the actual amount of nicotine absorbed (Gorrod and Wahren, 1993). The most common sites of absorption of nicotine will be considered in turn.

2.2.1.1 Inhalation

Cigarette smoke is a concentrated aerosol of liquid particles suspended in an atmosphere consisting mainly of nitrogen, oxygen and carbon dioxide. Many factors, such as the tobacco blend, additives, wrapping paper, length of tobacco rod, and the filter design considerably modify the composition of smoke from a smoked cigarette (Busto *et al.*, 1989).

Absorption of nicotine through cigarette smoke is affected by factors such as particle size, smoke pattern, smoke pH, and oral/buccal pH. Only minimal amounts are absorbed from the buccal mucosa and the gastro-intestinal tract since nicotine is highly ionised in smoke. Absorption of nicotine through the oral mucosa has been demonstrated to be a function of oral pH; at a pH 5 approximately 3 percent of a nicotine dose is absorbed; at a pH 8 absorption rises to 20 percent (Busto *et al.*, 1989).

The oral irritation due to nicotine is known to be a direct function of the amount of nicotine present in un-ionised form (Kozlowski and Klein, 1978). It is only when nicotine reaches the alveoli in the lungs that significant absorption occurs. At this site the factors which affect distribution and deposition include tidal volume, inspiratory and expiratory flow rates, vital capacity, lung morphology, particle size and density (Busto *et al.*, 1989).

The absorption of nicotine is also influenced by the number of puffs taken. The puff volume and the depth of inhalation are also important. Due to the complexity of the smoking process, the dose of nicotine consumed by the smoker cannot be predicted from the nicotine content of tobacco or its absorption characteristics. Only 25 percent of the total nicotine content of a cigarette is present in the mainstream smoke (Busto *et al.*, 1989).

Plasma nicotine concentrations were increased on average by 17.3 ng/ml (from a mean value of 1.4 to a mean value of 18.7 ng ml) in male subjects following intense puffing on 4 smoke-free cigarettes over a 20-minute period. Peak nicotine levels occurred in 35 to 40 minutes (5 to 10 minutes after discontinuance of puffing), suggesting that most of the nicotine was absorbed through the mouth and upper airways as opposed to the alveoli. Very little nicotine was absorbed when the smoke-free cigarettes were puffed like conventional cigarettes. The rate of nicotine absorption resembled that obtained from nicotine chewing gum (Russell *et al.*, 1987).

2.2.1.2 Gastro-intestinal

Insufficient data exist to quantitatively assess the absorption of nicotine after oral administration. According to physiochemical and pharmacokinetic principles the oral bioavalability of nicotine would be expected to be less than 20 percent. Absorption from the oral mucosa is the principal site of nicotine absorption in subjects who chew tobacco or nicotine gum (Svensson, 1987), but absorption by this route is highly pH dependent.

While not administered orally for therapeutic purposes, the gastro-intestinal absorption of nicotine may be toxicologically important. Nicotine should exist as a diprotonated ion at pH values found in the stomach, while the monoprotonated form would predominate at the pH of the intestine. In addition, if the non-renal clearance of nicotine is assumed to approximate hepatic clearance, the first-pass extraction of nicotine would be extensive, resulting in only about 25 to 30 percent of the drug which has been absorbed reaching the systemic circulation. Thus, under normal physiological conditions, the availability of nicotine after oral administration would be expected to be quite low (Svensson, 1987). However, when nicotine reaches the small intestines it is well absorbed because of the more alkaline pH and larger surface area (Busto *et al.*, 1989).

2.2.1.3 Oral Mucosa

The percentage absorption of nicotine from the buccal surface following the use of ion-exchange gum depends on the total amount of nicotine and the rate and vigour of chewing (Nemeth-Coslett, 1989). Rapid and vigorous chewing produces higher peak levels and is associated with more adverse effects.

Nicotine chewing gum (Nicorette® 4 mg) and an identical placebo gum were administered on different days, in a double-blind cross over study. All the subjects were healthy non-smokers. After 3 minutes of chewing, 72 percent to 96 percent of the nicotine was absorbed (Nyberg *et al.*, 1982).

Swallowing of gum without chewing resulted in 15 percent bioavailability in dogs (Ferno *et al.*, 1973). Swallowing versus buccal absorption of nicotine released from the gum may significantly alter nicotine levels, due to first-pass elimination of nicotine when swallowed.

In normal clinical use the gum produces plasma nicotine concentrations averaging only one-third of that of cigarette smoking (West and Russell, 1986). The mean steady state levels obtained after chewing 2 and 4 mg nicotine gum hourly in patients with lung disease were 11.8 and 23.4 ng/ml, respectively (Mc Nabb *et al.*, 1982). This compares with a mean plasma nicotine trough level during usual smoking of 15.7 ng/ml and a mean trough level of 18.3 ng/ml with hourly smoking of a cigarette with a nicotine yield of 1.1 mg (Mc Nabb *et al.*, 1982).

2.2.1.4 Nasal

Nicotine is well absorbed from snuff, resulting in plasma levels similar to those of cigarette smokers, (Russell *et al.*, 1981). Blood nicotine and cotinine concentrations were measured in 27 volunteers before and after taking 2 mg snuff. In healthy subjects, nicotine, from a 2 percent aqueous solution administered intranasally, was better and more rapidly absorbed than from a 2 mg nicotine chew piece (Russell *et al.*, 1983). However, considerable intersubject variation in plasma nicotine levels was observed. Some investigators feel that the intranasal route is a more optimal method of nicotine delivery in smoking cessation attempts. However, more detailed studies regarding factors influencing the nasal absorption of nicotine and its efficacy and safety are needed before intranasal nicotine can be recommended (Svensson, 1987).

Since 1987 nasal administration systems have been developed to closely approximate cigarette delivery for improved efficacy in clinical application and for more control in systematic testing of nicotine. They produce lower plasma nicotine concentrations with slower rise times compared to cigarettes. It is not yet known what blood concentrations or rates of delivery will best aid smoking cessation. By varying nicotine delivery, researchers hope to find better treatments and to elevate success rates by tailoring treatment to the smoker. Increasing the rate of nicotine administration via a nasal route is one of the more recent forms of treatment being developed and tested (Schneider *et al.*, 1996). A nasal gel was the first delivery system to be tested. The gel was abandoned because of user problems and was followed by tests of an aerosol and a nasal spray. The aerosol was abandoned because of a ban on chlorofluorocarbons (CFCs) and was followed by the testing of a formulation of nicotine nasal spray to be introduced for treatment (Schneider *et al.*, 1996).

2.2.1.5 Dermal Application

After sitting for 15 minutes, on a bench wetted with a 40 percent nicotine solution, a florist showed signs of nicotine toxicity (Faulkner, 1933). In addition to being a common route of administration associated with accidental poisoning, the dermal absorption from a patch has appeared on the market as an adjuvant to smoking cessation.

The amount of nicotine released from transdermal systems has been calculated in trials (total nicotine concentration in the patch minus the residual nicotine remaining in the used system), with values ranging from 43 to 85 percent (Benowitz *et al.*, 1991b). However, this is not a direct measure of the amount of nicotine absorbed since some may be lost at the edge of the system and, therefore, would not reach the systemic circulation. The actual amount of nicotine absorbed has been estimated to be 36 percent (Benowitz *et al.*, 1991b), and 90 percent (Bannon *et al.*, 1989) depending on the system used.

The efficiency of absorption from transdermal systems will be determined, in part, by the adhesive qualities of the system, which ensure that the drug reservoir is in close contact with the skin. The absolute bioavailability of nicotine delivered via a transdermal system containing 52.5 mg of nicotine has been reported to be 82 percent (in comparison with an intravenous dose of deuterium-labelled nicotine (Benowitz *et al.*, 1991a). Metabolism of nicotine by the skin does not appear to occur. Following application of a transdermal system no significant concentrations of nicotine could be detected in plasma (Palmer *et al.*, 1992).

A number of studies have been performed to investigate the pharmacokinetics of transdermal nicotine following single applications of different doses. The results showed dose-related increases in plasma nicotine concentrations. Plasma nicotine concentrations after transdermal delivery were similar to those achieved with nicotine chewing gum (Palmer *et al.*, 1992).

Nicotine absorption appears to be slow following transdermal application, with peak plasma concentrations at 90 minutes after drug administration (Rose *et al.*, 1984).

2.2.1.6 Urinary Bladder

The absorption of nicotine from the urinary bladder seems to follow the same criteria as those which govern its absorption from the oral cavity since the pH of the urine greatly influences the

rate of reabsorption of excreted nicotine (Feyerabend and Russell, 1978). The reabsorption of nicotine from the bladder may be of practical importance. There is a possibility that smoking behaviour may be influenced by the amount of nicotine reabsorbed from the bladder since a fast rate of reabsorption could maintain the plasma nicotine levels at a higher level for a longer time. This hypothesis was proved by rendering the urine of test subjects acidic. Acidifying the urine led to increased smoking (Schachter, 1978).

2.2.2 Distribution

The route of administration is an important factor in determining the tissue distribution of nicotine. It is often stated that the lag time between cigarette smoking and entry of nicotine into the brain is less than that after intravenous injection. This has never been directly investigated and is based on the assumption that the time to travel from the lungs to the aorta, and subsequently to the brain, is shorter than that from an intravenous injection site. Nicotine does enter the brain very quickly. However, brain levels decline rapidly as nicotine is distributed to other parts of the body. Like many other drugs, nicotine (pKa 7.9) is extensively distributed into virtually all tissues of the body (Gorrod and Wahren, 1993).

2.2.2.1 Protein Binding

There appears to be some debate as to the degree of plasma protein binding. Protein binding, primarily to albumin, ranges from 4.9 percent to 20 percent (Benowitz *et al.*, 1982; Svensson, 1987). This range means that the ratio of bound concentration to the total concentration is <0.2 and thus nicotine is said to display little or no plasma protein binding (Rowland and Tozer, 1980). As a consequence, the distribution of nicotine will not be significantly affected by disorders which alter plasma protein concentrations. The volume of distribution is dependent on the body weight and has been estimated to be between one and three times body weight in man.

2.2.2.2 Enterohepatic Circulation

The presence of significant amounts of nicotine in the gastro-intestinal (GI) tract after intravenous dosing suggests that passive diffusion or enterohepatic circulation does occur (Andersson *et al.*, 1965).

2.2.2.3 Placenta

Although disappearance of nicotine from plasma and elimination of nicotine and its metabolites are not affected by pregnancy in humans, the distribution of nicotine is altered in this state (Klein and Gorrod, 1978). Nicotine readily crosses the placenta (Svensson, 1987). The disappearance of nicotine from foetal circulation was slower than that from the mothers. In smoking mothers, nicotine has been detected in umbilical vein serum and amniotic fluid at concentrations higher than that in maternal serum (Luck and Nau, 1984a). Cotinine has also been detected in the amniotic fluid of smoking mothers and those exposed to environmental cigarette smoke.

2.2.2.4 Breast Milk

The concentration of nicotine in breast milk has been shown to be almost three times that in serum (Luck and Nau, 1984b). The daily dose of nicotine received by a breastfeeding infant has been calculated to be between 5.9 and 9.3 µg/kg (Atkinson *et al.*, 1988). This dosage may be clinically important.

2.2.2.5 Saliva

Following topical application of 9 mg of nicotine base (as a 30 percent aqueous solution) to the underside of the left forearm of a non-smoker, salivary nicotine concentrations were 50 ng/ml and 85 ng/ml at 30 and 90 minutes, respectively (Rose *et al.*, 1984).

2.2.2.6 Distribution Kinetics

Nicotine, being a weak lipophilic base, is rapidly and widely distributed to tissue compartments. The volume of distribution at steady state is relatively large and highly variable in humans. In a study using a constant nicotine infusion and measuring blood concentrations of nicotine for 3 hours after the end of the infusion, the average metabolic clearance of nicotine was 1085 ml/min (Benowitz *et al.*, 1982). Smokers appear to have a decreased volume of distribution (2 L/kg) compared to non-smokers (3 L/kg) (Kyerematen *et al.*,1982).

2.2.3 Elimination

2.2.3.1 Metabolism

The predominant route of nicotine elimination is hepatic metabolism. (Gorrod and Jenner, 1975). The metabolism of nicotine involves both oxidative and conjugating pathways and yields a complex pattern of metabolites (Gorrod and Jenner, 1975) figure 2.2.3.1.

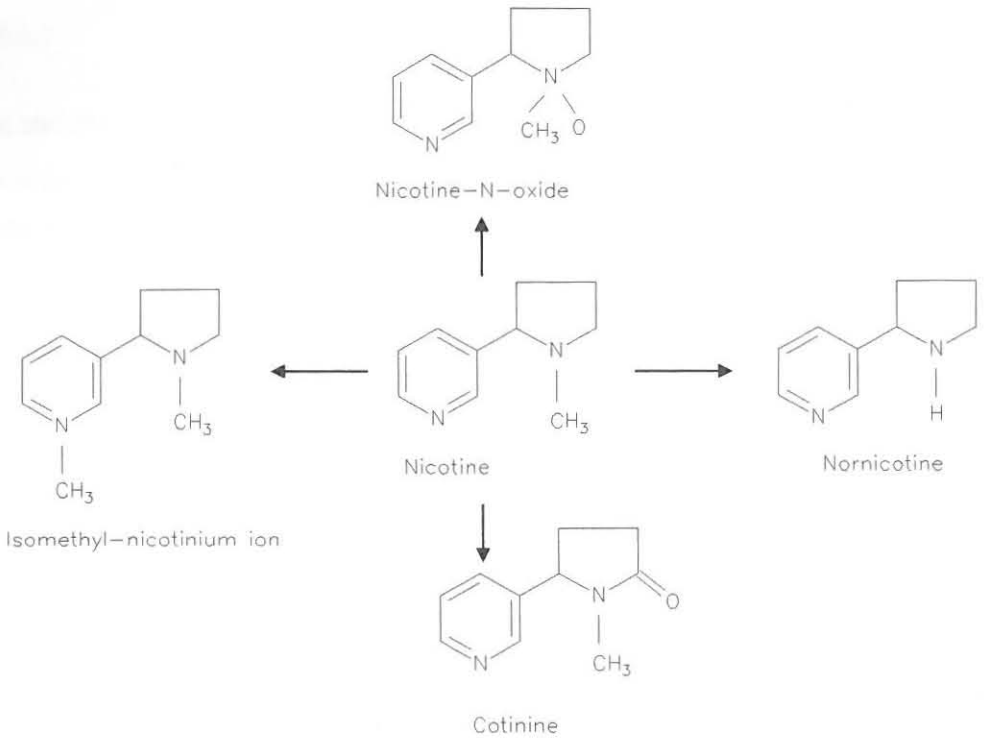


Figure 2.2.3.1 Major Metabolic Pathways of Nicotine in Humans

After intravenous administration, nicotine obeys first-order pharmacokinetics and is described by a two-compartment model (Gorrod and Jenner, 1975). The liver metabolises 70 percent to 75 percent (Svensson, 1987). Small amounts are also metabolised in the lungs and kidneys (Turner *et al.*, 1975). Nicotine administered transdermally does not appear to be metabolised by the skin, since analysis of skin strips taken from smokers following application of transdermal systems was unable to detect cotinine in the epidermis (Palmer *et al.*, 1992). Marked interindividual variability in the rate of nicotine metabolism was observed, as is the

case for rapidly metabolised drugs. Cigarette smoking accelerates the metabolism of many drugs, including nicotine (Beckett *et al.*, 1971).

More than 20 metabolites of nicotine have been identified of which some are shown in figure 2.2.3.1. The principal metabolites are isomethylnicotinium ion, nornicotine, cotinine, and nicotine-N-oxide (Svensson, 1987). Cotinine, a product of oxidation of the pyrrolidine ring of nicotine, accounts for approximately 70 percent to 80 percent of nicotine metabolism and is present in plasma at approximately 10 times the concentration of nicotine (Benowitz *et al.*, 1983a).

The metabolism of nicotine to cotinine is a two-step process via an intermediary metabolite, the nicotine iminium ion. The first step is metabolism by a CYP450 enzyme, most likely CYP2A6, while the second step is metabolism by aldehyde oxidase (Benowitz, 1996). Under uncontrolled urinary pH conditions approximately 10 percent of an intravenous nicotine dose is excreted unchanged in urine. Cotinine is mainly eliminated by the liver (Beckett *et al.*, 1971).

2.2.3.2 Renal Excretion

As in the case of absorption of nicotine, the excretion of this alkaloid is also pH dependent. At a urine pH of 5.5 or less, nicotine is almost completely ionised and can therefore not be reabsorbed through the renal tubules. Ten to 20 percent is excreted unchanged by the kidneys. With a urinary pH under 5, 23 percent is excreted unchanged; with a pH above 7.0, only 2 percent is excreted unchanged (Rosenberg *et al.*, 1980).

2.2.3.3 Breast Milk

Nicotine is excreted in breast milk, with milk concentrations exceeding those in serum (Svensson, 1987).

2.2.4 Pharmacokinetics

The elimination half-lives of nicotine and cotinine are longer in non-smokers than in smokers. The half-life of nicotine is approximately 0.8 hours in smokers and 1.3 hours in non-smokers

(Kyerematen *et al.*, 1982). Another author reports an elimination half-life for nicotine of 2 to 2.2 hours (Feyerabend *et al.*, 1985).

The half-life of cotinine appears to be 10 to 20 hours (Hall *et al.*, 1984).

Nicotine exhibits a biexponential decline in plasma concentration following intravenous administration. The non-renal blood clearance of nicotine averages about 1200 ml/min (72 L/h). This value approaches normal hepatic blood flow, indicating that nicotine clearance is dependent on hepatic blood flow (Benowitz and Jacob, 1985). The renal clearance of nicotine is highly dependent upon urinary pH. Under conditions of urinary alkalinisation, nicotine renal clearance averaged 17 ml/min. Upon urinary acidification, however, renal clearance increased to 245 ml/min. Correspondingly, total clearance increased from 778 ml/min to 1027 ml/min. These data indicate that nicotine undergoes glomerular filtration, tubular secretion and tubular reabsorption (Rosenberg *et al.*, 1980).

2.2.5 Chronopharmacokinetics

The chronopharmacokinetics of nicotine were studied in eleven healthy subjects over a 48 hour period. This was done to examine blood levels of nicotine throughout the day under steady state dosing conditions. Resultant pharmacokinetic data were modelled to determine the effects of meals and circadian influences on the clearance of nicotine (Gries *et al.*, 1996). These researchers found a progressive increase in plasma nicotine concentrations overnight during a 24-hour intravenous infusion of nicotine. This suggested a decline in nicotine clearance overnight. There was a significant circadian variation in nicotine clearance, but the magnitude of the circadian change in clearance was much smaller than the effect of meals on nicotine clearance.

The times of day when peak and trough clearances were observed are of interest. The peak was seen at approximately 11:00 and the trough at between 18:00 and 03:00. This could be associated with hepatic perfusion which is greater during the day than at night. Circadian changes in nicotine kinetics have implications in understanding blood nicotine concentrations during nicotine replacement therapy, particularly with transdermal nicotine delivery systems.

2.3 Pharmacodynamics

2.3.1 Central Nervous System (CNS) Effects

Nicotine is known to cause the liberation of biogenic amines in the central nervous system and it seems reasonable to suggest that changes in the release of amines such as epinephrine, norepinephrine and acetylcholine may contribute to the arousal effect observed when a cigarette is smoked. The sedation, which is frequently observed after smoking, may be the result of the 5-hydroxytryptamine (serotonin) release which has been reported to occur from a number of tissues, including the brain, following cigarette smoking (Schievelbein, 1982). Yoshida *et al.* (1980) reported that the synaptosome fraction from brain tissue contains "nicotine-cholinergic" receptors. The effects of nicotine on catecholamine release have subsequently been confirmed (Cryer *et al.*, 1976).

Palmer *et al.* (1992) reported that nicotine binds to peripheral and CNS cholinergic nicotinic receptors (autonomic ganglia, adrenal medulla and neuromuscular junctions). The actions of nicotine in the CNS are thought to be important in the development of addiction. Nicotine has multiple effects in the brain and activates neurochemical pathways, one of the most relevant probably being the enhancement of mesolimbic dopaminergic function. Additional central actions lead to increases in arousal, attention and reaction time, and decreases in anxiety and stress reactions.

2.3.2 Cardiovascular Effects

Nicotine is known to affect cardiovascular function via sympathetic neural stimulation. Sympathomimetic effects of nicotine are mediated by several mechanisms. Central nervous system-mediated sympathetic stimulation can occur via activation of peripheral chemoreceptors, a direct effect on the brain stem, and / or effects on more caudal portions of the spinal cord. Intrapulmonary chemoreceptors may also contribute to brain-mediated sympathetic arousal. The site that appears to be most sensitive to low levels of nicotine is the carotid chemoreceptor. Peripheral mechanisms include catecholamine release from the adrenal

glands and direct release or enhancement of catecholamines from vascular nerve endings (Benowitz, 1996).

Sympathetic neural stimulation results in heart rate acceleration and a transient increase in blood pressure, with a resultant increase in cardiac output. The coronary blood vessels appear to be constricted by nicotine. Substantial, although not complete, tolerance develops to heart rate acceleration and other cardiovascular effects of nicotine (Benowitz, 1996). In healthy smokers nicotine obtained from smoking a cigarette produces direct effects on cardiac function including an increase in blood pressure (5 to 10 mm Hg), heart rate (by 10 to 20 beats/min), cardiac output and coronary blood flow. Vascular effects include cutaneous vasoconstriction with a subsequent reduction in skin temperature, systemic vasoconstriction and an increase in muscle perfusion. The cardiovascular effects of nicotine were not as pronounced in chronic smokers, probably due to the apparent development of tolerance (Benowitz, 1986).

2.3.3 Endocrine and Metabolic Effects

Metabolic effects of nicotine are of interest in regard to body weight. On average, cigarette smokers weigh 4 kg less than non-smokers (Williamson *et al.*, 1991). Lower body weight appears to be maintained primarily by an increase in metabolic rate, with concomitant appetite suppression.

Nicotine has a variety of endocrine effects that are of biological interest. Neurotransmitters are released that could influence the psychotropic effects and addiction to nicotine. Nicotine can also release endorphins and could possibly have antinociceptive effects (Seyler *et al.*, 1986).

2.4 Nicotine Replacement

Nicotine replacement therapy has been available for more than 10 years. Available formulations include nicotine polacrilex gum, transdermal nicotine (patches), and nicotine nasal spray. A nicotine inhaler is also being developed. The mechanism whereby nicotine replacement therapy can aid smoking cessation has been thought to be relief of nicotine withdrawal symptoms. Nicotine replacement products differ considerably in their patterns, rates, and quantities of dosing and resultant pharmacological effects (Benowitz, 1996).

2.4.1 Transdermal Nicotine

It has long been appreciated that nicotine can be absorbed after topical administration. Green-tobacco sickness is an illness occurring in harvesters of tobacco believed to be secondary to percutaneous absorption of nicotine from contact with wet tobacco leaves.(Gehlbach *et al.*, 1974).

Transdermal nicotine delivery systems are designed to deliver nicotine into the systemic circulation via the skin. Transdermal nicotine systems were approved by the FDA in 1991. The partial replacement of plasma nicotine, which would otherwise have been obtained from cigarettes, reduces the severity of nicotine withdrawal symptoms and so allows the smoker to abstain from smoking more easily. The transdermal systems are available in 16 and 24 hour application regimens, and are recommended for daily use for up to 20 weeks, including a series of weaning-off courses.

Transdermal nicotine systems have been well tolerated in clinical trials, with local irritation at the site of application being the most common adverse event. Mild gastric-, CNS-, and sleep disturbances have also been reported (Palmer *et al.*, 1992).

2.4.1.1 Pharmacodynamic Properties

Peripheral effects observed following administration of nicotine include increase in some cardiac variables (heart rate, blood pressure, cardiac output and coronary blood flow), changes in endocrine and metabolic function, cutaneous and systemic vasoconstriction, and a decrease in muscular tone. Nicotine also appears to be involved in the regulation of body weight, possibly by increasing metabolism and energy expenditure.

The pharmacodynamic effects of nicotine derived from transdermal administration appear similar to, or less pronounced than those observed following smoking (Palmer *et al.*, 1992).

2.4.1.2 Pharmacokinetic Properties

Transdermal systems are designed to deliver nicotine at a more constant rate than other forms of administration, thus achieving more stable plasma nicotine concentrations during the application period. Application of the patch results in a dose proportional increase in plasma nicotine concentrations, although an lag-time of 0.25 to 4 hours may be observed prior to detection of nicotine in the plasma. Steady state concentrations of plasma nicotine of 10 to 23 µg/L are achieved within 2 to 4 days of repeated application, and are approximately half those seen after *ad libitum* smoking over 15 hours. The site of application does not appear to markedly affect the absorption of nicotine. The bioavailability of nicotine is approximately 80 percent, which may be due to the loss of nicotine from the edges of the system (Palmer *et al.*, 1992).

2.4.1.3 Therapeutic Efficacy

The efficacy of transdermal nicotine as an aid to smoking cessation has been evaluated in a number of placebo-controlled trials. Abstinence rates of 30 percent to 40 percent have been reported during the first 6 weeks of treatment in subjects without behavioural support, compared with 4 to 21 percent in placebo recipients (Palmer *et al.*, 1992).

2.4.1.4 Tolerability

A significant proportion of patients experiences dermatological adverse events with the transdermal delivery system. This has led to discontinuation of therapy in 1.4 percent to 7.1 percent of patients. Systemic adverse events such as CNS-, gastric- and sleep disturbances, sweating, muscle and limb pain, paraesthesia, cough and palpitations have been reported. There appears to be some risk of adverse cardiovascular reactions in patients who continue to smoke during application of transdermal nicotine patches (Palmer *et al.*, 1992).

2.4.1.5 Dosage and Administration

The recommended initial dose of transdermal nicotine to assist in the cessation of smoking is up to 22 mg/24h. Treatment may be discontinued when smoking cessation has been achieved (Palmer *et al.*, 1992).

2.4.1.6 Patients with Cardiac Disease

Transdermal nicotine does not cause a significant increase in cardiovascular events in high-risk outpatients with cardiac disease. However, the efficacy of transdermal nicotine as an aid to smoking cessation in such patients is limited and may not be sustained over time (Joseph *et al.*, 1996).

2.4.2 Nasal Nicotine Delivery

Nasal administration systems have been developed to more closely approximate cigarette delivery of nicotine for improved efficacy in clinical application and more control in systemic testing of nicotine (Schneider *et al.*, 1996).

2.4.2.1 Nicotine Nasal Gel

The potential for a nasal form of administration was first based on the concept that even snuff would be a safer alternative to smoking. The intent was to develop a treatment simulating cigarette delivery of nicotine as an alternative to nicotine gum (Schneider *et al.*, 1996).

Schneider *et al.* (1996) discussed different nasal formulations. The first pure nicotine nasal form of administration developed, was a gel consisting of a 0.1 ml droplet containing 2 mg of nicotine in a 2 percent aqueous solution with a pH of 5.0. In order to keep the solution in the nostril for absorption, the viscosity was increased with a cellulose derivative. The gel was self-administered by squeezing it into the nostril with a pipette.

The nicotine gel data demonstrated that nasal administration could produce a faster-rising, higher plasma concentration than nicotine gum with a time to onset of action closer to that of a cigarette (Jarvis *et al.*, 1987).

In an open trial testing potential efficacy, 26 participants used 1 and 2 mg nasal gel with consumption averaging 18 mg a day. Blood nicotine concentrations, measured at random in the first 10 days, averaged 7 µg/L (Jarvis *et al.*, 1987).

2.4.2.2 Nasal Absorption by Placem...

Johansson *et al.* (1991) tested the nasal application of nicotine to the nasal conchae and the nasal septum by droplet. They also tested the next generation of nasal spray preparations, compared to intravenous injection of nicotine.

The following 4 conditions were tested: (1) application of nicotine base to the nasal septum; (2) application of nicotine base to the nasal conchae; (3) nicotine delivered by nasal spray: and (4) an intravenous injection of nicotine.

The bioavailability of nicotine following nasal administration was significantly lower compared to intravenous administration. Mean absolute bioavailability at the septum was 76 percent, at the conchae 64 percent and for the spray 58 percent. The authors reported no significant differences in rates of absorption for the various modes of nasal nicotine administration.

2.4.2.3 Nicotine Nasal Spray

Nicotine nasal spray (NNS) and nicotine nasal aerosol (NNA) systems were designed to reduce problems experienced with the gel, namely to enhance absorption, decrease nasal irritation and increase acceptability (Schneider *et al.*, 1996).

The NNS delivers a fixed dose of nicotine solution by squeezing a plastic nozzle held in the nostril; the nozzle is attached to a multi-dose bottle. The NNA is a pressure metered-dose dispenser containing chlorofluorocarbon (CFCs) propellant gases mixed with a nicotine solution in a multi-dose canister for nasal delivery. The NNA system was later abandoned because of the use of CFCs (Schneider *et al.*, 1996).

2.4.2.3.1 Pharmacokinetic Properties

Placebo-controlled, double-blind clinical trials using the NNS 1 mg system were performed and gave the following results. Blood concentrations assessed in the first trial showed mean plasma nicotine concentrations of 16.0 ng/ml at 4 weeks or 40 percent of smoking values, which were 39.7 ng/ml (Sutherland *et al.*, 1992).

The nasal administration of nicotine appears to be effective and has potential as a controlled means for administering nicotine. Its pharmacokinetic profile is temporally similar to that of a

cigarette although the blood concentrations are lower and more consistent with other treatment systems such as nicotine gum (Schneider *et al.*, 1996).

2.4.2.3.2 Therapeutic Efficacy

In a study done by Sutherland *et al.* (1992) with NNS and placebo it was demonstrated that NNS was significantly superior to placebo for short and long term sustained abstinence. At one year the active treatment *vs* placebo success rates were 26 percent *vs* 10 percent.

2.4.2.3.3 Tolerability

A number of localised adverse effects have been reported with NNS use, including nasal irritation, throat irritation, sneezing, rhinorrhoea, lacrimation and coughing. Most participants experienced the first five symptoms, with 73 percent to 100 percent reporting symptoms on at least one occasion (Sutherland *et al.*, 1992).

2.4.3 Nicotine Gum

The first nicotine replacement medication was a transmucosally delivered product, i.e. nicotine polacrilex (nicotine gum), approved in 2 mg form by the FDA in 1984. The 4 mg form, approved in 1992, enabled patients to achieve higher plasma nicotine concentrations with less effort (Henningfield, 1995).

2.4.3.1 Pharmacokinetic Properties

In contrast to smoking, which involves rapid absorption of nicotine, the use of nicotine replacement medication generally provides slower, lower, and less variable plasma nicotine concentrations (Henningfield, 1995).

Chewing nicotine polacrilex typically releases 50 percent of its nicotine into the mouth (Benowitz, 1993). Thus, 10 to 12 doses per day provide approximately 10 mg nicotine per day from the 2-mg form and 20 mg nicotine per day from the 4-mg form, or approximately one third to one half the usual daily intake of a person who smokes 30 cigarettes a day (Benowitz, 1993). The medication is buffered with 30 mg of sodium carbonate and sodium bicarbonate to

enhance absorption of the nicotine (Henningfield *et al.*, 1990). When chewing, the gum releases nicotine at a slow, uniform rate.

Absorption depends on the vigour of chewing, but 90 percent of the nicotine is absorbed within 30 minutes of chewing. Chewing nicotine gum does not reproduce the rapid rise in nicotine blood levels as in cigarette smoking (Hughes *et al.*, 1984).

2.4.3.2 Therapeutic Efficacy

Nicotine polacrilex medication is efficacious in a variety of settings in helping smokers abstain from tobacco. In terms of absolute cessation rates, nicotine gum increased one-year cessation rates by 5 percent to 20 percent in most studies. In terms of relative cessation rates, the cessation rates with nicotine gum were 50 percent to 100 percent greater than the rates with placebo or no gum conditions (Hughes *et al.*, 1984).

2.4.3.3 Tolerability

In a study done by Nyberg *et al.* (1982), it was shown that chewing gum containing 4 mg nicotine causes insignificant changes in heart rhythm, blood pressure, finger skin temperature and calf and hand blood flow. A small but statistically significant increase in heart rate occurred when the gum was chewed for 30 minutes. The only serious side effect due to nicotine gum that has been reported by smokers is palpitations (5/1,000) (Hughes *et al.*, 1984).

The minor side effects of gum are caused by chewing and the resultant nicotinic effects. Chewing the gum can cause air swallowing, belching, and jaw ache. The nicotine in the gum can cause sore throat, upset stomach, hiccups, nausea and rarely, mouth ulcers (Hughes *et al.*, 1984). An adverse effect that is of major concern is dependence on the gum. However only 5 percent to 9 percent of all subjects who were prescribed the gum continued to use the gum for one year or more (Hughes *et al.*, 1984).

3. Study Methods

This was an open, laboratory-blind, multiple-dose, randomised, 2-way cross-over study designed to compare the pharmacokinetics and relative bioavailability of nicotine and its major metabolite, cotinine, in cigarette smokers after administration of nicotine by means of either chewing nicotine resin chew pieces (Nicorette®), or buccal application from a metered-dose applicator (Quit®), following a period of controlled smoking.

3.1 Study Population

3.1.1 Number of Subjects

Thirty six (36) healthy male and female subjects, who fulfilled the inclusion criteria (Section 3.1.2), did not meet any of the exclusion criteria (Section, 3.1.3), and who gave written, informed consent, entered the study. Subjects were recruited through South Africa Clinical Trials (SACT) from the George area in the Republic of South Africa.

3.1.2 Inclusion Criteria

Volunteers complying with the following criteria were included in the study:

- males and females with a history of smoking between 15 and 20 cigarettes per day of the strength envisaged for this study, for at least the past year,
- aged 18 to 54 years (inclusive),

- healthy on the basis of extensive medical and laboratory investigations (Section 3.1.6) performed within 2 weeks of participation,
- written, informed consent obtained after ample information had been provided verbally and in writing,
- non-existence of any of the exclusion criteria (Section 3.1.3),
- body weight within 20 percent of the ideal weight according to Body Mass Index as used by SACT (Appendix 15),
- female subjects had to be sexually inactive or practising reliable barrier methods of contraception (the use of hormonal contraception was not allowed),
- able and willing to be admitted to the study site for the duration of the study period i.e. from 20:00 on Day 0 until 07:30 on Day 10.

3.1.3 Exclusion Criteria

Volunteers meeting any of the following criteria were excluded from enrolment:

- any significant clinical or clinically significant laboratory abnormality,
- a major illness during the 3 months before commencement of study-related procedures,
- history of hypertension (supine systolic BP more than 180 mm Hg or diastolic BP more than 95 mm Hg),
- resting heart rate of more than 100 bpm or less than 40 bpm on the screening day,
- history of hypersensitivity to nicotine,
- history of bronchial asthma,
- history of thrombo-embolic phenomena,

- use of any medication up t[illegible]ne admission day,
- participation in another study with an experimental drug within 4 weeks of commencement of study-related procedures,
- treatment within the previous 3 months with any drug with a well-defined potential for toxicity in a major organ or system (for example, chloramphenicol, which may cause bone marrow suppression),
- donation of blood during the 8 weeks before the admission day,
- volunteers known or suspected not to comply with the study directives and/or known or suspected not to be reliable or trustworthy,
- volunteers known or suspected to be drug dependent,
- volunteers known or suspected not to be able to understand and evaluate the information that is given to them as part of the formal information policy ("informed consent"),
- pregnancy or lactation.

3.1.4 Justification for In- and Exclusion Criteria

The criteria are set to ensure a homogeneous volunteer population without accompanying diseases interfering with the conduct and scientific evaluation of the study.

3.1.5 Withdrawal Criteria

- subjects not wishing to continue with the study, irrespective of reason,
- unwanted effects from the study drug,
- abnormal findings in laboratory or physical examinations,
- intercurrent illness requiring medication that could invalidate data,

- protocol violation by subjects.

3.1.6 Pre-Study Screening

Volunteers were examined within two weeks of the admission day to assess their eligibility to participate. Each volunteer screened received detailed instructions on the study performance, restrictions, obligations, remuneration and possible adverse events that may be experienced as a result of the nicotine applications.

The examinations and investigations included:

- medical and physical examination,
- measurements of height and body mass,
- vital signs: heart rate, systolic and diastolic blood pressure in recumbent and standing position and body temperature,
- haematology: leukocytes, erythrocytes, haemoglobin, haematocrit, platelets, neutrophils, eosinophils, lymphocytes,
- clinical chemistry: potassium, urea, creatinine, uric acid, calcium, protein, albumin, bilirubin, ALP, GGT, AST, ALT, glucose,
- urinalysis (Multistix® SG, Bayer Diagnostics Division): pH, specific gravity, protein, glucose, ketones, bilirubin, blood,
- ECG (standard 12 lead),
- pregnancy urine slide test (Immunological HCG test, Roche Diagnostics Division): performed with the knowledge and consent of female subjects.

3.1.7 Post-Study Clinical and Safety Evaluation

Haematological and clinical chemistry investigations were done on the morning of study day 10. Post-study laboratory investigations with values outside the normal ranges could be

repeated to establish if and when they in the normal ranges. They would, however, be reviewed against the clinical background and other relevant special investigations, and in relation to the administered drugs before a decision was taken to repeat the investigation in question. The clinical investigator did assess the clinical relevance of all laboratory values outside the normal ranges.

3.1.8 Drop-Outs

Thirty-six healthy subjects were entered into the study, 30 males and 6 females. Thirty-four subjects (28 males and 6 females) completed the study and all were considered suitable. Two subjects were withdrawn from the study. Subjects 25 and 34 were both withdrawn from the study due to concomitant disease (influenza) which required treatment. Subject 25 was withdrawn on day 6 (Quit® regimen) and subject 34 on day 1 (cigarette regimen).

3.2 Study Drugs

3.2.1 Nicotine Regimens

All volunteers were exposed to Regimen 1 (smoking cigarettes) during the first 3 days of admission. Regimens 2 and 3 were dispensed in randomised order according to the randomisation schedule in Appendix 1.

3.2.1.1 Ensuring Steady State

Regimen 1

The volunteers could choose to smoke one of 3 brands of cigarettes, listed in table 3.2.1.1. One cigarette (always from the same brand for a specific volunteer) was smoked hourly from 07:30 till 22:30. Each cigarette was smoked over a period of approximately 10 minutes. This regimen was followed from Day 1 to Day 3.

Table 3.2.1.1 Cigarettes Offered to Volunteers

Trade Name	Manufacturer	Contents per cigarette smoked, as per government agreed method	
		Tar (mg)	Nicotine (mg)
Chesterfield®	Intercontinental Tobacco Company (Pty) Ltd.	15	1.3
John Rolfe®	Transatlantic Tobacco Company (Pty) Ltd.	14	1.2
Peter Stuyvesant®	American Cigarette Co. (Overseas) Ltd.	15	1.4

3.2.1.2 Reference Product

Regimen 2

Trade name : Nicorette®

Manufacturer : Adcock Ingram Self Medication

Registration number : P/34/187,188

Dosage form : Chew pieces containing nicotine resin complex, equivalent to 2 mg nicotine

Dose : One chew piece was chewed every 2 hours (from 07:30 till 22:30 for a period of 30 minutes

Packaging : Blister packs

3.2.1.3 Test Product

Regimen 3

Trade name : Quit® buccal spray

Manufacturer : WRAPSA (Pty) Ltd on behalf of Noble Pharmaceuticals (Pty) Ltd

Registration number : 29/34/0392

Dosage form	:	Buccal spray, delivering approximately 1 mg of nicotine in ethanol solution 70µl spray
Dose	:	One spray to the buccal mucosa, hourly from 07:30 till 22:30, for 3 days
Packaging	:	20 ml canisters, each equipped with a metered-dose, mechanically-operated pump dispenser.

3.2.2 Dispensing Procedures

Products dispensed to the investigator were documented on a drug accountability sheet. Products dispensed to the volunteers were recorded on the drug dispensing form. The investigator dispensed the study medication only to volunteers included in the study by following the procedures set out in the study protocol.

3.2.3 Application Instructions

The procedures followed for the different modes of nicotine application were as follows:

Regimen 1: Cigarette Smoking

Every hour volunteers smoked one cigarette over a period of 10 minutes at a rate of one puff every 60 seconds. The smoking period started hourly on the half hour, from 07:30 till 22:30, and continued for 3 days.

Regimen 2: Nicorette®

Every two hours volunteers "chewed" the chew pieces for 30 minutes. Chewing started on the half hour. This procedure was followed from 07:30 until 22:30, and continued for 3 days. "Chewing" implies compressing the chew piece between the teeth a few times, then letting it rest in the mouth, repeating the cycle every minute or so for 30 minutes, swallowing all saliva. The chew pieces were discarded after 30 minutes. No fluids were allowed until 10 minutes after removal of the chew piece from the mouth.

Regimen 3: Quit®

Every hour, on the half-hour, from 07:30 until 22:30, one spray was applied to the volunteer's buccal mucosae by the investigator. This procedure continued for 3 days.

No fluids were allowed until 10 minutes after application.

3.2.4 Supply, Storage and Dispensing

The cigarettes and Nicorette® were provided by SACT whilst Quit® was provided by Noble Pharmaceuticals (Pty) Ltd. All study material was stored in a limited access area at the study site. Study materials (cigarettes, chew pieces and buccal spray) were dispensed before each application according to the randomisation schedule. The investigator confirmed the correct application to each volunteer according to the randomisation schedule.

3.2.5 Packaging and Labelling

All the Quit® canisters were appropriately labelled by the author.

3.2.6 Drug Inventory

SACT kept records of the receipt and administration of the study materials, which were not allowed to be used for purposes other than as directed by the protocol. The principal investigator retained the remainder of the study material.

3.2.7 Volunteer Compliance

Compliance was ensured by administering the study material under medical surveillance.

3.2.8 Concomitant Medication

No concomitant treatments were permitted during the study. However, if use of a drug appeared necessary during the study, the decision to use the drug was to be taken by the

clinical investigator, if possible after discussion with the principal investigator. The clinical investigator would record the following on the case report form (CRF):

- the reason for treatment,
- the generic and brand name and formulation of the drug,
- the daily dosage and route of administration,
- the duration of the treatment.

3.2.9 Verification of Nicotine Delivery from the Quit® Canisters

Five of the metered dose canisters that were used in the trial were tested to determine the precision and accuracy of the delivery of the dose by the delivery system. From each of the canisters five spray samples were collected and the nicotine concentration determined by gas-chromatography (GC). The results are tabulated below (table 3.2.9) and confirm the precision of the delivery of the dose by the device.

Table 3.2.9 Nicotine Delivery from Quit® Canisters

Collection	Canister 1 mg	Canister 2 mg	Canister 3 mg	Canister 4 mg	Canister 5 mg
1	1.04	1.07	1.05	1.06	1.04
2	1.05	1.06	1.06	1.05	1.04
3	1.07	1.04	1.05	1.06	1.03
4	1.06	1.04	1.05	1.05	1.02
5	1.06	1.05	1.05	1.05	1.03
Mean	1.06	1.05	1.05	1.05	1.03
CV%	0.98	1.11	0.33	0.41	0.78

3.3 Study Procedures

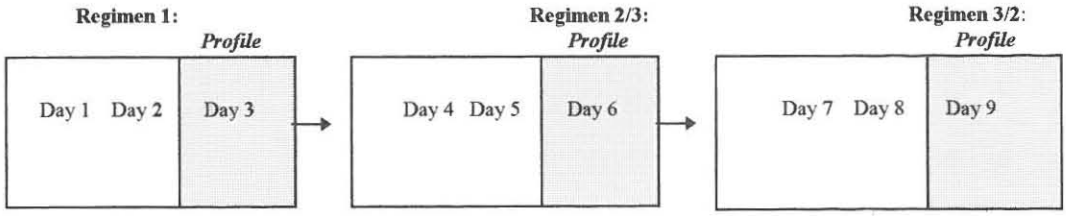
The author performed the clinical trial at SACT in George and the special investigations (sections 3.1.6 and 3.1.7) were done by Drs Turner, Mather, Dietrich, Street and Partners George. Nicotine and cotinine assays were performed by the author, J.B. du Plessis in the Department of Pharmacology, University of the Orange Free State (UOFS)

3.3.1 Admission Period

Volunteers eligible for inclusion, were admitted to the study site for the 9-day study period. They were randomised upon admission on Day 0 (20:00) and received nicotine in the form of three different regimens. Each regimen was applied for 3 consecutive days (from 07:30 until 22:30 each day).

3.3.1.1 Study Flow Diagram

Screening took place (within two weeks of admission to the research site. Eligible subjects were admitted to the research site at 20:00 on Day 0)



Day 10 (07:30)
Post-study evaluation and discharge

Nicotine applications (during admission period):

Regimen 1: • Cigarettes smoked hourly, from 07:30 till 22:30 (From Days 1 to 3)

Randomised Period: (Days 4 to 9)

Regimen 2: • Nicorette® chewed every second hour, from 07:30 till 22:30 (x 3 days)

Regimen 3: • Quit® buccal spray applied hourly, 07:30 till 22:30 (x 3 days)

3.3.2 Study Schedule

Study Day	Procedures
Day 0 (20:00):	Admission
Day 1 (07:30)	*Beginning of cigarette smoking period*
Days 1	Trough blood sampling at 07:25
and 2	Cigarette dispensing, standardised meals and fluids
Day 3	Trough blood sampling at 07:25
	Cigarette dispensing, standardised meals and fluids
	Blood and urine sampling for pharmacokinetic profiles
Day 4 (07:30):	*Beginning of second nicotine application period (randomised to either Quit® or Nicorette®)*
Days 4	Trough blood sampling at 07:25
and 5	Dispensing of trial medication; standardised meals and fluids
Day 6	Trough blood sampling at 07:25
	Dispensing of trial medication; standardised meals and fluids
	Blood and urine sampling for pharmacokinetic profiles
Day 7 (07:30):	*Beginning of third nicotine application period (cross over phase)*
Days 7	Trough blood sampling at 07:25
and 8	Dispensing of trial medication; standardised meals and fluids
Day 9	Trough blood sampling at 07:25
	Dispensing of trial medication; standardised meals and fluids
	Blood and urine sampling for pharmacokinetic profiles
Day 10 (07:30):	*Post-study safety evaluation, and discharge from study site.*

3.3.3 Pharmacokinetic Profile

3.3.3.1 Sampling

Blood

Venous blood (10 ml) was collected into heparinised, labelled, monovettes:

- *Trough samples:* one sample daily at 07:25 (total of 9 samples), by venepuncture.
- *Profile*: third day of each nicotine regimen i.e. on Days 3, 6 and 9, with 10-minute intervals, for a 2-hour period, starting just before the nicotine application at 15:30, till 17:30 (13 x 3 samples), through an indwelling venous cannula (Appendix 3).

The actual sampling times were documented. Within 30 minutes of collection, the blood samples were centrifuged at *Ca.* 1200 g at 4°C for 10 minutes and from each sample 2 aliquots of plasma were transferred to labelled polypropylene tubes. All labels contained the following information: study number, analyte, time of day, volunteer's number, blood sample number and study day. Plasma samples were stored at -20°C until nicotine and cotinine were assayed.

Urine

Urine was collected into large labelled plastic bottles over the entire 24-hours on the third day of each regimen, starting at 07:30 (immediately after application) until 07:30 the next morning (before cross-over to the next regimen).

Urine sampling intervals, on Days 3, 6 and 9:

- The bladder was emptied just before nicotine application at 07:30
- U1 07:30 - 11:30
- U2 11:30 - 15:30
- U3 15:30 - 19:30
- U4 19:30 - 22:30

- U5 22:30 - 07:30

The volumes of collected urine were recorded and 2 aliquots of each urine sample were transferred to labelled polypropylene tubes. All labels contained the following information: study number, analyte, collection interval, volunteer's number, urine sample number and study day. Urine samples were handled at room temperature and stored at -20°C until nicotine and cotinine were assayed.

3.3.4 Safety Assessments

3.3.4.1 Recording of Adverse Events (AE)

All adverse events which were reported by volunteers or observed by the investigator (including clinically relevant abnormal laboratory results and vital signs) were recorded in the CRF (AE-page) regardless of their causal relationship (see Section C under Definitions). AE were recorded daily during the admission period.

Definitions

A Adverse Events

An adverse event is any undesirable/unusual experience occurring in a healthy volunteer or patient coinciding with the intake of an investigational or marketed drug, whether or not considered to be related to the drug. It includes:

- change in clinical condition or worsening (change in nature, severity or (frequency) of conditions present at the onset of the study,
- volunteer deterioration due to the primary illness,
- intercurrent illnesses,
- drug interactions,
- related or possibly related to concomitant medications.

Important abnormal laboratory values as well as significant shifts from baseline within the normal range, which the clinical investigator considers to be clinically important.

It includes also those undesirable / unusual experiences which occur in the active drug-free periods with placebo or in the comparison group.

Undesired drug events are AEs for which a founded suspicion exists that the event is caused by the study drug.

Serious Adverse Events (SAE)

A serious adverse event is:

- any event that is fatal or life threatening,
- any event that is permanently disabling,
- any event that requires or prolongs hospitalisation,
- any event that involves cancer, congenital anomaly or occurs as a result of an overdose.

A SAE has to be reported to the principal investigator, sponsor, Ethics Committee and the South African Medicines Council (MCC) within 24 hours (by telephone or fax after the clinical investigator becomes aware of the occurrence of such an event (see under E).

B Intensity of Adverse Events

The different categories of intensity (severity) were characterised as follows:

- **Mild:** The AE is transient and easily tolerated by the volunteer, causing no limitation of usual activities.
- **Moderate:** The AE causes some limitation of usual activities. The volunteer may experience annoying discomfort.

- **Severe:** The AE causes inability to perform usual activities. The volunteer may experience intolerable discomfort or pain.

C Definition of AE Causality

The clinical investigator determined the relationship of any AE to the study drug according to the following criteria:

- **Definite:** A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by improvement on stopping or reducing the dosage of the drug; and reappearance of the reaction on repeated exposure.

- **Probable:** A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by improvement on stopping or reducing the dosage of the drug; and that could not be reasonably explained by the known characteristics of the patient's clinical state.

- **Possible:** A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.

- **Unlikely:** A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug but, that could reasonably be explained by known characteristics of the patient's clinical state.

- **Not related:** Any event that does not meet the above criteria; where there is sufficient information that the aetiology of the event is in no sequence to the study drug.

- **Not assessable:** A judgement of the relation to study drug is not possible; the statements that are available won't suffice for a definite judgement.

D Monitoring and Recording of Adverse Events

The recording of every single AE/SAE had to meet special requirements:

- detailed patient data,
- exact documentation of the event,
- exact description of temporal sequence to the therapy course,
- documentation of severity,
- documentation of the results of diagnostic and therapeutic measurements,
- results of a repeated exposure (re-exposure) if possible,
- details of the development and outcome including medical judgement,
- as much data as possible have to be obtained which are important for judgement concerning the relationship of the AE/SAE to study drug,
- critical examination of the relationship to study drug.

All AEs had to be charted according to this scheme when spontaneously reported by the subject, observed by the investigator or elicited by general questioning.

E Registration Procedures of AEs/SAEs

The clinical investigator was responsible for recording all AEs in the CRF which occurred during the study (including clinically important deviations of laboratory values from normal ranges), regardless of their relationship to the study drug.

Occurrence of any SAEs (including death, irrespective of the reason) had to be notified immediately (within 24 hours), the latest being the next working day, to the principal investigator, sponsor, the Ethics Committee and MCC.

The first report would contain a detailed description of the observed symptoms and the concomitant therapy. The clinical investigator should have judged the possible causal relationship between the event and the study drug, arranged additional examinations at his own discretion to clarify if the event was connected with the study drug. He could consult a specialist if necessary.

All AEs and SAEs had to be followed up until an outcome was known. This outcome had to be reported in the CRF and to the principal investigator, sponsor, the Ethics Committee and MCC, in the event of a SAE.

3.3.4.2 Laboratory Assessments

Pre-study laboratory tests were performed (blood and urine) on the screening day (as specified in Section 3.1.6), and were repeated on blood samples obtained on the morning of Day 10 (post-study).

The reference ranges and methods of the laboratory investigations are described in the Investigator's Study File. All haematology and clinical chemistry assays were done by the laboratory of Drs Turner, Mather, Dietrich, Street & Partners, George.

Results of pre-study laboratory investigations outside the normal ranges did not necessarily lead to exclusion of a subject from this study. Post-study laboratory investigations with values outside the normal ranges were repeated to establish if and when these values returned to within the normal ranges. Values outside the normal ranges were reviewed against the clinical background and other relevant special investigations, and in relation to the study medication, before a decision was taken to repeat the investigations in question. The clinical investigator assessed the clinical relevance of all laboratory values outside the normal ranges.

The total blood volume collected for pre- and post-study special investigations did not exceed 30 ml, excluding the required repeat investigations.

3.3.4.3 Medical Surveillance

The study was conducted under close medical surveillance. All findings were recorded and reported in detail. This comprised spontaneous reports by the volunteers as well as reports

after interrogation by the investigator ngs resulting from the surveillance of the volunteers.

3.3.5 Restrictions on Volunteers

Medicines: With the exception of the study products administered during the study, all volunteers were to refrain from taking any medicines, including those sold over the counter, for 2 weeks before the admission day and for the duration of the study. If any such medicines were taken, this was to be reported to the clinical investigator.

Diet and Fluid Intake: Standardised meals were served daily during the admission period, at approximately 08:00, 13:00 and 19:00 and standardised snacks at 11:00, 16:00 and 21:00. The meals and the snacks conformed to a Western diet and were standardised with respect to content and quantity for each 3-day "treatment" period.

There were no restrictions on maximum water intake. Volunteers received a minimum quantity of 2.0 litres of fluid (including juice, caffeine-free warm beverages and water) per 24-hour period, according to the flow-chart (Appendix 2).

Alcohol, caffeine and smoking: The ingestion of food and beverages containing alcohol or caffeine was not allowed for the duration of the admission period. Smoking continued according to habit until 22:30 on the evening of admission (Day 0). From then onwards, volunteers were only allowed to smoke during Regimen 1, i.e. the first 3 days of the study. They were only allowed to smoke cigarettes dispensed on the study site, at the times specified in the flow-chart (Appendix 2).

Physical activity: There were no restrictions regarding physical activity as organised and overseen by the SACT-personnel.

Clinic stay: Volunteers were admitted to the SACT study site by 20:00 on Day 0, and remained there under supervision until the morning of Day 10 (approximately 07:30).

3.3.6 Obligation of Volunteers

Volunteers adhered to the instructions given in the protocol, as summarised in the volunteer information form and were obliged to notify the clinical investigator should they be unable to follow the procedures or experience an adverse event, whatever the time of day or night. The clinical investigator was informed of any serious or unexpected adverse event and of the administration of additional medication.

3.3.7 Administrative Aspects

3.3.7.1 Ethical Considerations / Informed Consent

The volunteers were informed verbally and in writing about the nature of the study, the risks involved and the discomfort to which they would be exposed and also of their right to interrupt their participation at any time of their own free will. They confirmed their consent in writing.

Volunteer information included the following points:

- study objectives;
- effects and potential undesirable concomitant phenomena associated with the trial;
- medication;
- risks and additional examinations in connection with the trial;
- sequence of study events; assignment to the individual treatments by randomisation;
- the necessity to avoid any concomitant medication;
- voluntary nature of participation in the study and the possibility of withdrawing from the study at any time without stating reasons;
- forwarding of the study data in anonymous form to the sponsor;
- remuneration involved.

3.3.7.2 Mandatory Approval

Written approval from the Ethics Committee of the University of the Free State and the South African Medicines Control Council (MCC) were obtained before commencement of the study-related procedures.

3.3.7.3 Good Clinical Practice/Quality Assurance

The conduct of the study complied with the local legal requirements and with the following recommendations and guidelines:

- the Declaration of Helsinki (Hong Kong Revision, 1989);
- good Clinical Practice for Trials on Medicinal Products in the European Community (1990);
- investigation of Bioavailability and Bioequivalence (1992).

Auditing was carried out by Quality Assurance Officers from FARMOVS. A Quality Assurance report is appended (Appendix 4).

3.3.7.4 Remuneration of Volunteers

Compensation was made for loss of time and for inconvenience as a result of participation in the study. Subjects who did not complete the study for *bona fide* reasons were compensated *pro rata*. Violation of the protocol could, however, have resulted in forfeiture of the agreed remuneration. Protocol violation was defined as the wilful disobeying of instructions communicated verbally or in writing. Decisions on protocol violations rested solely on the clinical investigator.

3.3.7.5 *Adherence to the Protocol*

As the study progressed, any additions or changes to the protocol deemed necessary were to be worked out by mutual written agreement between the principal investigator and the sponsor. The amendment signature pages were signed by the protocol signatories before

implementation of the amendments. The Ethics Committee and MCC were provided with copies of the amendments.

3.3.7.6 Premature Discontinuation of Volunteers

Volunteers would have been withdrawn from the study for the following reasons:

- at their own request without stating reasons;
- at the discretion of the investigator;
- if adverse events (including intercurrent illness) developed which ruled out continuation with the study or required another treatment;
- failure to comply with the protocol;
- if changes in laboratory results remained clinically relevant in the opinion of the investigator.

If any volunteer failed to complete the study, the reasons were specified in the CRF. Any volunteer who did not complete the study underwent all post-study safety evaluations as stipulated in (Section 3.1.7). Drop-outs would only be replaced if more than 6 volunteers failed to complete the study (Section 3.5).

3.3.7.7 Case Report Forms

Case report forms suitable for this study were developed. One CRF was completed for every volunteer enrolled in the study.

3.3.7.8 Record Keeping

The principal investigator ensured that adequate and accurate records of all observations and other data pertinent to the study were maintained and agreed to their archiving for at least 15 years. Upon mutual agreement between the sponsor and FARMOVS, plasma and urine samples were to be kept for at least 3 months after the final report had been issued.

3.4 Biometric Analysis

3.4.1 General

The Division of Biometry, FARMOVS Research Centre for Clinical Pharmacology and Drug Development, University of the Orange Free State, Bloemfontein, provided guidance and assistance with the study design and evaluation of data.

3.5 Sample Size Calculation

In a preliminary study with 11 subjects the within-subject coefficient of variation of the variable AUD_{ss} appeared to be 30%. Thirty six volunteers were thus entered in the study, in order to complete the study with at least 30 volunteers.

For a bioequivalence range of 0.8 to 1.25, a within-subject coefficient of variation of 30% and a "test/reference" mean ratio between 0.95 and 1.05, n = 36 subjects are needed to achieve a power of 75 % to show bioequivalence (Diletti *et al.*, 1991).

3.6 Pharmacokinetic Variables

3.6.1 Plasma:

To compare the rate and extent of absorption of nicotine, and the rate and extent of formation of cotinine from the three nicotine regimens, the following steady state pharmacokinetic variables were calculated for each volunteer and regimen over 2 dosing intervals for regimens 1 and 3, and over 1 dosing interval for regimen 2, using the actual sampling intervals (relative to nicotine applications):

- the maximum concentration (C_{max}),
- the minimum concentration (C_{min}),
- the time to maximum concentration (T_{max}),

- the area under the plasma concentration vs time data pairs (AUD_{ss}),
- the peak-trough fluctuation (% PTF),
- the plateau time ($T75\%C_{max}$),

The variable AUD_{ss} is the primary measure of the extent of absorption and formation (bioavailability) of nicotine and cotinine, respectively.

C_{max} was read directly from the observed concentrations. For cigarettes and Quit® the mean C_{max} (0-1h and 1-2h) for each dosing interval were also calculated.

C_{min} was read directly from the observed concentrations. For cigarettes and Quit® the mean C_{min} (0-1h and 1-2h) for each dosing interval were also calculated.

T_{max} was read directly from the observed concentrations as blood sampling time corresponding to C_{max}. For cigarettes and Quit®the mean T_{max} (0-1h) and mean T_{max} (0-2h) for each dosing interval and T_{max} (0-2h) for Nicorette® was calculated.

AUD_{ss} was calculated according to the linear trapezoidal rule from 0h to 2h after drug administration.

T 75% C_{max} is defined as the time that the plasma nicotine and cotinine concentration remained above 75% of the observed maximum concentration.

%PTF is a variable which provides information regarding the rate of absorption at steady state; the greater the %PTF, the faster the absorption. % PTF was calculated as follows:

$$\%PTF = 100\%(C_{max}-C_{min})/C_{av},$$

where C_{av} is average steady state concentration given by

$$C_{av} = AUD_{ss}/2h$$

3.6.2 Urine:

Urine volumes and the concentration of nicotine and cotinine in urine were recorded for each collection interval for each volunteer and each regimen. The fractional and cumulative urine volumes and urinary nicotine and cotinine excretion, also as a percentage of the dose, were calculated.

3.7 Presentation of Data and Descriptive Statistics

3.7.1 Plasma:

The individual plasma nicotine and cotinine concentrations, as well as the actual sampling intervals, are tabulated for each volunteer, regimen, and scheduled sampling time, together with descriptive statistics for each regimen and sampling time. Concentrations below the LLOQ are indicated by BLQ. All BLQ values were substituted by half the LLOQ value for calculation of the descriptive statistics.

The individual and mean plasma nicotine and cotinine concentration *vs* actual time profiles for each volunteer and regimen, as well as the mean plasma nicotine and cotinine concentration *vs* scheduled time profiles for each regimen are presented graphically.

The individual values of the plasma nicotine and cotinine pharmacokinetic variables (Section 6) are tabulated for each subject and regimen, with descriptive statistics for each regimen. The individual and geometric mean differences between the three nicotine regimens for the pharmacokinetic variables C_{max}, C_{min}, AUD_{ss}, %PTF and T75% C_{max} are presented in section 6 (Nicotine: table 6.4, for Nicorette® and Quit®; table 6.4.1 for all three regimens. Cotinine: Table 6.5 for Nicorette® and Quit®; table 6.5.1 for all three regimens).

3.7.2 Urine:

The fractional and cumulative urine volumes and cumulative urinary nicotine and cotinine excretion, as well as the actual sampling intervals, are tabulated for each volunteer, regimen and collection interval, together with descriptive statistics for each regimen and collection

interval. Concentrations below the LLOQ are indicated by BLQ. All BLQ values are substituted by half the LLOQ value for calculation of the descriptive statistics.

3.8 Analysis of Bioequivalence

3.8.1 Plasma:

The two nicotine replacement products (Regimens 2 and 3) were compared with respect to the pharmacokinetic variables C_{max}, C_{min}, AUD_{ss}, %PTF, and T75% C_{max} using an analysis of variance with volunteer, product and period effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "test/reference" mean ratios of these variables were calculated for nicotine and cotinine. Plasma nicotine and cotinine concentration *vs* time profiles are presented graphically. "Bioequivalence" of the "test product" (Quit®) and the "reference product" (Nicorette®) was assessed on the basis of the confidence intervals for the primary variables AUD_{ss} and C_{max}, in relation to the conventional bioequivalence range of 80% to 125% for AUD_{ss} and 70% to 143% for C_{max}. The pharmacokinetic variables of the two nicotine replacement products were compared descriptively to those of Regimen 1 (cigarettes). The statistical analyses of the pharmacokinetic variables were performed using the Biopro (V3.1) , a program developed in the Division of Biometry. It is written in MS Fortran (V5.1) and runs under the MS-DOS operating system.

3.8.2 Urine:

The two nicotine replacement products (Regimens 2 and 3) were compared with respect to the urine volumes and cumulative urinary nicotine and cotinine excretion using an analysis of variance with sequence, volunteer (sequence), product and period effects. Point estimates and 90% confidence intervals for the "test/reference" mean ratios of these variables were calculated and presented graphically. "Bioequivalence" of the "test product" (Quit®) and the "reference product" (Nicorette®) was assessed on the basis of those confidence intervals, in relation to the conventional bioequivalence range of 80% to 125% for cumulative excretion of nicotine and

cotinine. The pharmacokinetic variables of the two nicotine replacement products were compared descriptively to those of Regimen 1 (cigarettes).

3.9 Safety Variables

3.9.1 Adverse Events

A questionnaire was completed by every volunteer at study completion. The questionnaire included the following information:

- whether or not heartburn, bloated feeling, hiccups, sneezing and abnormal dreams occurred, graded according to intensity/severity.
- occurrence of any other events.

All adverse events which were reported by volunteers or observed by the investigator were recorded in the Case Report Form regardless of their causal relationship.

3.9.2 Special Investigations

Blood samples were taken for haematology and clinical chemistry evaluations during screening and at post-study follow up. Values outside the normal ranges were reviewed against the clinical background and other relevant special investigations, and in relation to the study medication, before a decision was taken to repeat the investigation in question. The clinical investigator assessed the clinical relevance of all laboratory values outside the normal ranges.

3.10 Subject Demographics

Thirty-six caucasian subjects were enrolled. The mean age of the subjects was 27 years (SD = 10.3), minimum 18 years, maximum 54 years. The mean weight of the subjects was 74.5 kg (SD = 11.0), minimum 54.5 kg, maximum 111.5 kg. Demographic data are shown in Table 3.10.

Table 3.10 Demographic Data of All Subjects Who Entered The Study

Subject	Gender	Age - years	Height - cm	Weight - kg	Cigarette brand smoked during Regimen 1
1	Male	22	189	81.0	Peter Stuyvesant
2	Male	21	179	66.9	Peter Stuyvesant
3	Male	27	184	86.3	Peter Stuyvesant
4	Female	47	169	63.2	Chesterfield
5	Male	21	177	80.5	Peter Stuyvesant
6	Male	20	174	82.1	Peter Stuyvesant
7	Male	41	170	82.5	Chesterfield
8	Female	23	166	64.5	Peter Stuyvesant
9	Female	50	152	75.1	Peter Stuyvesant
10	Male	19	188	86.3	Peter Stuyvesant
11	Male	21	187	79.4	Peter Stuyvesant
12	Male	19	180	68.5	Chesterfield
13	Male	30	188	95.4	Chesterfield
14	Male	25	177	73.1	Chesterfield
15	Male	21	183	73.1	Peter Stuyvesant
16	Male	20	177	67.0	Peter Stuyvesant
17	Male	19	190	83.5	Chesterfield
18	Male	19	176	64.6	Peter Stuyvesant
19	Male	18	182	68.0	Peter Stuyvesant
20	Male	23	185	67.5	Peter Stuyvesant
21	Male	19	177	78.0	Chesterfield
22	Male	51	182	78.0	John Rolfe
23	Male	30	182	76.6	Chesterfield
24	Male	54	179	85.1	Peter Stuyvesant
25	Male	22	181	111.5	Peter Stuyvesant
26	Male	19	176	70.4	Peter Stuyvesant
27	Male	27	173	82.0	Peter Stuyvesant
28	Male	32	182	67.1	Chesterfield
29	Male	18	176	66.4	Peter Stuyvesant
30	Female	18	168	56.0	Peter Stuyvesant
31	Female	18	172	63.0	Chesterfield
32	Male	28	181	72.4	Peter Stuyvesant
33	Male	33	164	54.5	Peter Stuyvesant
34	Male	26	182	72.5	Peter Stuyvesant
35	Male	24	172	70.4	Peter Stuyvesant
36	Female	40	163	69.5	Chesterfield

3.11 Disposition of Subjects

Of the 36 subjects entered into the study, 30 were males and 6 females. Thirty-four subjects (28 males and 6 females) completed the study. Two subjects were withdrawn from the study.

Subjects 25 and 34 were both withdra... from the study due to common colds which required symptomatic treatment. Subject 25 was withdrawn on day 6 (Quit®) and Subject 34 on day 1 (cigarettes).

4. Analytical Methods

4.1 Chemical Overview

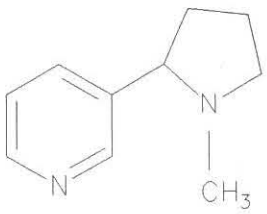
4.1.1 Analytes

4.1.1.1 Nicotine

Chemical name: 3-(1-Methyl-2-pyrrolidinyl)pyridine

Chemical composition: $C_{10}H_{14}N_2$

Molecular weight: 162.2



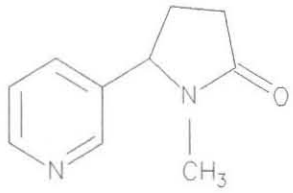
Analytical standard: Merck Lot no. 43613736

4.1.1.2 Cotinine

Chemical name: 1 Methyl-5-(3-pyridinyl)-2-pyrrolidinone

Chemical composition: $C_{10}H_{12}N_2O$

Molecular Weight: 176.2



Analytical standard: Sigma Lot no. 121H40152

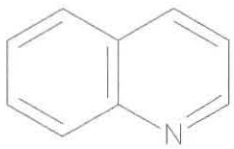
4.1.2 Internal Standard

4.1.2.1 Quinoline

Chemical name: Quinoline

Chemical composition: C_9H_7N

Molecular Weight: 129.16



Analytical standard: Merck Lot no. 70167362

4.2 Plasma Extraction Procedure

To 1.0 ml plasma was added 50 µl of internal standard solution (200 ng/50 µl quinoline in 0.01 M HCl) and 1.0 ml 1 M NaOH. 200 µl Dichloromethane/ethanol (2+1) was added and the sample vortexed for 1 min. After centrifugation for 10 min at 6000 rcf the plasma layer was

drawn off and the dichloromethane transferred into an autosampler vial, and 4 µl injected onto the GC column.

4.3 Urine Extraction Procedure

To 0.5 ml urine was added 50µl of internal standard solution (200 ng/50 µl quinoline in 0.01 M HCl) and 0.5 ml 5 M NaOH. 200 µl Dichloromethane/ethanol (2+1) was added and the sample vortexed for 1 min. After centrifugation for 10 min at 6000 rcf the urine layer was drawn off and the dichloromethane decanted into a autosampler vial, and 2µl injected onto the GC column.

4.3.1 Reagents and Chemicals

Reagent	Grade	Supplier	Ref. No.
Dichloromethane	B & J High Purity	Baxter	300-4
Ethanol	Analytical Reagent	BDH	10107
Sodium hydroxide	Analytical Reagent	BDH	30167

Water is purified by RO 20SA (Millipore) reverse osmosis system and Milli-Q® (Millipore) polishing system.

4.4 Instrumental and Chromatographic Conditions

4.4.1 Instrument

Hewlett-Packard model 5890 Series II gas chromatograph.

4.4.2 Analytical Column

WCOT fused silica capillary column: 15m x 0.32 mm I.D. x 0.25 µ film thickness of CP-Sil-19 CB (CHROMPAC).

4.4.3 Injection

Hewlett-Packard model 6890A autosampler.

Injection port temperature:	170 °C
Injection mode:	Splitless with a valve time of 1.0 minute and a single-taper injection port liner.

4.4.4 Detection

NPD:	280 °C

4.4.5 Pneumatics

Carrier gas:	Helium (2 ml/min at 80°C)
Capillary column head pressure:	15 psi
Detector "Make up":	Nitrogen (30 ml/min)
NPD:	Air (100 ml/min)
NPD:	Hydrogen (6 ml/min)

4.4.6 Oven Temperatures

Temperature program: 40 °C (0.5 min) - 40 °C/min -250 °C (1 min).

4.4.7 Recording

Hewlett-Packard 3365 Series II Chem Station. All data were captured and stored in both electronic form and as printout.

4.4.8 Retention Times

Quinoline:	2.93-2.94 min
Nicotine:	3.24-3.25 min
Cotinine:	4.84-4.85 min

4.5 Pre-Study Validation

The pre-study validation for this assay procedure was performed in accordance with the FARMOVS Analytical Services Division Standard Operating Procedures and Acceptance Criteria current at that time.

4.6 Preparation of Plasma Calibration Standards and Quality Controls

Calibration standards were prepared in biological fluid by preparation of a stock solution in a suitable solvent and spiking a pool of normal biological fluid which was serially diluted with normal biological fluid to attain the desired concentrations. All volumetric operations were performed by weighing and the masses of biological fluid were converted to volumes when calculating concentrations. Quality controls were prepared in biological fluid by an analyst other than the author who performed the study assays by the same method as used for the calibration standards. The calibration standards were aliquoted into tubes and stored under the same conditions as the trial samples; approximately -20°C and normally in the same freezer.

The preparation of serum standards and controls used in this study are presented in sections 4.6.1 to 4.6.4 and the preparation of standards and controls used for the urine analysis are reported in sections 4.7.1 to 4.7.4.

4.6.1 Calculation of Calibration Standards Concentrations Prepared in Biological Fluid: Nicotine

Study Number: **Farmovs 18/96**
Analyte: **Nicotine**
Biological fluid: **Plasma** Specific Gravity: 1.0269 kg/l

Key:
A = Mass of empty container.
B = Mass of container and normal 0.02M HCl
C = Total mass of container plus normal plus spiked 0.02M HCl
D = Concentration (µg/ml or ng/ml) in HCl.
E = Mass of empty plasma container
F = Mass of plasma container plus normal plasma
G = Vol of HCl solution spiked in plasma
H = Concentration of analyte in plasma

Preparation of Stock Solution STD L

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Conc. analyte (µg/ml)
0.02M HCl	1.000	8.000	251.29	251.29	31.84

Preparation of Calibration Standards

Sample Code & No.	Source Solution	A	B	C	D Conc in HCl ug/ml	E	F	G Volume(ul) spiked in plasma	Source Solution	H Conc in plasma ng/ml
STD K (L)					31.8	111.33	151.64	200	STD L	162
STD J (K)					31.8	103.37	143.48	150	STD L	122
STD I (J)	*STD K*	58.060	68.040	78.070	16.0	110.94	150.96	200	STD I	81.9
STD H (I)	*STD I*	55.470	65.430	75.490	8.02	104.99	145.91	200	STD H	40.2
STD G (H)	*STD H*	56.020	65.980	75.810	3.98	128.98	169.82	200	STD G	20.0
STD F (G)	*STD G*	54.610	64.630	74.580	1.98	78.60	118.71	200	STD F	10.2
STD E (F)	*STD F*	56.970	66.940	76.800	0.987	111.84	151.35	200	STD E	5.13
STD D (E)	*STD E*	56.660	66.620	76.460	0.490	110.55	151.16	400	STD D	4.96
STD C (D)	*STD D*	57.520	67.490	77.560	0.246	126.82	207.24	400	STD C	1.26
STD B (C)	*STD C*	11.582	16.587	21.606	0.123	104.60	184.33	400	STD B	0.636
STD BB (B)					0.123	103.07	183.09	200	STD B	0.317

4.6.2 Calculation of Calibration Quality Control Concentrations Prepared in Biological Fluid: Nicotine

Study Number: **Farmovs 18/96**
Analyte: **Nicotine**
Biological fluid: **Plasma** Specific Gravity: 1.0269 kg/l

Key:
A = Mass of empty container.
B = Mass of container and normal 0.02M HCl
C = Total mass of container plus normal plus spiked 0.02M HCl
D = Concentration (µg/ml or ng/ml) in HCl.
E = Mass of empty plasma container
F = Mass of plasma container plus normal plasma
G = Vol of HCl solution spiked in plasma
H = Concentration of analyte in plasma

Preparation of Stock Solution QC G

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Conc. analyte (µg/ml)
0.02M HCl	1.000	5.000	190.380	190.380	26.26

Sample Code & No.	Source Solution	A	B	C	D Conc in HCl ug/ml	E	F	G Volume(ul) spiked in plasma	Source Solution	H Conc in plasma ng/ml
QC F					26.3	109.98	189.67	400	QC G	135
QC E					26.3	112.69	192.56	200	QC G	67.5
QC D	*QC F*	11.680	21.598	26.004	8.08	110.68	191.43	50	QC D	5.14
QC C	*QC D*	11.757	21.659	23.366	1.19	117.80	157.36	50	QC C	1.54
QC B	*QC C*	11.769	21.676	30.605	0.563	109.05	149.71	50	QC B	0.711
QC A	*QC B*	11.657	21.657	31.643	0.281	109.38	149.85	50	QC A	0.357

4.6.3 Calculation of Calibration Standards Concentrations Prepared in Biological Fluid: Cotinine

Analyte: **Cotinine**
Biological fluid: **Plasma** Specific Gravity 1.0269 kg/l
Key:
A = Mass of empty container.
B = Mass of container and normal 0.02M HCl
C = Total mass of container plus normal plus spiked 0.02M HCl
D = Concentration (µg/ml or ng/ml) in HCl.
E = Mass of empty plasma container
F = Mass of container plus normal plasma
G = Vol of solution spiked in plasma
H = Concentration of analyte in plasma

Preparation of Stock Solution STD L

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Conc. analyte (µg/ml)
0.02M HCl	1.000	80.444	251.29	251.29	320.12

Sample Code & No.	Source Solution	A	B	C	D Conc in HCl ug/ml	E	F	G Volume(ul) spiked in plasma	Source Solution	H Conc in plasma ng/ml
STD K (L)					320.1	111.33	151.64	200	STD L	1631
STD J (K)					320.1	103.37	143.48	150	STD L	1229
STD I (J)	*STD K*	58.060	68.040	78.070	160.5	110.94	150.96	200	STD I	823
STD H (I)	*STD I*	55.470	65.430	75.490	80.63	104.99	145.91	200	STD H	405
STD G (H)	*STD H*	56.020	65.980	75.810	40.05	128.98	169.82	200	STD G	201
STD F (G)	*STD G*	54.610	64.630	74.580	19.96	78.60	118.71	200	STD F	102
STD E (F)	*STD F*	56.970	66.940	76.800	9.922	111.84	151.35	200	STD E	51.6
STD D (E)	*STD E*	56.660	66.620	76.460	4.931	110.55	151.16	400	STD D	49.9
STD C (D)	*STD D*	57.520	67.490	77.560	2.478	126.82	207.24	400	STD C	12.7
STD B (C)	*STD C*	11.582	16.587	21.606	1.241	104.60	184.33	400	STD B	6.39
STD BB (B)					1.241	103.07	183.09	200	STD B	3.18

4.6.4 Calculation of Calibration Quality Control Concentrations Prepared in Biological Fluid: Cotinine

Study Number: **Farmovs 18/96**
Analyte: **Cotinine**
Biological fluid: **Plasma** Specific Gravity: 1.0269 kg/l

Key:
A = Mass of empty container.
B = Mass of container and normal 0.02M HCl
C = Total mass of container plus normal plus spiked 0.02M HCl
D = Concentration (µg/ml or ng/ml) in HCl.
E = Mass of empty plasma container
F = Mass of plasma container plus normal plasma
G = Vol of HCl solution spiked in plasma
H = Concentration of analyte in plasma

Preparation of Stock Solution QC G

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Conc. analyte (µg/ml)
0.02M HCl	1.000	49.096	190.380	190.380	257.88

Sample Code & No.	Source Solution	A	B	C	D Conc in HCl ug/ml	E	F	G Volume(ul) spiked in plasma	Source Solution	H Conc in plasma ng/ml
QC F					257.9	109.98	189.67	400	QC G	1329
QC E					257.9	112.69	192.56	200	QC G	663
QC D	QC F	11.680	21.598	26.004	79.32	110.68	191.43	50	QC D	50.4
QC C	QC D	11.757	21.659	23.366	11.66	117.80	157.36	50	QC C	15.1
QC B	QC C	11.769	21.676	30.659	5.547	109.05	149.71	50	QC B	7.00
QC A	QC B	11.657	21.677	31.643	2.766	109.38	149.85	50	QC A	3.51

4.7 Preparation of Urine Calibration Standards and Quality Controls

4.7.1 Calculation of Calibration Standards Concentrations Prepared in Biological Fluid: Nicotine

Study Number: Farmovs 18/96
Analyte: Nicotine
Biological fluid: Urine Specific Gravity: 1.0000
Key:
A = Mass of empty container.
B = Mass of container + normal biological fluid.
C = Total mass of container + normal + spiked biological fluid
D = Concentration of analyte in the biological fluid ng/ml

Preparation of Nicotine Stock Solution CA for Spiking STD N:

Solvent Used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Volume spiked (µl)	Concentration analyte (µg/ml)
0.02M HCl	1.000	17.000	288.701	288.701	10898	58.88

Preparation of Nicotine Calibration Standards:

Sample Code & No.	Source Solution	A	B	C	D ng/ml
STD N	*Stock CA*	129.023	255.994		4655
STD M	*STD N*	110.708	129.824	173.597	3240

4.7.2 Calculation of Calibration Standards Concentrations Prepared in Biological Fluid: Nicotine

Study Number: Farmovs 18/96
Analyte: Nicotine
Biological fluid: Urine Specific Gravity: 1.0000
Key:
A = Mass of empty container.
B = Mass of container + normal biological fluid.
C = Total mass of container + normal + spiked biological fluid
D = Concentration of analyte in the biological fluid ng/ml

Preparation of Nicotine Stock Solution SA for Spiking STD L:

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Volume spiked (µl)	Concentration analyte (µg/ml)
HCl	1.000	15.000	250.080	250.080	10140	59.98

Preparation of Nicotine Calibration Standards:

Sample Code & No.	Source Solution	A	B	C	D ng/ml
STD L	*Stock SA*	111.340	362.110		2331
STD K	*STD L*	103.070	153.280	203.140	1161
STD J	*STD K*	110.920	160.890	215.270	605
STD I	*STD J*	110.390	160.300	214.290	315
STD H	*STD I*	109.880	159.270	212.550	163
STD G	*STD H*	118.070	168.880	218.640	80.8
STD F	*STD G*	109.060	159.600	210.260	40.4
STD E	*STD F*	109.990	160.970	214.570	20.7
STD D	*STD E*	104.600	155.520	206.720	10.4
STD C	*STD D*	110.680	161.120	213.570	5.30
STD B	*STD C*	119.890	169.150	219.970	2.69
STD CC	*STD B*	116.590	166.650	217.380	1.35
STD BB	*STD CC*	118.530	168.220	220.810	0.696

4.7.3 Calculation of Calibration Standards Concentrations Prepared in Biological Fluid: Cotinine

Study Number: Farmovs 18/96
Analyte: Cotinine
Biological fluid: Urine Specific Gravity: 1.0000
Key:
A = Mass of empty container.
B = Mass of container + normal biological fluid.
C = Total mass of container + normal + spiked biological fluid
D = Concentration of analyte in the biological fluid ng/ml

Preparation of Cotinine Stock Solution CA for Spiking STD N:

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Volume spiked (µl)	Concentration analyte (µg/ml)
HCl	1.000	17.690	288.701	288.701	10898	61.27

Preparation of Cotinine Calibration Standards:

Sample Code & No.	Source Solution	A	B	C	D ng/ml
STD N	*Stock CA*	129.023	255.994		4844
STD M	*STD N*	110.708	129.824	173.597	3371

4.7.4 Calculation of Calibration Standards Concentrations Prepared in Biological Fluid: Cotinine

Study Number: Farmovs 18/96
Analyte: Cotinine
Biological fluid: Urine Specific Gravity: 1.0000
Key:
A = Mass of empty container.
B = Mass of container + normal biological fluid.
C = Total mass of container + normal + spiked biological fluid
D = Concentration of analyte in the biological fluid ng/ml

Preparation of Cotinine Stock Solution SA for Spiking STD L:

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Volume spiked (µl)	Concentration analyte (µg/ml)
HCl	1.000	15.288	250.080	250.080	10140	61.13

Preparation of Cotinine Calibration Standards:

Sample Code & No.	Source Solution	A	B	C	D ng/ml
STD L	*Stock SA*	111.340	362.110		2376
STD K	*STD L*	103.070	153.280	203.140	1184
STD J	*STD K*	110.920	160.890	215.270	617
STD I	*STD J*	110.390	160.300	214.290	321
STD H	*STD I*	109.880	159.270	212.550	166
STD G	*STD H*	118.070	168.880	218.640	82.3
STD F	*STD G*	109.060	159.600	210.260	41.2
STD E	*STD F*	109.990	160.970	214.570	21.1
STD D	*STD E*	104.600	155.520	206.720	10.59
STD C	*STD D*	110.680	161.120	213.570	5.40
STD B	*STD C*	119.890	169.150	219.970	2.74
STD CC	*STD DD*	116.590	166.650	217.380	1.3795
STD BB	*STD CC*	118.530	168.220	220.810	0.7093

4.7.5 Calculation of Calibration Quality Control Concentrations Prepared in Biological Fluid: Nicotine

Study Number: Farmovs 18/96
Analyte: Nicotine
Biological Fluid: Urine Specific Gravity: 1.0000
Key:
A = Mass of empty container.
B = Mass of container + normal biological fluid.
C = Total mass of container + normal + spiked biological fluid
D = Concentration of analyte in the biological fluid ng/ml

Preparation of Nicotine Stock Solution QA for Spiking QC F:

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Volume spiked (µl)	Concentration analyte (µg/ml)
HCl	1.000	11.000	189.500	189.500	9980	58.05

Preparation of Nicotine Quality Controls:

Sample Code & No.	Source Solution	A	B	C	D ng/ml
QC F	*Stock QA*	110.946	236.402		4277
QC E	*QC F*	108.468	129.970	169.214	2763

4.7.6 Calculation of Calibration Quality Control Concentrations Prepared in Biological Fluid: Cotinine

Study Number: Farmovs 18/96
Analyte: Nicotine
Biological Fluid: Urine Specific Gravity: 1.0000
Key:
A = Mass of empty container.
B = Mass of container + normal biological fluid.
C = Total mass of container + normal + spiked biological fluid
D = Concentration of analyte in the biological fluid ng/ml

Preparation of Nicotine Stock Solution QB for Spiking QC D:

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Volume spiked (µl)	Concentration analyte (µg/ml)
HCl	1.000	15.000	252.050	252.050	6730	59.51

Preparation of Nicotine Quality Controls:

Sample Code & No.	Source Solution	A	B	C	D ng/ml
QC D	*Stock QB*	125.900	375.430		1563
QC C	*QC D*	103.370	153.280	203.800	786
QC JJ	*QC C*	109.220	159.400	210.460	397
QC II	*QC JJ*	110.560	161.030	211.580	198
QC B	*QC II*	110.950	160.700	211.990	101
QC HH	*QC B*	111.140	161.130	212.890	51.2
QC A	*QC HH*	117.510	167.760	218.810	25.8
QC GG	*QC A*	106.100	157.320	208.000	12.8
QC FF	*QC GG*	111.780	162.130	215.150	6.59
QC EE	*QC FF*	109.700	159.100	211.260	3.38
QC DD	*QC EE*	110.910	160.760	213.740	1.74
QC CC	*QC DD*	112.510	163.070	214.190	0.876
QC BB	*QC CC*	114.510	164.810	213.740	0.432

4.7.7 Calculation of Calibration Quality Control Concentrations Prepared in Biological Fluid: Cotinine

Study Number: Farmovs 18/96
Analyte: Cotinine
Biological Fluid: Urine Specific Gravity: 1.0000
Key:
A = Mass of empty container.
B = Mass of container + normal biological fluid.
C = Total mass of container + normal + spiked biological fluid
D = Concentration of analyte in the biological fluid ng/ml

Preparation of Cotinine Stock Solution QA for Spiking QC F:

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Volume spiked (µl)	Concentration analyte (µg/ml)
HCl	1.000	12.983	189.500	189.500	9980	68.51

Preparation of Cotinine Quality Controls:

Sample Code & No.	Source Solution	A	B	C	D ng/ml
QC F	*Stock QB*	110.946	236.402		5048
QC E	*QC F*	108.468	129.270	169.214	3320

4.7.8 Calculation of Calibration Quality Control Concentrations Prepared in Biological Fluid: Cotinine

Study Number: Farmovs 18/96
Analyte: Cotinine
Biological Fluid: Urine Specific Gravity: 1.0000
Key:
A = Mass of empty container.
B = Mass of container + normal biological fluid.
C = Total mass of container + normal + spiked biological fluid
D = Concentration of analyte in the biological fluid ng/ml

Preparation of Cotinine Stock Solution QB for Spiking QC D:

Solvent used	SG solvent (kg/l)	Mass analyte (mg)	Mass solvent (g)	Volume solvent (ml)	Volume spiked (µl)	Concentration analyte (µg/ml)
HCl	1.000	17.389	252.050	252.050	6730	68.99

Preparation of Cotinine Quality Controls:

Sample Code & No.	Source Solution	A	B	C	D ng/ml
QC D	*Stock QB*	125.900	375.430		1812
QC C	*QC D*	103.370	153.280	203.800	911
QC JJ	*QC C*	109.220	159.400	210.460	460
QC II	*QC JJ*	110.560	161.030	211.580	230
QC B	*QC II*	110.950	160.700	211.990	117
QC HH	*QC B*	111.140	161.130	212.890	59.4
QC A	*QC HH*	117.510	167.760	218.810	29.9
QC GG	*QC A*	106.100	157.320	208.000	14.9
QC FF	*QC GG*	111.780	162.130	215.150	7.64
QC EE	*QC FF*	109.700	159.100	211.260	3.92
QC DD	*QC EE*	110.910	160.760	213.740	2.02
QC CC	*QC DD*	112.510	163.070	214.190	1.02
QC BB	*QC CC*	114.510	164.810	213.740	0.501

4.7.9 Plasma Calibration Curve Data

Calibration Curve: Plasma Nicotine

Calibration Standards used: STD C - STD L

Calibration Range: 0.636 - 162 ng/ml

Regression Equation: Wagner $\ln(y) = a(\ln x)^2 + b(\ln x) + c$

a coefficient: 0.0284

b coefficient: 0.8250

c coefficient: -4.4799

r^2: 0.9977

Calibration Curve used for Method Validation.

STD Code	Nominal Conc. (ng/ml)	Back-calculated Conc. (ng/ml)	% Bias
STD L	162	167	2.8
STD L	162	145	-10.6
STD K	122	123	0.6
STD J	81.9	84.4	3.0
STD I	40.2	42.6	5.9
STD H	20.0	22.2	10.9
STD G	10.2	10.9	7.2
STD F	5.13	4.56	-11.2
STD E	4.96	4.56	-8.1
STD D	1.26	1.1O	-12.8
STD C	.636	.743	16.8

Standards C,D,E,G,H,I and J were used in the analysis of samples.

Calibration Curve: Plasma Cotinine

Calibration Standards used: STD B - STD L

Calibration Range: 3.18 - 1631 ng/ml

Regression Equation: Wagner $\ln(y) = a(\ln x)^2 + b(\ln x) + c$

a coefficient: 0.0394

b coefficient: 0.6025

c coefficient: -5.1876

r^2: 0.9962

Calibration Curve used for Method Validation.

STD Code	Nominal Conc. (ng/ml)	Back-calculated Conc. (ng/ml)	% Bias
STD L	1631	1365	-16.3
STD K	1229	1220	-0.7
STD J	823	949	15.3
STD I	405	492	21.5
STD H	*201	*	*
STD G	102	96.7	-5.2
STD F	51.6	47.0	-8.9
STD E	49.9	50.3	0.8
STD D	12.7	10.5	-17.0
STD C	6.39	6.88	7.7
STD B	3.18	3.50	10.1

*Standard Rejected

Standards C,D,E,G,H,I and J were used in the analysis of samples

4.7.10 Urine Calibration Curve Data

Calibration Curve: Urine Nicotine

Calibration Standards used: STD D - STD N

Calibration Range: 10.4 - 4655 ng/ml

Regression Equation: Wagner $\ln(y) = a(\ln x)^2 + b(\ln x) + c$

a coefficient: -0.0249

b coefficient: 1.1193

c coefficient: -5.4244

r^2: 0.9995

Calibration Curve used for Method Validation

STD Code	Nominal Conc. (ng/ml)	Back-calculated Conc. (ng/ml)	% Bias
STD N	4655	4848	4.1
STD N	4655	4922	5.7
STD M	3240	3183	-1.8
STD M	3240	3123	-3.6
STD L	2331	2235	-4.1
STD L	2331	2104	-9.8
STD K	1161	1172	0.9
STD J	605	655	8.2
STD I	315	339	7.5
STD H	163	170	4.5
STD G	80.8	78.6	-2.8
STD F	40.4	38.0	-6.0
STD F	40.4	39.3	-2.7
STD E	20.7	20.0	-3.2
STD E	20.7	20.0	-3.5
STD D	10.4	10.8	4.2
STD D	10.4	10.9	4.5

Standards E, F, G, H, I, J, K, L, M and N were used in the analysis of samples

Calibration Curve: Urine Cotinine

Calibration Standards used: STD D - STD N

Calibration Range: 10.6 - 4844 ng/ml

Regression Equation: Wagner $\ln(y) = a(\ln x)^2 + b(\ln x) + c$

a coefficient: -0.0180

b coefficient: 1.0631

c coefficient: -5.6565

r^2: 0.9991

Calibration Curve used for Method Validation

STD Code	Nominal Conc. (ng/ml)	Back-calculated Conc. (ng/ml)	% Bias
STD N	4844	5300	9.4
STD N	4844	4864	0.4
STD M	3371	3324	-1.4
STD M	3371	3149	-6.6
STD L	2376	2283	-3.9
STD L	2376	2071	-12.8
STD K	1184	1299	9.7
STD J	617	681	10.4
STD I	321	343	7.0
STD H	166	172	3.5
STD G	82.3	79.9	-2.9
STD F	41.2	39.0	-5.3
STD F	41.2	37.7	-8.5
STD E	21.1	20.3	-3.7
STD E	21.1	20.5	-3.0
STD D	10.6	11.5	8.7
STD D	10.6	10.9	3.1

Standards E, F, G, H, I, J, K, L, M and N were used in the analysis of samples

4.7.11 Study Assay Performance Validation

Quality Controls for Method Validation of Nicotine in Plasma:

Accuracy is measured as percent bias and precision is measured as coefficient of variation (CV percent)

Code	QC B	QC C	QC D	QC E	QC F
Nominal	.711	1.54	5.14	67.5	135
Replicates					
1	.834	1.69	5.80	72.1	136
2	.837	1.48	5.79	68.4	135
3	.829	1.51	4.90	69.8	125
4	.931*	1.43	4.91	67.0	120
5	R	R	5.15	64.9	125
MEAN	0.8577	1.519	5.315	68.41	128.2
%BIAS	120.6	98.7	103.4	101.4	95.0
CV%	5.7	6.5	8.4	4.0	5.3

* = Response outside accepted range.

[ ] = Outlier not included in statistics. Outliers calculated only on columns with N >= 5.

R = Rejected

Quality Controls for Method Validation of Cotinine in Plasma:

Accuracy is measured as percent bias and precision is measured as coefficient of variation (CV percent)

Code	QC B	QC C	QC D	QC E	QC F
Nominal	7.0	15.1	50.4	663	1329
Replicates					
1	7.46	17.0	R	805*	1363
2	6.99	13.8	63.3*	692	1396
3	7.69	14.2	50.7	669	1178
4	7.45	12.8	53.6	688	1173
5	7.12	13.2	51.6	670	1153
6	R	15.0	R	R	R
MEAN	7.341	14.33	56.85	705.0	1252.7
%BIAS	104.9	94.9	110.6	106.3	94.3
CV%	3.8	10.6	12.0	8.1	9.3

* = Response outside acceptance range.

[ ] = Outlier not included in statistics. Outliers calculated only on columns with N >= 5.

R = Rejected

Quality Controls for Method Validation of Nicotine in Urine:

Accuracy is measured as percent bias and precision is measured as coefficient of variation (CV percent)

Code	QC F	QC E	QC D	QC C	QC JJ	QC II	QC B	QC HH	QC A	QC GG
Nominal	4277	2763	1563	786	397	198	101	51.2	25.8	12.8
Replicates										
1	4339	[3517]*	[1800]	907	442	195	88.7	43.5	20.6*	10.8
2	4005	2732	1481	802	407	200	91.4	45.1	23.0	12.0
3	3935	2814	1466	760	394	191	94.1	45.9	23.4	11.6
4	4052	2860	1451	742	393	192	94.3	46.1	22.9	12.7
5	4139	2762	1452	740	390	193	89.6	45.7	22.5	11.6
MEAN	4094	2792	1462	790	405	194	91.6	45.3	22.5	11.8
%BIAS	95.7	101	93.6	101	102	97.9	90.7	88.4	87.2	91.8
CV%	3.8	2.0	1.0	8.8	5.3	1.8	2.8	2.4	4.9	6.0

* = Response outside accepted range.

[ ] = Outlier not included in statistics. Outliers calculated only on columns with N >= 5.

Quality Controls for Method Validation of Cotinine in Urine

Accuracy is measured as percent bias and precision is measured as coefficient of variation (CV percent)

Code	QC F	QC E	QC D	QC C	QC JJ	QC II	QC B	QC HH	QC A	QC GG
Nominal	5048	3320	1812	911	460	230	117	59.4	29.9	14.9
Replicates										
1	[5226]	[4336]*	[2414]*	1187*	551	210	[85.4]*	[39.6]*	[17.6]*	F
2	4699	3351	2018	1116*	535	263	117	56.4	26.7	13.8
3	4613	3408	2043	1044	546	259	123	60.9	29.2	15.1
4	4739	3476	1961	1000	529	278*	127	57.9	29.7	14.5
5	4780	3369	2024	998	533	256	127	59.2	28.1	12.7
MEAN	4708	3401	2011	1069	539	253	124	58.6	28.45	14.1
%BIAS	93.3	102	111	117	117	110	106	98.6	95.1	94.4
CV%	3.8	1.6	1.8	7.6	1.7	10.1	3.8	3.2	4.7	7.3

* = Response outside accepted range.

[ ] = Outlier not included in statistics. Outliers calculated only on columns with N >= 5.

Calibration Range: Nicotine and Cotinine

For the assignment of a valid calibration range bias is taken as measure of accuracy and coefficient of variation (CV%) is taken as measure of precision. Inter-day accuracy and precision for a valid range must be within 15 percent but within 20 percent at the lower limit of quantification. Results from the inter-day validation assays above indicate a valid calibration

range of 0.636 to 81.9 ng/ml for nicotine in plasma and 6.39-823 ng/ml for Cotinine in plasma. The urine values were 10.4 to 4655 ng/ml for nicotine and 10.6 to 4844 for Cotinine respectively.

The LLOQ was preliminarily set at the value of the lowest acceptable calibration standard used in the pre-study validation = 0.636 ng/ml for nicotine and 6.39 ng/ml for cotinine in plasma and 10.4 ng/ml for nicotine and 10.6 ng/ml for cotinine in urine.

4.7.12 Extraction Efficiency

Absolute recoveries of analyte and internal standard were determined in triplicate at C_{max}, 1/4 C_{max} and 3x LLOQ concentrations of the analyte in biological fluid.

Analyte Recovery for Nicotine in Plasma using Internal Standard (Quinoline) as External Standard

SAMPLE	ANALYTE CONC. ng/ml	MEAN OF PEAK HEIGHT		ABSOLUTE RECOVERY (%)	CV (%)
		AFTER EXTRACTION	PURE SOLUTIONS		
RC max	40.2	41424	37372	110.8	3.5
RC ave	10.2	9943	9482	104.9	6.0
RC min	4.96	5582	4602	121.3	5.1

Analyte Recovery for Cotinine in Plasma using Internal Standard (Quinoline) as External Standard

SAMPLE	ANALYTE CONC. ng/ml	MEAN OF PEAK HEIGHT		ABSOLUTE RECOVERY (%)	CV (%)
		AFTER EXTRACTION	PURE SOLUTIONS		
RC max	405	76387	238144	34.9	13.8
RC ave	10.2	18953	59926	31.6	2.2
RC min	49.9	9832	29280	33.6	6.0

Analyte Recovery for Nicotine in Urine using Internal Standard (Quinoline) as External Standard

SAMPLE	ANALYTE CONC. ng/ml	MEAN OF PEAK HEIGHT		ABSOLUTE RECOVERY (%)	CV (%)
		AFTER EXTRACTION	PURE SOLUTIONS		
RC max	786	418331	600590	69.7	2.6
RC ave	101	67069	77364	86.7	4.8
RC min	12.8	7958	9806	81.2	1.7

Analyte Recovery For Cotinine in Urine using Internal Standard (Quinoline) as External Standard

SAMPLE	ANALYTE CONC. ng/ml	MEAN OF PEAK HEIGHT		ABSOLUTE RECOVERY (%)	CV (%)
		AFTER EXTRACTION	PURE SOLUTIONS		
RC max	911	422272	594532	71.0	1.0
RC ave	117	64967	76564	84.9	5.2
RC min	14.9	7356	9745	75.5	3.0

Internal Standard (Quinoline) Recovery in Plasma using Analyte as External Standard

INTERNAL STANDARD ng/ml	MEAN OF PEAK HEIGHT		ABSOLUTE RECOVERY (%)	CV (%)
	EXTRACTION	SOLUTIONS		
200	110595	152818	72.4	2.6

Internal Standard (Quinoline) Recovery in Urine using Analyte as External Standard

INTERNAL STANDARD ng/ml	MEAN OF PEAK HEIGHT		ABSOLUTE RECOVERY (%)	CV (%)
	EXTRACTION	SOLUTIONS		
200	154482	150622	102.6	3.6

4.7.13 Stability

Stability of Analytes in Solution

Aqueous solutions of nicotine and cotinine stored at 0-4 °C were stable for at least one month.

Stability of Analytes in Matrix

No significant changes in nicotine and cotinine concentrations in plasma or urine stored at room temperature over 24 h were reported.

Freeze-Thaw Stability

No significant changes in nicotine and cotinine concentrations were reported after 3 freeze-thaw cycles between -20 °C and room temperature.

On-Instrument Stability

Nicotine and cotinine were stable on the autosampler for at least 9 hours as presented in the data below.

QC F 135 ng/ml Nicotine

Injection Time	Time Difference	Cumulative Time (hr)	Peak Ratio	Response Factor
15:08:00		0.00	1.295	9.590
17:16:00	2:08:00	2.13	1.279	9.474
19:26:00	2:10:00	4.30	1.182	8.753
21:34:00	2:08:00	6.43	1.130	8.370
23:41:00	2:07:00	8.55	1.182	8.756
		Mean	1.213	8.989
		SD	0.070	0.522
		CV	5.81%	5.81%

QC E 67.5 ng/ml Nicotine

Injection Time	Time Difference	Cumulative Time (hr)	Peak Ratio	Response Factor
15:22:00		0.23	0.650	9.622
17:31:00	2:09:00	2.38	0.614	9.099
19:40:00	2:09:00	4.53	0.627	9.295
21:48:00	2:08:00	6.67	0.601	8.899
23:55:00	2:07:00	8.78	0.581	8.606
		Mean	0.615	9.104
		SD	0.026	0.385
		CV	4.24%	4.24%

QC D 5.23 ng/ml Nicotine

Injection Time	Time Difference	Cumulative Time (hr)	Peak Ratio	Response Factor
15:36:00		0.43	0.0528	10.096
17:46:00	2:10:00	2.62	0.0526	10.057
19:55:00	2:09:00	4.78	0.0452	8.642
22:03:00	2:08:00	6.92	0.0455	8.700
0:09:00	2:06:00	9.02	0.0473	9.044
		Mean	0.0487	9.308
		SD	0.0038	0.718
		CV	7.72%	7.72%

QC F 1329 ng/ml Cotinine

Injection Time	Time Difference	Cumulative Time (hr)	Peak Ratio	Response Factor
15:08:00		0.00	3.357	2.526
17:16:00	2:08:00	2.13	3.453	2.598
19:26:00	2:10:00	4.30	2.833	2.132
21:34:00	2:08:00	6.43	2.819	2.121
23:41:00	2:07:00	8.55	2.762	2.079
		Mean	3.045	2.291
		SD	0.332	0.249
		CV	10.89%	10.89%

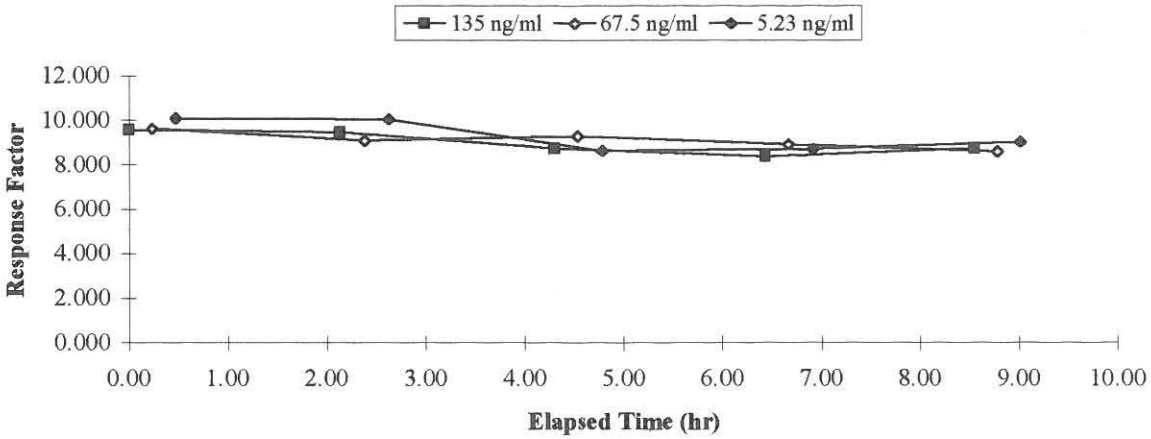
QC E 663 ng/ml Cotinine

Injection Time	Time Difference	Cumulative Time (hr)	Peak Ratio	Response Factor
15:22:00		0.23	1.833	2.764
17:31:00	2:09:00	2.38	1.546	2.332
19:40:00	2:09:00	4.53	1.488	2.245
21:48:00	2:08:00	6.67	1.537	2.318
23:55:00	2:07:00	8.78	1.492	2.250
		Mean	1.579	2.382
		SD	0.144	0.217
		CV	9.12%	9.12%

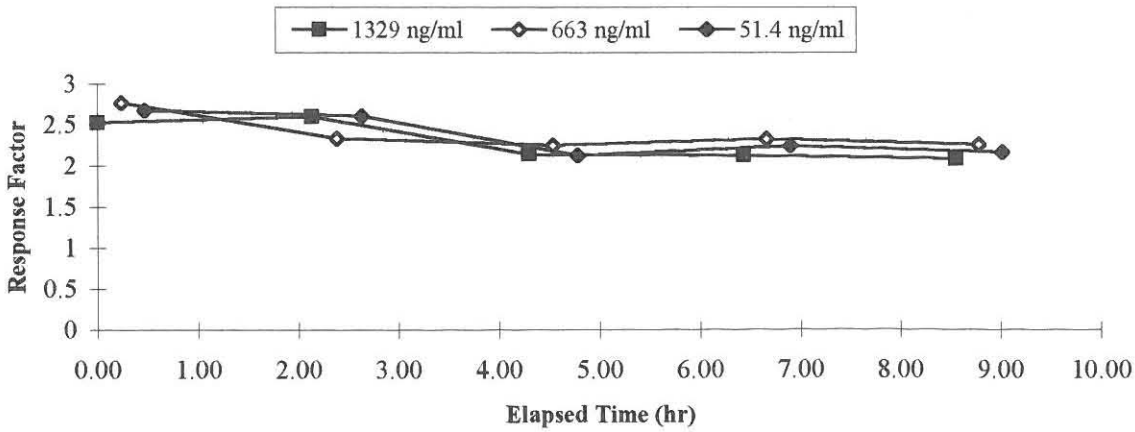
QC D 51.4 ng/ml Cotinine

Injection Time	Time Difference	Cumulative Time (hr)	Peak Ratio	Response Factor
15:36:00		0.47	0.1374	2.673
17:46:00	2:10:00	2.63	0.1337	2.601
19:55:00	2:09:00	4.78	0.1090	2.121
22:02:00	2:07:00	6.90	0.1149	2.325
0:09:00	2:07:00	9.02	0.1108	2.156
		Mean	0.1212	2.357
		SD	0.0134	0.260
		CV	11.04%	11.04%

FARMOVS 18/96
On-instrument Stability of Nicotine



FARMOVS 18/96
On-instrument Stability of Cotinine



4.7.14 Specificity

Specificity was determined by analysing "blank" biological fluids from six different sources without the addition of the internal standard. The chromatograms were inspected for peaks which may interfere with the analyte and the internal standard. No peaks were found that interfered with either the analytes or internal standard.

5. Within-Study Assay Performance

5.1 Study Execution

Samples were assayed in batches. A batch consisted of calibration standards (usually 6 to 10), quality controls (at high, medium and low concentrations), and study samples. The number of samples that can be assayed in a batch depends on factors such as the stability of the analyte in the biological fluid or in the extraction solvent and the length of the chromatographic runs. Attempts were always made to process complete profiles of a subject for each treatment in a batch. Thus in a given batch, profiles of treatments were alternated whenever possible. The calibration standards and quality controls were interspersed among the study samples in a predetermined manner. The quality controls which were processed in each batch comprise duplicates near the maximum, near the mean concentration and near 3 x LLOQ (where LLOQ represents the lower limit of quantification determined during the validation of the assay method) as well as two controls respectively near LLOQ and 2 x LLOQ. After the batch had been run, the chromatograms were inspected and checked against documented acceptance criteria.

The calibration curves were plotted, regression equations determined, and the quality controls calculated as unknowns using the regression equation giving the best overall results throughout the study.

5.1.1 Preparation of Calibration Standards and Quality Controls

Sufficient calibration standards and quality controls were prepared during the pre-study validation to serve as calibration standards and quality controls for the assay of the study samples. The preparation of these standards and controls has been presented under the Pre-Study Validation section.

5.1.2 Typical Batch Structure

Samples are designated in the run sheet table by a three digit code separated by commas consisting of *subject number, sampling time(hr),period*

Table 5.1.2 Typical Batch Structure

Inj. No.	Sample	Inj. No.	Sample	Inj. No.	Sample	Inj. No.	Sample
1	Respons	31	20,0.167,1	61	21,0.83,1	91	21,1.5,2
2	STD D	32	20,0.167,2	62	21,0.83,2	92	21,1.5,3
3	20,0.01,1	33	20,0.167,3	63	21,0.83,3	93	STD C
4	20,0.01,2	34	21,0.167,1	64	QC C	94	20,1.67,1
5	20,0.01,3	35	21,0.167,2	65	20,1.0,1	95	20,1.67,2
6	21,0.01,1	36	21,0.167,3	66	20,1.0,2	96	20,1.67,3
7	21,0.01,2	37	STD E	67	20,1.0,3	97	21,1.67,1
8	21,0.01,3	38	20,0.33,1	68	21,1.0,1	98	21,1.67,2
9	QC E	39	20,0.33,2	69	21,1.0,2	99	21,1.67,3
10	20,0.02,1	40	20,0.33,3	70	21,1.0,3	100	QC E
11	20,0.02,2	41	21,0.33,1	71	STD D	101	20,1.83,1
12	20,0.02,3	42	21,0.33,2	72	20,1.167,1	102	20,1.83,2
13	21,0.02,1	43	21,0.33,3	73	20,1.167,2	103	20,1.83,3
14	21,0.02,2	44	STD C	74	20,1.167,3	104	21,1.83,1
15	21,0.02,3	45	20,0.5,1	75	21,1.167,1	105	21,1.83,2
16	STD H	46	20,0.5,2	76	21,1.167,2	106	21,1.83,3
17	20,0.03,1	47	20,0.5,3	77	21,1.167,3	107	QC C
18	20,0.03,2	48	21,0.5,1	78	STD J	108	20,2.0,1
19	20,0.03,3	49	21,0.5,2	79	BLANK	109	20,2.0,2
20	21,0.03,1	50	21,0.5,3	80	20,1.33,1	110	20,2.0,3
21	21,0.03,2	51	STD G	81	20,1.33,2	111	21,2.0,1
22	21,0.03,3	52	20,0.67,1	82	20,1.3,3	112	21,2.0,2
23	QC D	53	20,0.67,2	83	21,1.33,1	113	21,2.0,3
24	20,0.1,1	54	20,0.67,3	84	21,1.33,2	114	STD I
25	20,0.1,2	55	21,0.67,1	85	21,1.33,3		
26	20,0.1,3	56	21,0.67,2	86	QC D		
27	21,0.1,1	57	21,0.67,3	87	20,1.5,1		
28	21,0.1,2	58	20,0.83,1	88	20,1.5,2		
29	21,0.1,3	59	20,0.83,2	89	20,1.5,3		
30	QC B	60	20,0.83,3	90	21,1.5,1		

5.2 Inter-day Accuracy and Precision

5.2.1 Back Calculated Calibration Standards Concentrations for Nicotine in Plasma

	STD C	STD D	STD E	STD G	STD H	STD I	STD J
Assigned value ng/ml	.636	1.26	4.96	10.2	20.0	40.2	81.9
N	31	35	19	19	19	19	19
Mean	0.666	1.21	4.863	10.5	20.5	40.6	80.4
CV%	9.7	10.1	4.1	3.6	4.3	4.8	2.7

5.2.2 Back Calculated Calibration Standards Concentrations for Cotinine in Plasma

	STD C	STD D	STD E	STD G	STD H	STD I	STD J
Assigned Value ng/ml	6.39	12.7	49.9	102	201	405	823
N	34	36	19	19	19	19	19
Mean	6.51	12.6	47.8	102	211	418	793
CV%	6.3	7.0	4.4	4.6	4.1	7.5	4.8

5.2.3 Quality Control Sample Data:Concentration of Nicotine in Plasma

	QC B	QC C	QC D	QC E
Assigned Value ng/ml	.711	1.54	5.14	67.5
N	18	38	38	38
Mean	.801	1.51	5.31	67.6
CV%	10.5	13.1	6.1	5.6

5.2.4 Quality Control Sample Data:Concentration of Cotinine in Plasma

	QC B	QC C	QC D	QC E
Assigned Value ng/ml	7.00	15.1	50.4	663
N	19	38	38	38
Mean	7.02	14.0	50.1	650
CV%	8.6	10.7	9.6	10.0

5.2.5 Back Calculated Calibration Standards Concentrations for Nicotine in Urine

	STD E	STD F	STD G	STD H	STD I	STD J	STD K	STD L	STD M	STD N
Assigned Value ng/ml	20.7	40.4	80.8	163	315	605	1161	2331	3240	4655
N	11	9	8	8	8	8	8	9	18	18
Mean	21.6	39.4	77.1	155	313	628	1254	2444	3301	4416
CV%	6.1	8.6	7.7	2.7	2.3	2.7	2.8	2.2	6.1	7.7

5.2.6 Back Calculated Calibration Standards Concentrations for Cotinine in Urine

	STD E	STD F	STD G	STD H	STD I	STD J	STD K	STD L	STD M	STD N
Assigned Value ng/ml	21.1	41.2	82.3	166	321	617	1184	2376	3371	4844
N	8	8	8	8	8	8	8	9	17	15
Mean	24.6	41.4	83.2	145	304	597	1193	2418	3426	4772
CV%	9.2	15.3	16.1	6.5	6.8	4.9	2.2	4.6	8.6	6.3

5.2.7 Quality Control Sample Data:Concentration of Nicotine in Urine

	QC A	QC B	QC C	QC D	QC F
Assigned Value ng/ml	25.8	101	786	1563	4277
N	7	7	17	18	19
Mean	24.1	84.9	781	1576	4081
CV%	5.5	3.6	3.7	4.7	6.6

5.2.8 Quality Control Sample Data:Concentration of Cotinine in Urine

	QC A	QC B	QC C	QC D	QC F
Assigned Value ng/ml	29.9	117	911	1812	5048
N	6	6	17	18	15
Mean	31.3	108	969	1953	4808
CV%	11.4	3.2	6.9	6.0	5.2

5.2.9 Calculation of Results

Results are calculated using the PhIRSt chromatographic data-reporting package. Peak heights/areas are electronically read automatically from the report files generated by Hewlett-

Packard 3365 Series II Chem Station. Data are automatically summarised, calibration curves calculated according to pre-set regression equations and concentrations interpolated by the program. Results are presented in printed ordered tables with performance statistics per batch and later summarised to give overall study statistics. This package has been validated in Canada by the manufacturer to FDA requirements.

5.2.10 Final Lower Limit of Quantification (LLOQ)

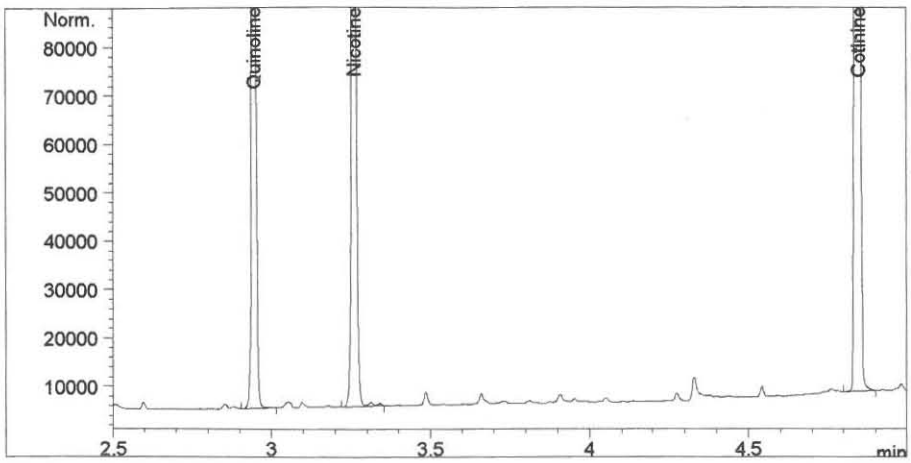
The lower limit of quantification (LLOQ) is initially determined from the data obtained for the assayed quality controls during Pre-Study Validation or the Re-instatement Validation, since these data include determinations of the analyte at concentrations close to the limit of detection. The LLOQ is defined as that concentration of the analyte which can still be determined with acceptable precision (CV% < 20) and accuracy (bias < 20 percent) for the purposes of the particular application. This limit is reappraised during the performance of the assay with actual clinical study samples. After all the clinical study samples have been analysed the limit of quantification is finally set at a value which is determined by the performance of the procedure with the quality controls which are processed with each batch of samples run. This is considered to be a more objective reflection of the assay performance under clinical study conditions than the validation data alone.

The LLOQ for the assay method during this study was finally set at the lowest acceptable calibration standard used consistently during the assay of the study samples = 0.636 ng/ml for nicotine and = 6.39 ng/ml for cotinine.

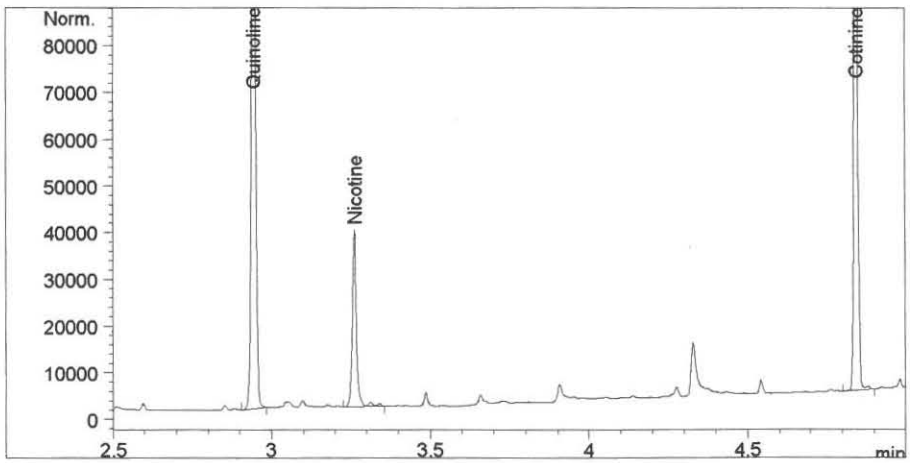
5.2.11 Representative Chromatograms of Plasma Extracts

5.2.11.1 Calibration Standards Chromatograms

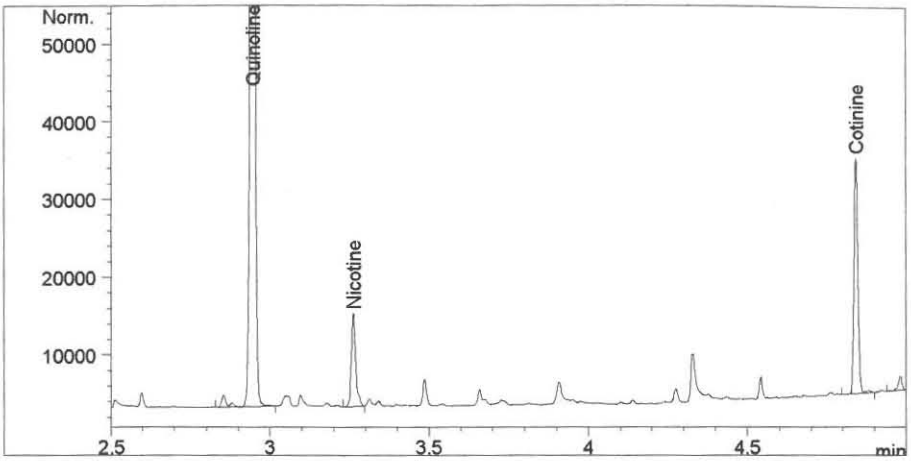
Calibration Standard J (Nicotine: 81.9 ng/ml, Cotinine: 823 ng/ml)



Calibration Standard G (Nicotine: 10.2 ng/ml, Cotinine: 102 ng/ml)

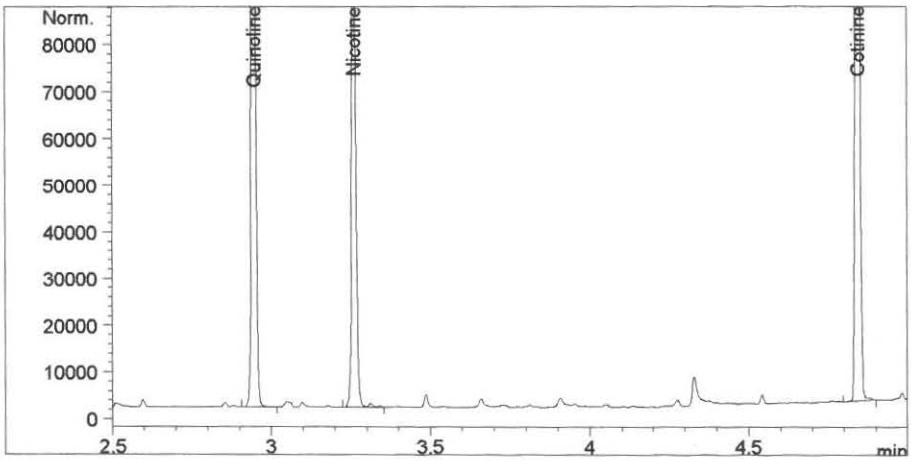


Calibration Standard D (Nicotine: 1.26 ng/ml, Cotinine: 12.7 ng/ml)

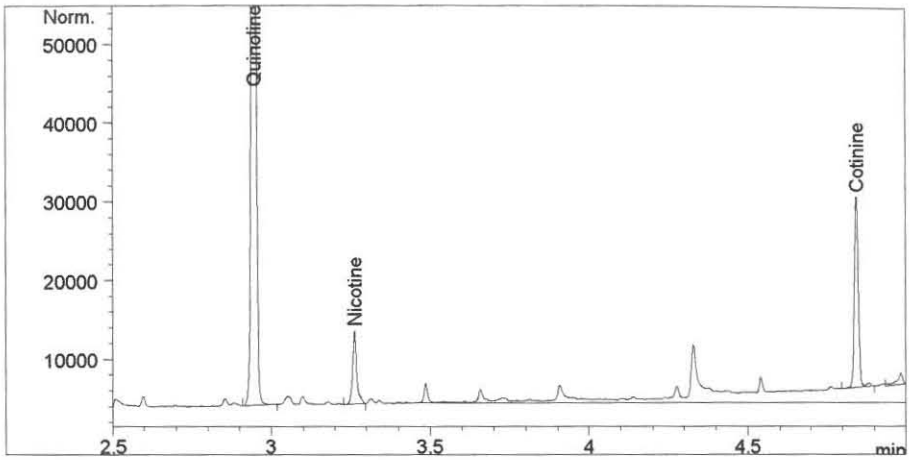


5.2.11.2 Quality Controls Chromatograms

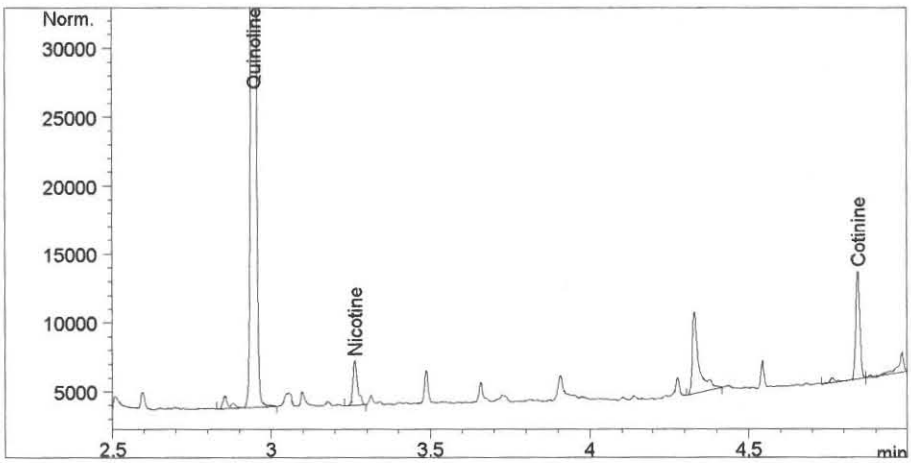
Quality Control E (Nicotine: 67.5 ng/ml, Cotinine: 663 ng/ml)



Quality Control D (Nicotine: 5.23 n[illegible].4 ng/ml)

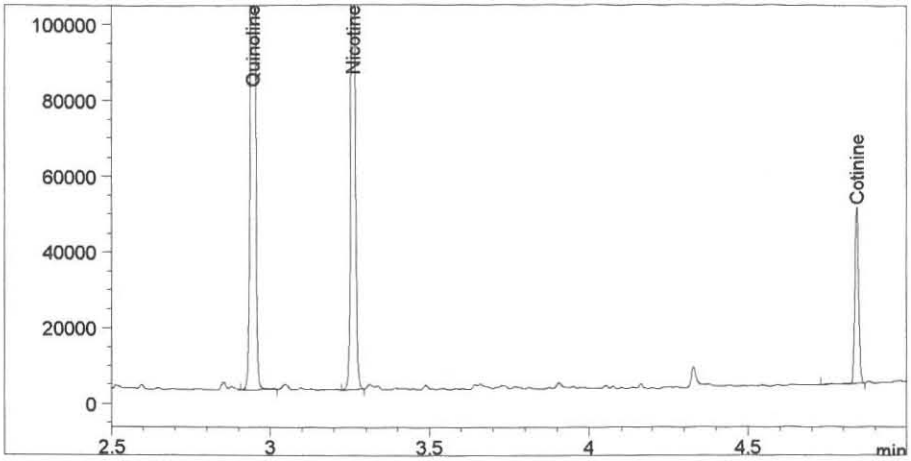


Quality Control C (Nicotine: 1.54 ng/ml, Cotinine: 15.1 ng/ml)

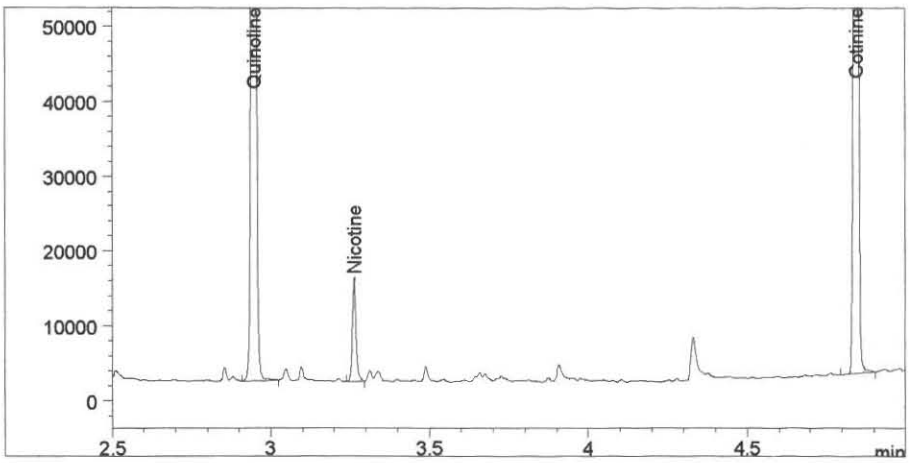


5.2.11.3 Study Samples Chromatograms

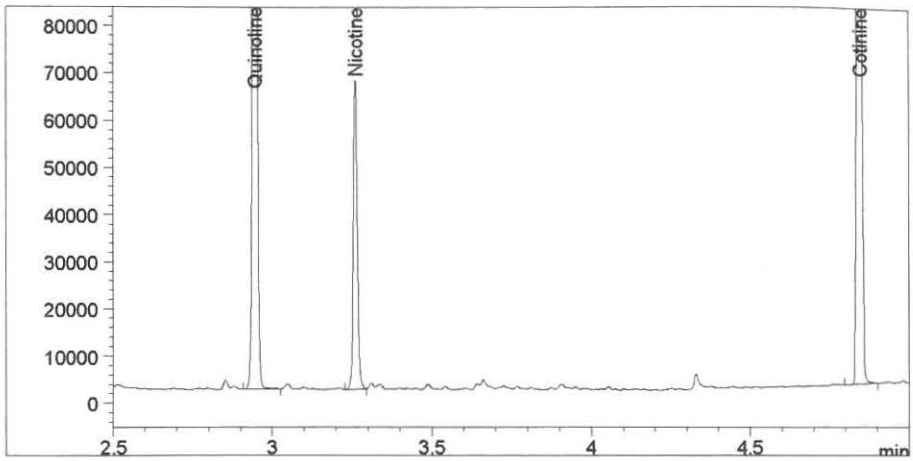
Subject 3, Day 3, B2 (Nicotine: 60.4 ng/ml. Cotinine: 74.6 ng/ml)



Subject 2, Day 2, B0 (Nicotine: 3.93 ng/ml, Cotinine: 352 ng/ml)

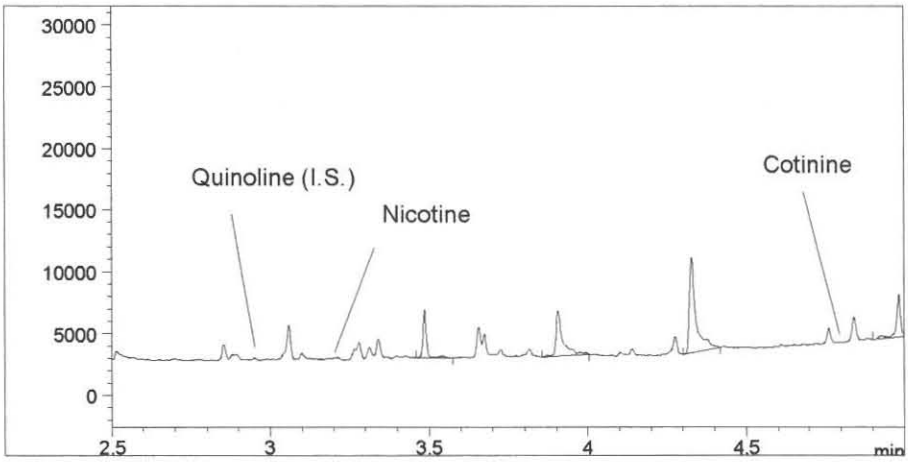


Subject 2, Day 3, B5 (Nicotine: 34.4 ng/ml, Cotinine: 710 ng/ml)

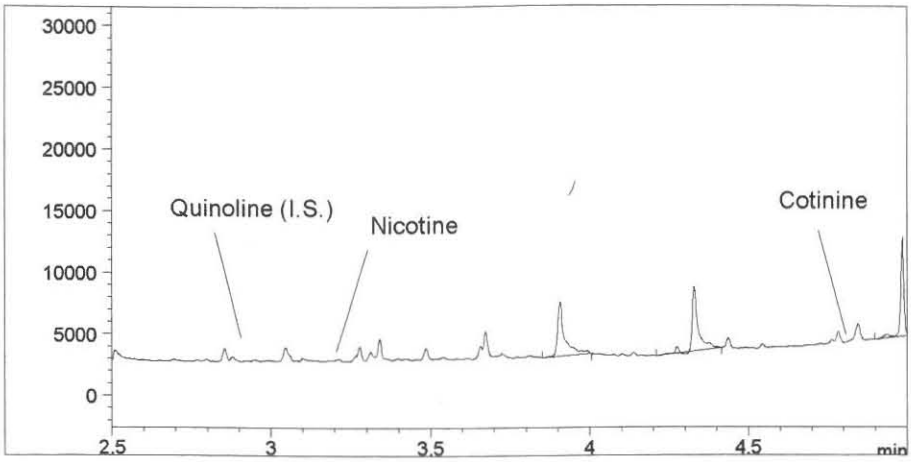


5.2.11.4 Blank Study Samples Chromatograms

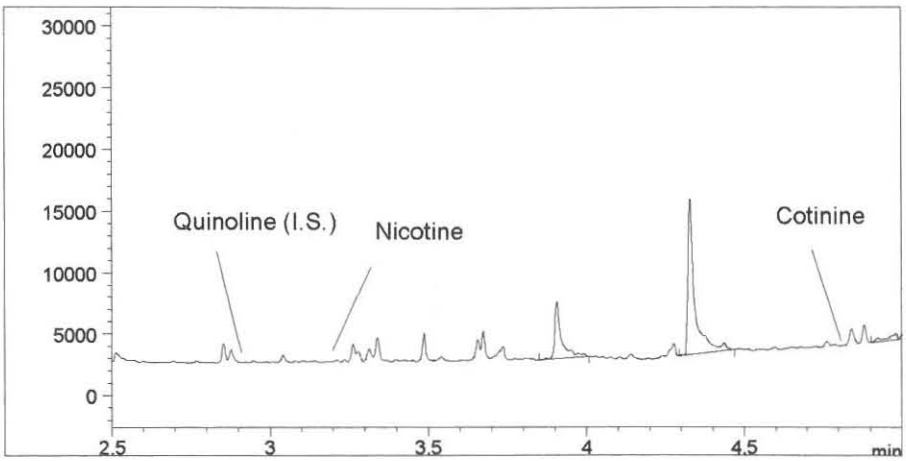
Blank Plasma 1



Blank Plasma 2



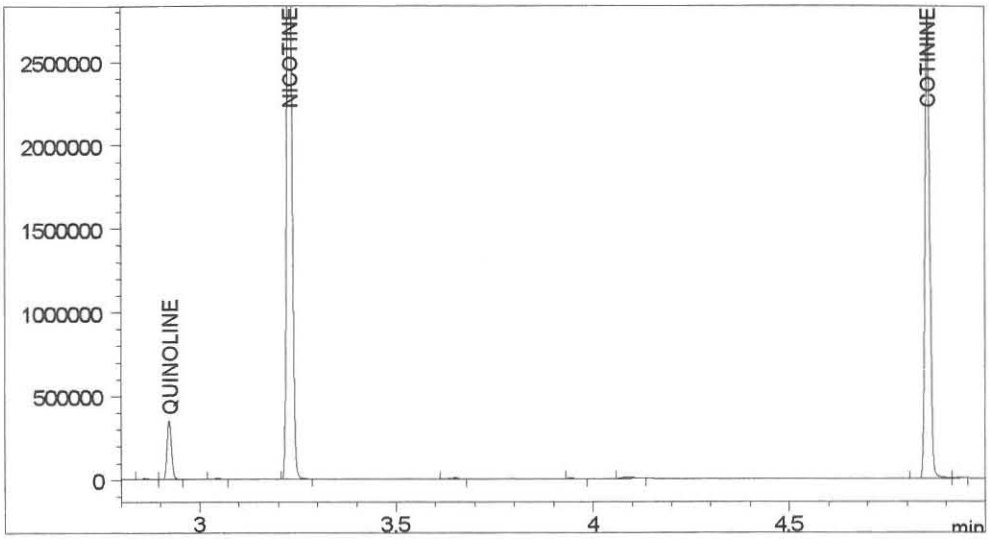
Blank Plasma 3



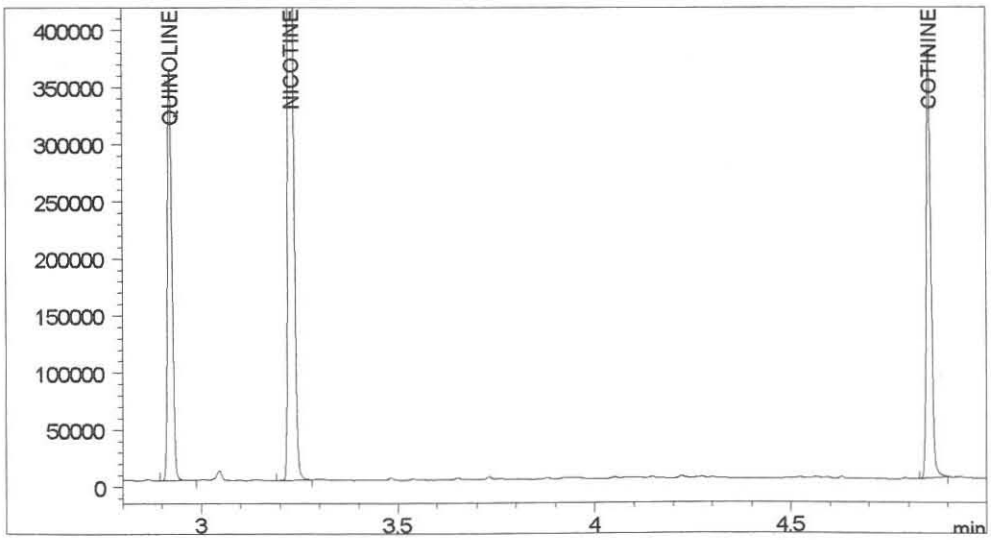
5.2.12 Representative Chromatograms of Urine extracts

5.2.12.1 Calibration Standards Chromatograms

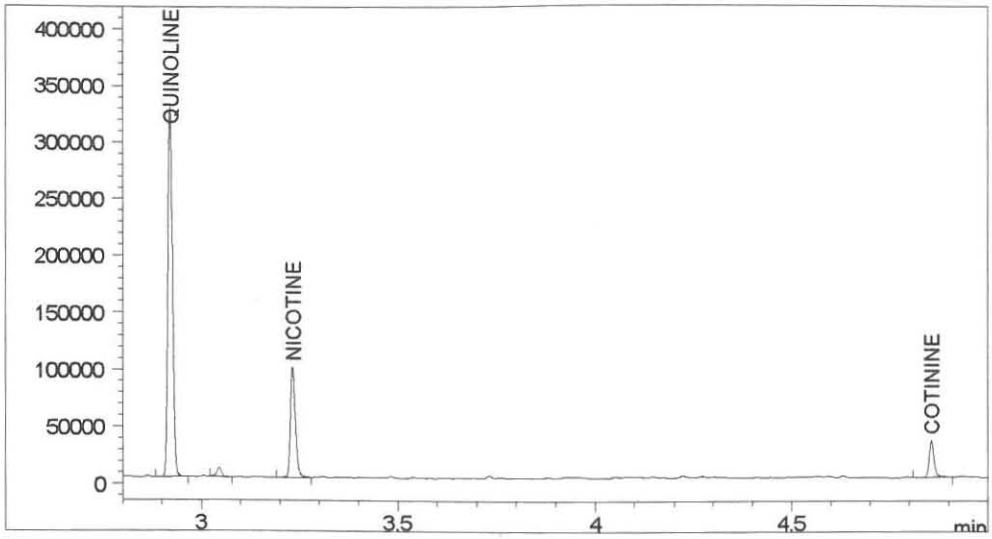
Calibration Standard M (Nicotine: 3240 ng/ml, Cotinine: 3371 ng/ml)



Calibration Standard J (Nicotine: 605 ng/ml, Cotinine: 617 ng/ml)

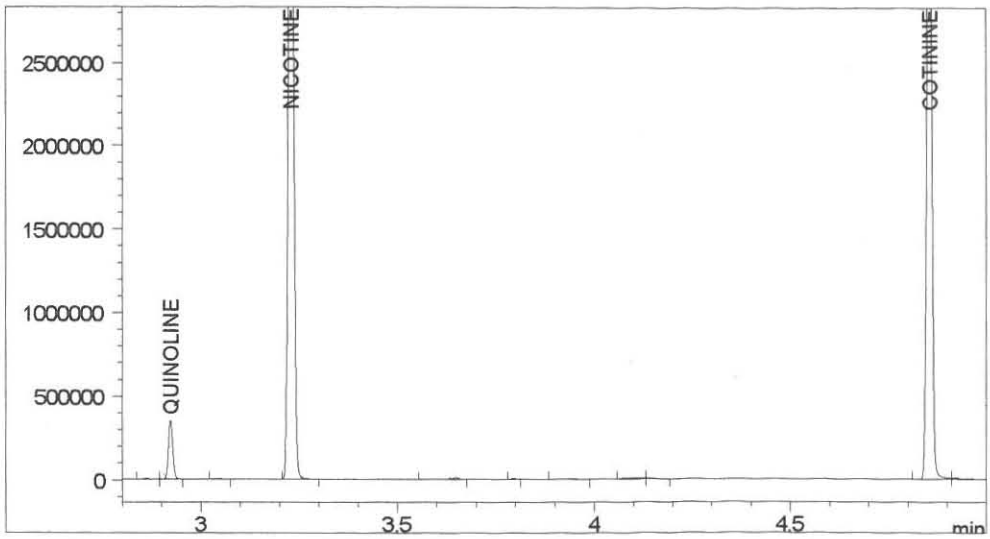


Calibration Standard G (Nicotine: 80.8 ng/ml, Cotinine: 82.3 ng/ml)

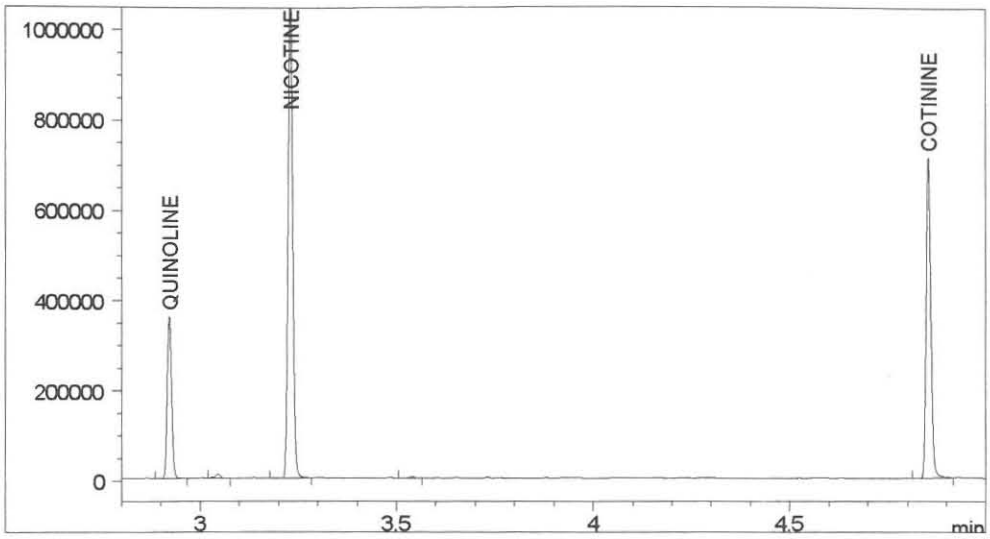


5.2.12.2 Quality Controls Chromatograms

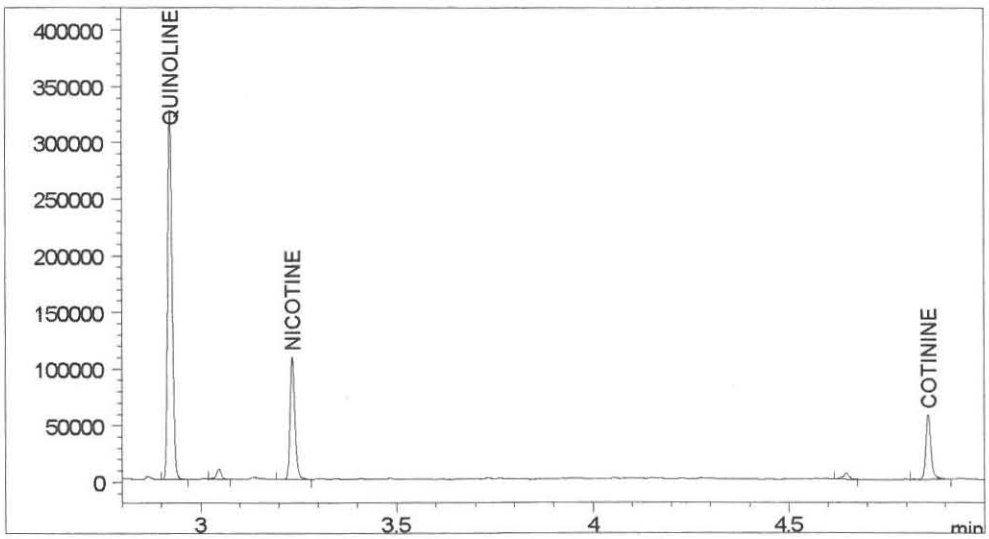
Quality Control F (Nicotine: 4277 ng/ml, Cotinine: 5048 ng/ml)



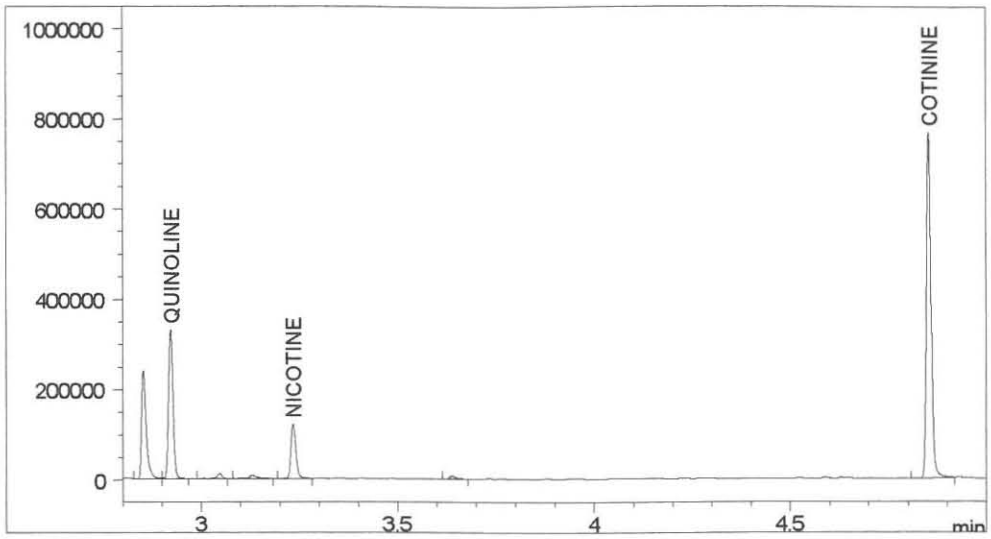
Quality Control C (Nicotine: 786 ng/ml, Cotinine: 911 ng/ml)



Quality Control B (Nicotine: 101 ng/ml, Cotinine: 117 ng/ml)

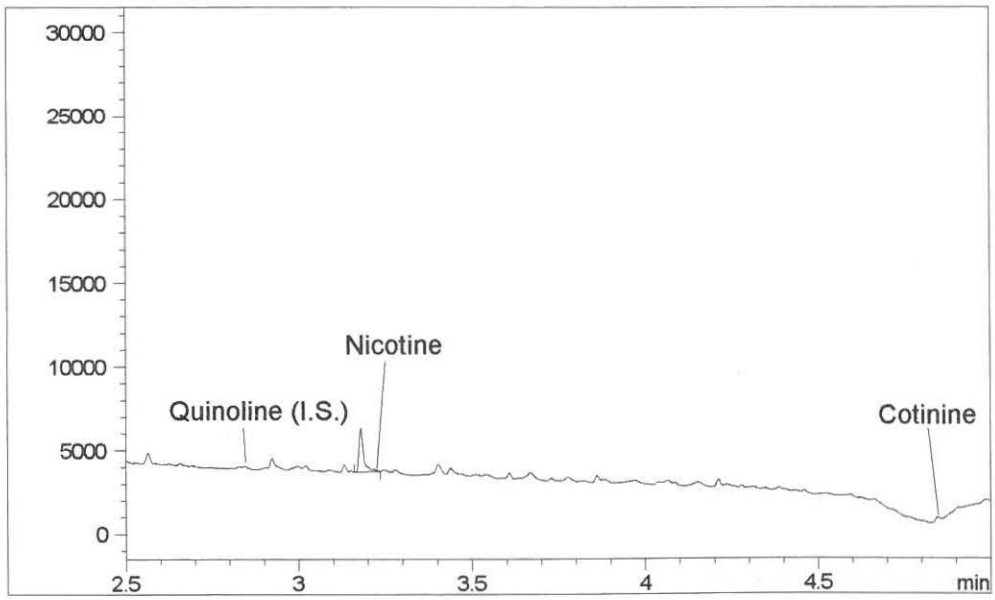


Subject 2, Day 9, Urine 1 (Nicotine: 97.3 ng/ml, Cotinine: 1126 ng/ml)

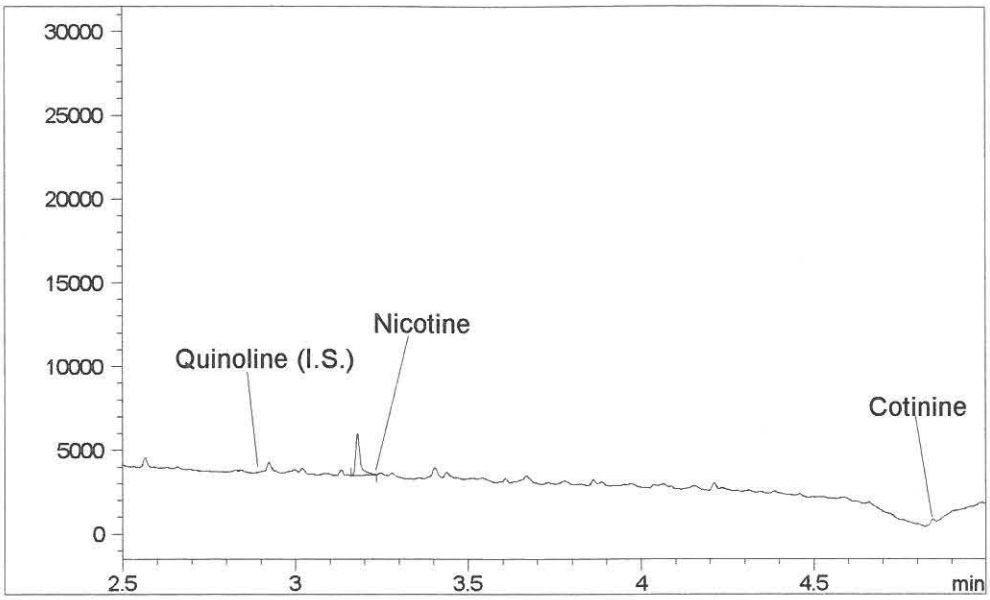


5.2.12.4 Blank Study Samples Chromatograms

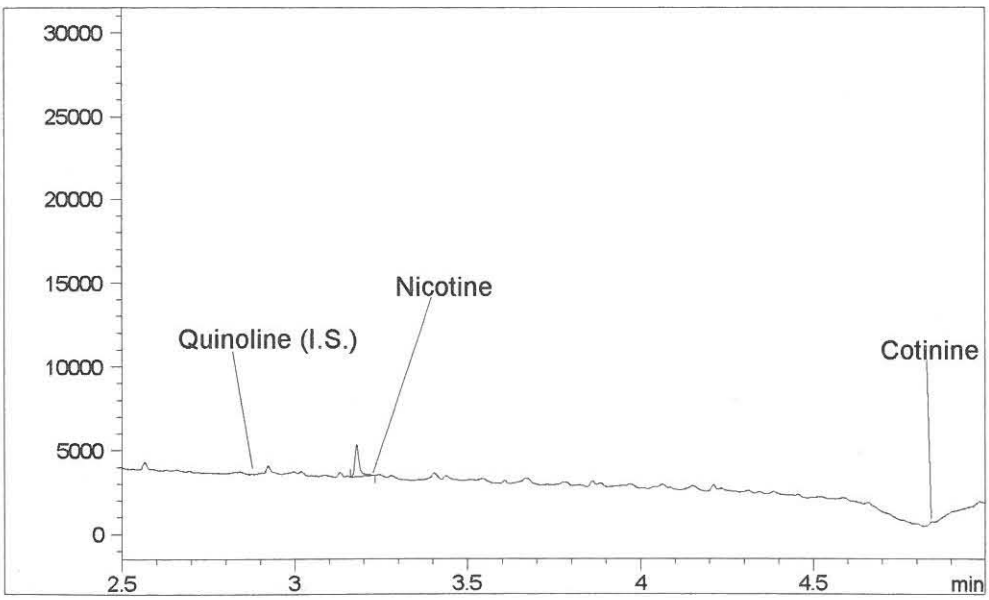
Blank Urine 1



Blank Urine 2



Blank Urine 3



6. Results

6.1 Plasma Nicotine and Cotinine Pharmacokinetics

6.1.1 Plasma Concentrations and Pharmacokinetic Variables

The actual blood sampling intervals and the plasma nicotine and cotinine concentrations (ng/ml), are presented in Appendices 9 and 12. Graphical representations of the geometric mean concentrations are depicted in figure 6.1 (nicotine) page 108 and figure 6.4 (cotinine) page111. The individual concentrations are depicted graphically in Appendices 10 (nicotine) and 13 (cotinine).

The pharmacokinetic variables C_{max}, C_{min}, T_{max}, AUD_{ss}, %PTF and T75% C_{max} for nicotine and cotinine are tabulated in Appendices 11 and 14, respectively. The geometric means, geometric standard deviation, arithmetic means, arithmetic standard deviation and ranges of the pharmacokinetic variables are presented in summary tables of the pharmacokinetic results (Tables 6.4 and 6.4.1 for nicotine and 6.5 and 6.5.1 for cotinine, respectively).

The plasma cotinine concentrations measured at 07:30 on three consecutive days of cigarette smoking, including the first morning after admission to the research centre, indicate that the study was conducted at true steady state conditions (Table 6.1.1).

Table 6.1.1 Trough Cotinine Concentrations

Mean (SD) daily (7:30) trough plasma cotinine concentrations (ng/ml) during period of cigarette smoking		
Day 1	Day 2	Day 3
290 (150)	322 (146)	327 (141)

Subject No 30 appeared to be a "puffer" who did not inhale cigarette smoke and as a consequence had very low plasma nicotine and cotinine concentrations whilst smoking cigarettes. The descriptive statistics for the nicotine and cotinine pharmacokinetic variables for the cigarette phase were therefore calculated excluding this subject. This subject was, however, included in all other analyses, and specifically in the comparison of the two replacement products.

6.1.2 Point Estimation and Confidence Intervals

The point estimates and confidence intervals for the true "test/reference" mean ratios with Quit® as the test regimen and Nicorette® as the reference regimen mean ratios of the pharmacokinetic variables C_{max}, C_{min}, AUD_{ss}, %PTF and T75% C_{max} are given in the summary table of the pharmacokinetic results (Tables 6.4 and 6.4.1 for nicotine and 6.5 and 6.5.1 for cotinine, respectively), and are presented graphically (Figures 6.2 and 6.3 for nicotine and figures 6.5 and 6.6 for cotinine).

6.1.2.1 Nicotine:

The point estimates of the "test/reference" mean ratio of the variables C_{max}, C_{min}, %PTF and T75% C_{max} are 81%, 111%, 59% and 124%, respectively. The point estimate of the mean ratio of the variable AUDC is 90%.

The 90% confidence interval for the "test/reference" mean ratio of the variables C_{max}, C_{min}, %PTF and T75% T_{max} are 74% to 87%, 102 to 119%, 51% to 68% and 96% to 161% respectively. The 90% confidence interval of the "test/reference" mean ratio of AUDC is 84% to 97%. Based on C_{max} and AUDC, Quit® and Nicorette® are bioequivalent with regard to the rate and extent of absorption of nicotine.

6.1.2.2 Cotinine:

The estimates of "test/reference" mean ratio of the variables C_{max}, C_{min}, %PTF and T75%C_{max} are 108%, 111% 91 and 134%, respectively. The estimate of the mean ratio of the variable AUDC is 109%.

The 90% confidence intervals for the "test/reference" mean ratios of the variables C_{max}, C_{min}, %PTF and T75% Cmax are 100% to 116%, 104 to 118%, 82% to 100% and 108 to 166%, respectively. The 90% confidence interval of the "test/reference" mean ratio of AUDC is 102% to 116%. Based on C_{max} and AUDC, Quit® and Nicorette® are bioequivalent.

6.2 Urine Nicotine and Cotinine Pharmacokinetics

Results pertaining to nicotine and cotinine excretion in urine at steady state over 24 hours are discussed and presented below.

6.2.1 Fractional and Cumulative Urine Volume Data

The fractional and cumulative urine data (0 to 24 hours) are presented in Appendix 5. Geometric mean urine excretion (ml) on the third day of each regimen was as follows: 1803 (cigarettes), 1738 (Nicorette®) and 1645 (Quit®).

6.2.2 Urine Nicotine and Cotinine Concentration Data

The urine nicotine and cotinine concentration data are presented in Appendix 6.

6.2.3 Cumulative Urinary Nicotine Excretion Data

The cumulative urinary nicotine excretion data (0 to 24 hours) are presented in Appendix 7 (Figure 7). Geometric mean urinary excretion of nicotine (µg) was as follows: 3151 (cigarettes), 468, (Nicorette®) and 513 (Quit®).

6.2.4 Cumulative Urinary Cotinine Excretion Data

The cumulative urinary cotinine excretion data (0 to 24 hours) are presented in Appendix 8 (Figure 8). Geometric mean urinary excretion of cotinine (µg) was as follows: 3666 (cigarettes), 1439 (Nicorette®) and 1591 (Quit®).

6.2.5 Point Estimation and Confidence Intervals (0 to 24 hours)

6.2.5.1 Urine Volume

S A S
FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINE VOLUMES (ml)
Treatment 1 : CIGARETTES (Reference 1)
Treatment 2 : NICORETTE® (Reference 2)
Treatment 3 : QUIT® (Test)
Variable : 0 - 24h

GEOMETRIC MEANS

TREATMENT 1	1802.550
TREATMENT 2	1737.683
TREATMENT 3	1644.623

POINT AND CONFIDENCE INTERVAL ESTIMATES

t-Value	Degrees of Freedom	Alpha
1.9966	66	0.05
1.6683	66	0.10

Diff.	Ratio (%)	Point Estimate	95 % C.I.	90% C.I.
2 - 1		-64.9	(-265 : 161.3)	(-234 : 122.2)
	2 / 1	96.4	(85.3 : 108.9)	(87.0 : 106.8)
3 - 1		-158	(-347 : 56.13)	(-318 : 19.11)
	3 / 1	91.2	(80.7 : 103.1)	(82.4 : 101.1)
3 - 2		-93.1	(-282 : 121.0)	(-253 : 83.98)
	3 / 2	94.6	(83.7 : 107.0)	(85.4 : 104.8)

These data are clear proof of the reproducibility of the clinical method in as far as urine production under the given experimental conditions is concerned.

6.2.5.2 Nicotine Excretion

S A S
FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY (NICOTINE) EXCRETION (µg)
Treatment 1 : CIGARETTES (Reference 1)
Treatment 2 : NICORETTE® (Reference 2)
Treatment 3 : QUIT® (Test)
Variable : 0 - 24h

GEOMETRIC MEANS

TREATMENT 1	3150.672
TREATMENT 2	468.068
TREATMENT 3	513.392

POINT AND CONFIDENCE INTERVAL ESTIMATES

t-Value	Degrees of Freedom	Alpha
1.9966	66	0.05
1.6683	66	0.10

Diff.	Ratio (%)	Point Estimate	95 % C.I.	90% C.I.
2 - 1		-2683	(-2772 : -2572)	(-2758 : -2592)
	2 / 1	14.9	(12.0 : 18.4)	(12.4 : 17.7)
3 - 1		-2637	(-2735 : -2516	(-2721 : -2538)
	3 / 1	16.3	(13.2 : 20.1)	(13.7 : 19.4)
3 - 2		45.32	(-52.6 : 166.4)	(-37.9 : 144.7)
	3 / 2	109.7	(88.8 : 135.5)	(91.9 : 130.9)

The four- to five-fold difference in plasma nicotine C_{max} between smoking cigarettes and application of nicotine in the form of Quit® or Nicorette® is reflected in the six- to seven-fold difference in 24 hour urinary excretion of nicotine. This also applies to AUD_{ss}, in which case the difference between smoking of cigarettes and application of Quit® and Nicorette® is about four-fold. In contrast to plasma nicotine versus time data, Quit® administration gave rise to

higher 24 hour urinary excretion of nicotine than Nicorette® administration, although the difference was not significant.

6.2.5.3 Cotinine Excretion

S A S
FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY (COTININE) EXCRETION (µg)
Treatment 1 : CIGARETTES (Reference 1)
Treatment 2 : NICORETTE® (Reference 2)
Treatment 3 : QUIT® (Test)
Variable : 0 - 24h

GEOMETRIC MEANS

TREATMENT 1	3665.682
TREATMENT 2	1438.525
TREATMENT 3	1591.276

POINT AND CONFIDENCE INTERVAL ESTIMATES

t-Value	Degrees of Freedom	Alpha
1.9966	66	0.05
1.6683	66	0.10

Diff.	Ratio (%)	Point Estimate	95 % C.I.	90% C.I.
2 - 1		-2227	(-2443 : -1973)	(-2410 : -2017)
	2 / 1	39.2	(33.3 : 46.2)	(34.2 : 45.0)
3 - 1		-2074	(-2314 : -1793	(-2277 : -1842)
	3 / 1	43.4	(36.9 : 51.1)	(37.9 : 49.7)
3 - 2		152.8	(-86.5 : 434.3)	(-49.8 : 384.8)
	3 / 2	110.6	(94.0 : 130.2)	(96.5 : 126.7)

The almost two-and-a-half-fold difference in plasma cotinine C_{max} and AUD_{ss} between smoking of cigarettes and application of nicotine in the form of Quit® or Nicorette® is mimicked by the

same margin of difference in 24 hour urinary excretion of cotinine. As with nicotine, the urinary excretion of cotinine was marginally higher with Quit® compared to Nicorette®, which is in contrast with plasma cotinine concentration versus time data.

6.3 Summary Figures

PLASMA NICOTINE CONCENTRATION AT STEADY STATE

Geometric mean values (n = 34)

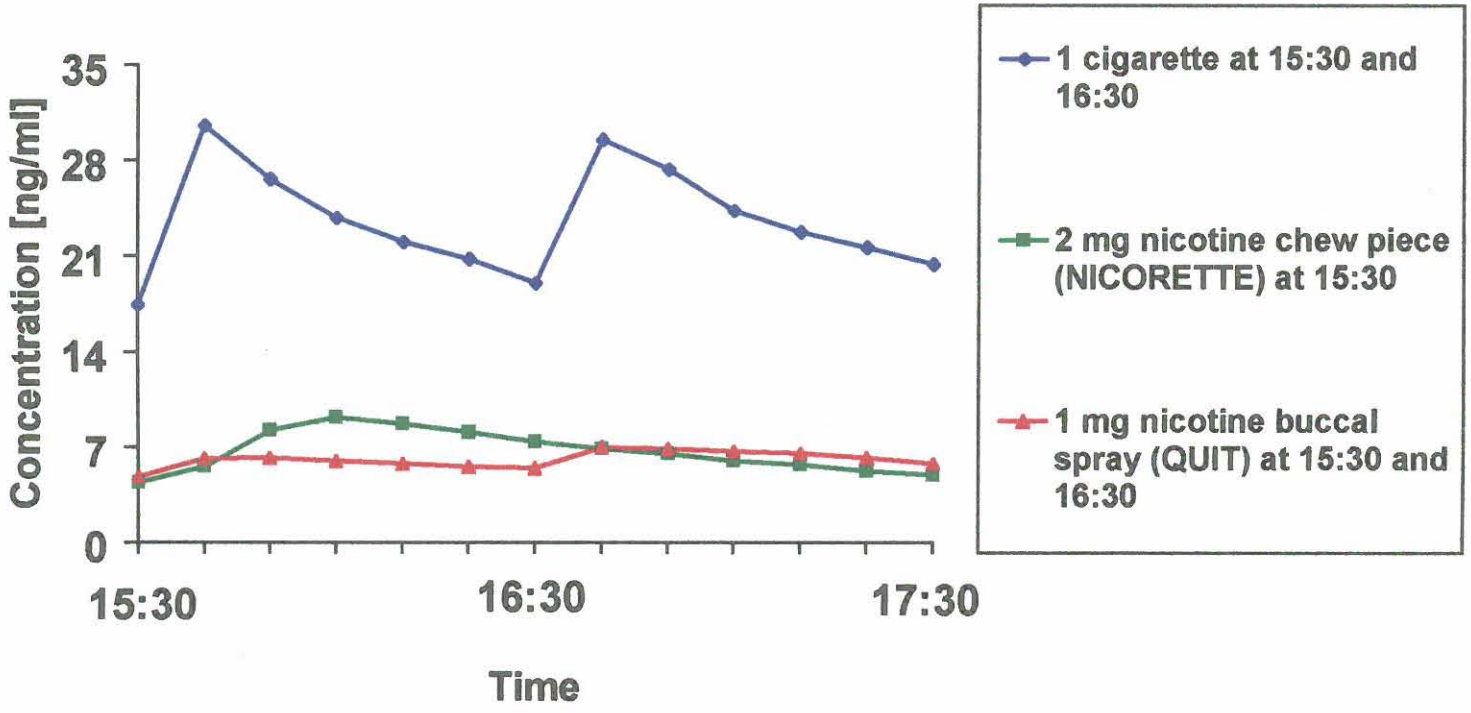


Figure 6.1: Plasma Nicotine Concentration at Steady State

Figure 6.2: Nicotine Pharmacokinetic variables C_{min}, AUD_{ss}, %PTF, $T75\%C_{max}$

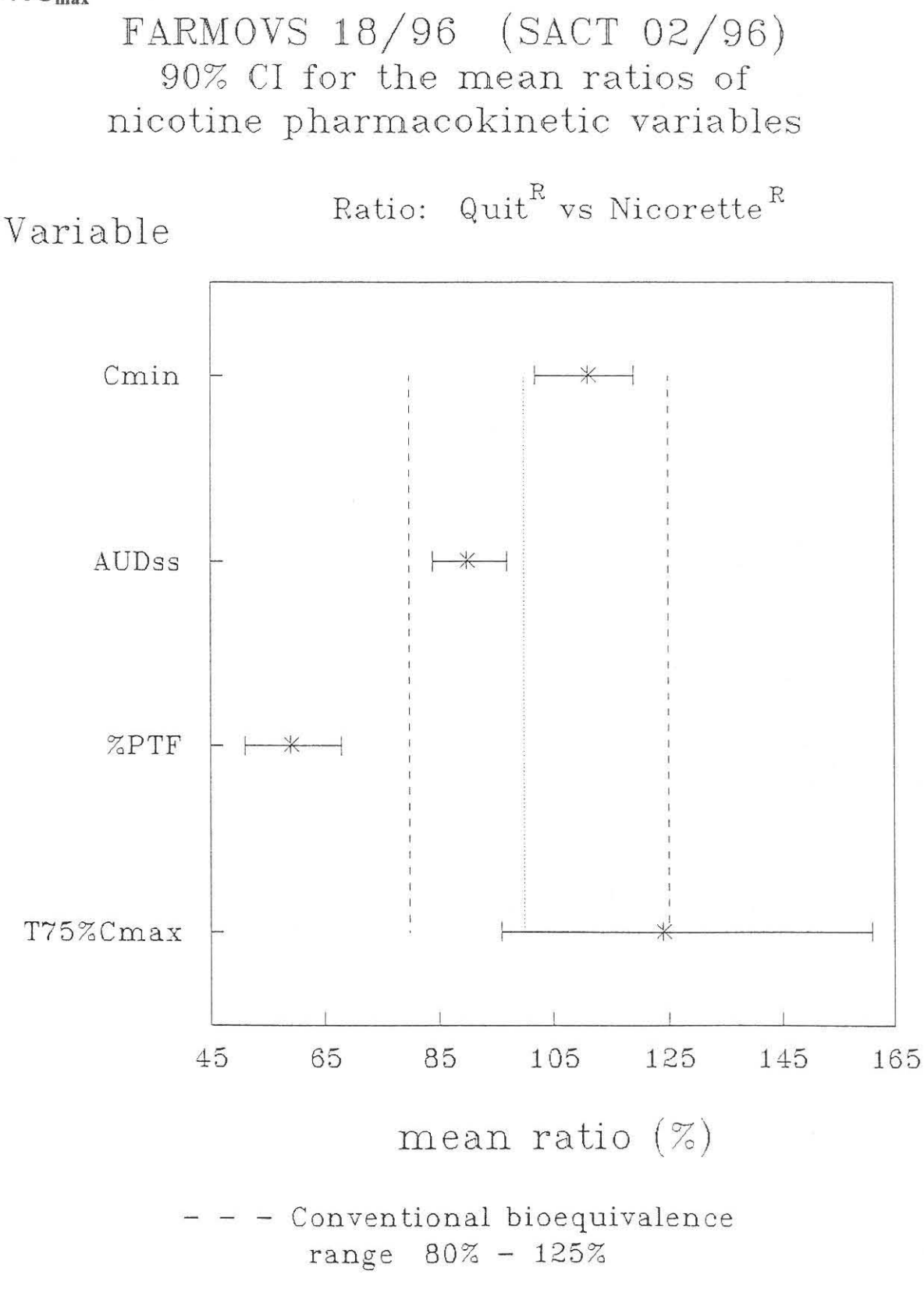
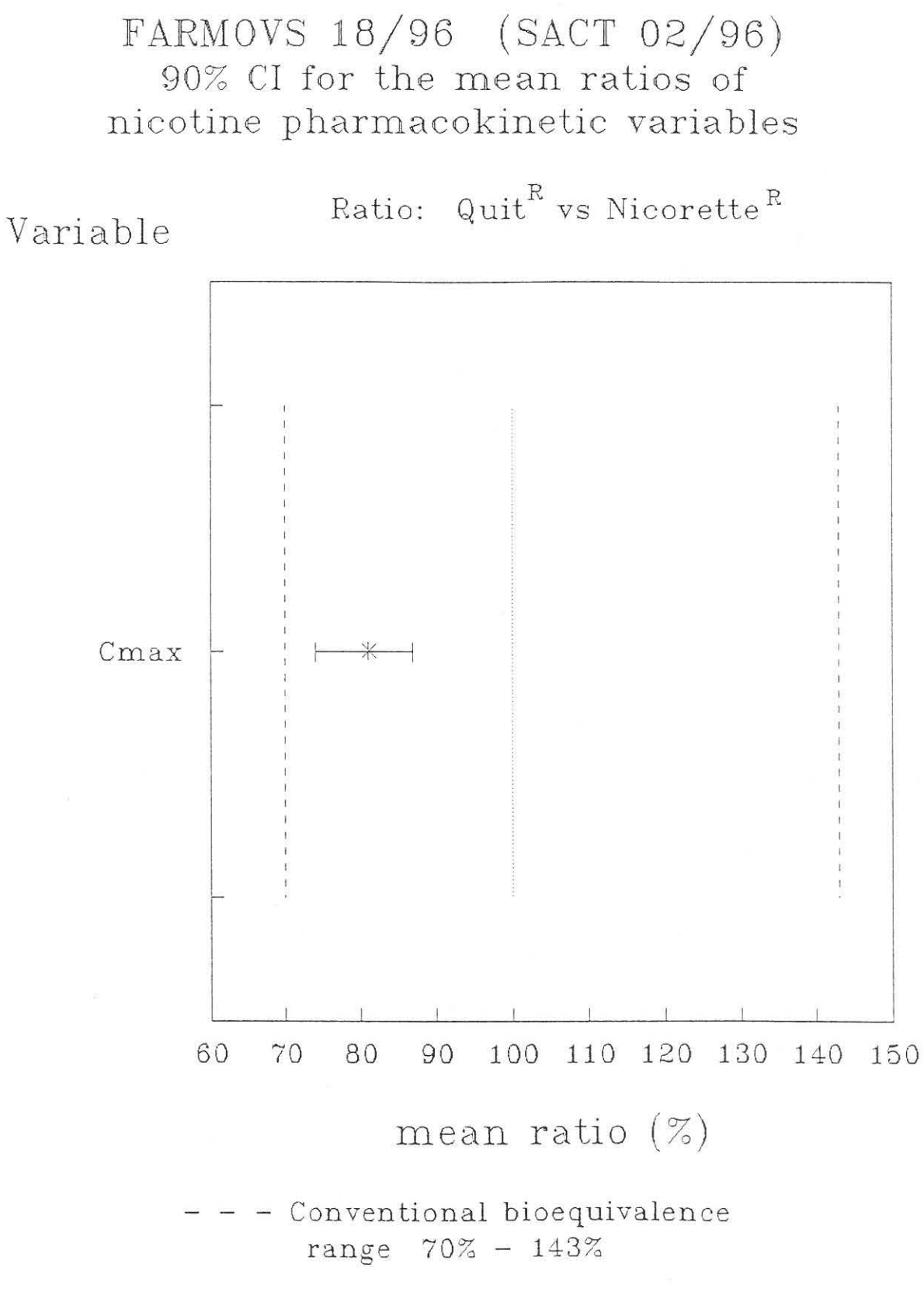


Figure 6.3: Nicotine Pharmacokinetic Variable C_{max}



PLASMA COTININE CONCENTRATION AT STEADY STATE

Geometric mean values (n = 34)

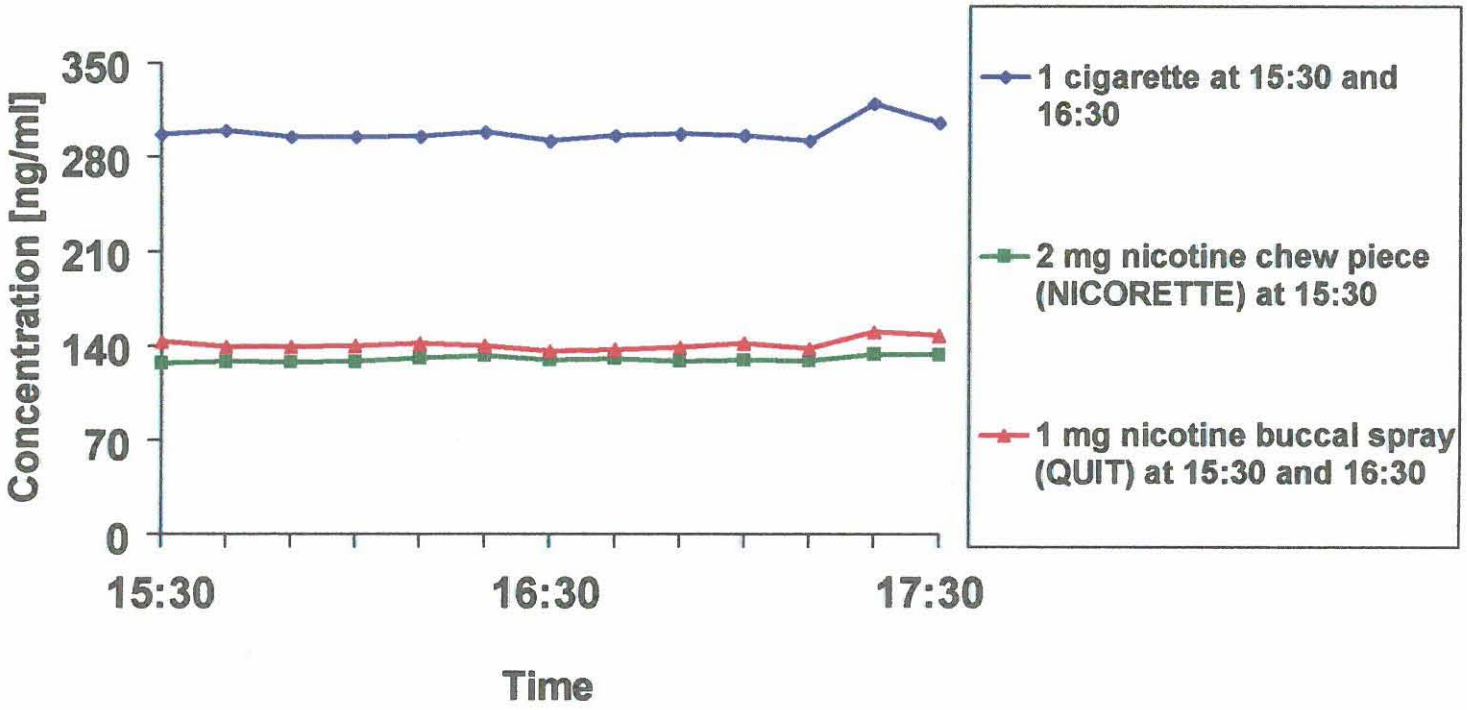


Figure 6.4: Plasma Cotinine Concentration at Steady State

Figure 6.5: Cotinine Pharmacokinetic Variables C_{min}, AUD_{ss}, %PTF, $T75\%C_{max}$

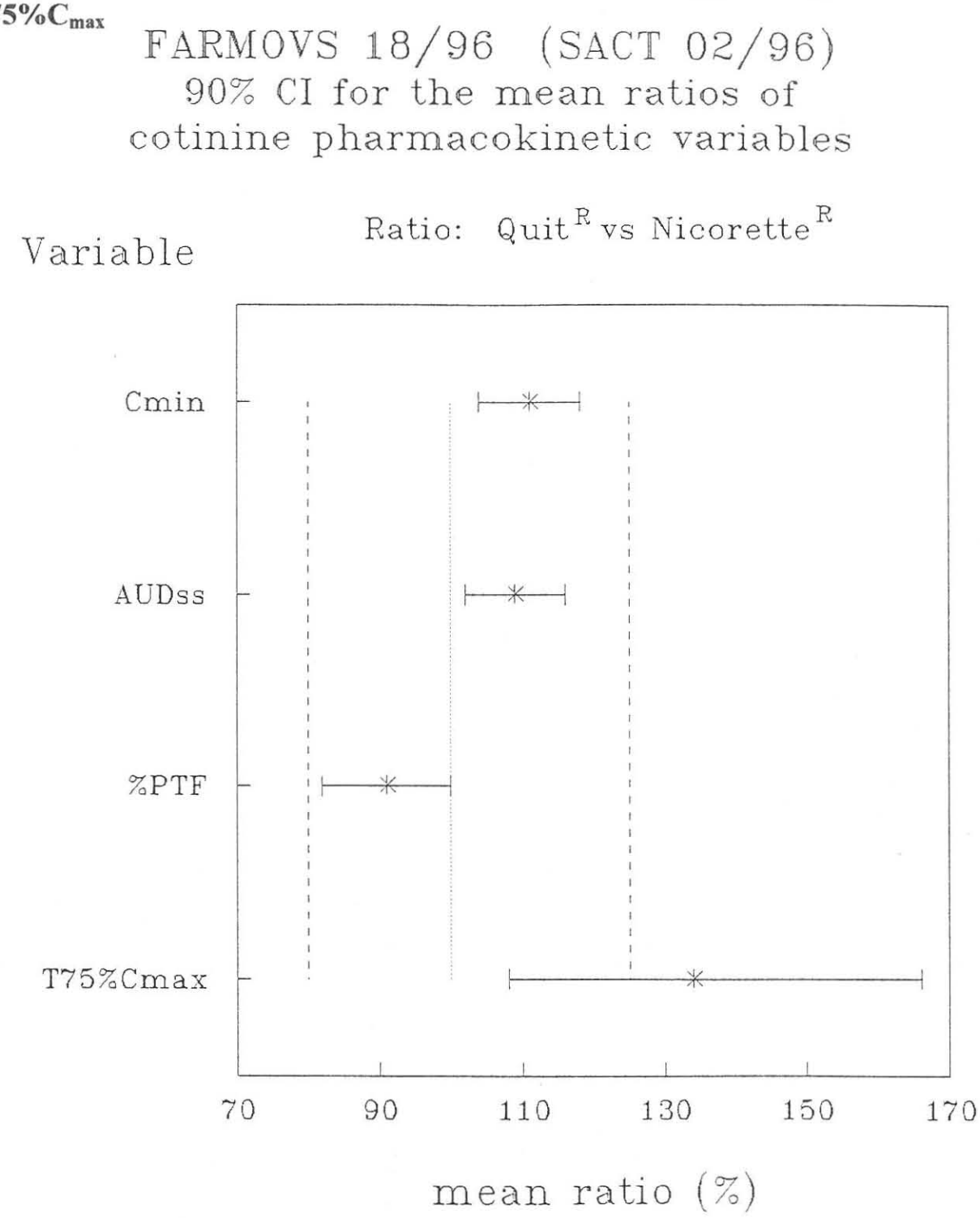
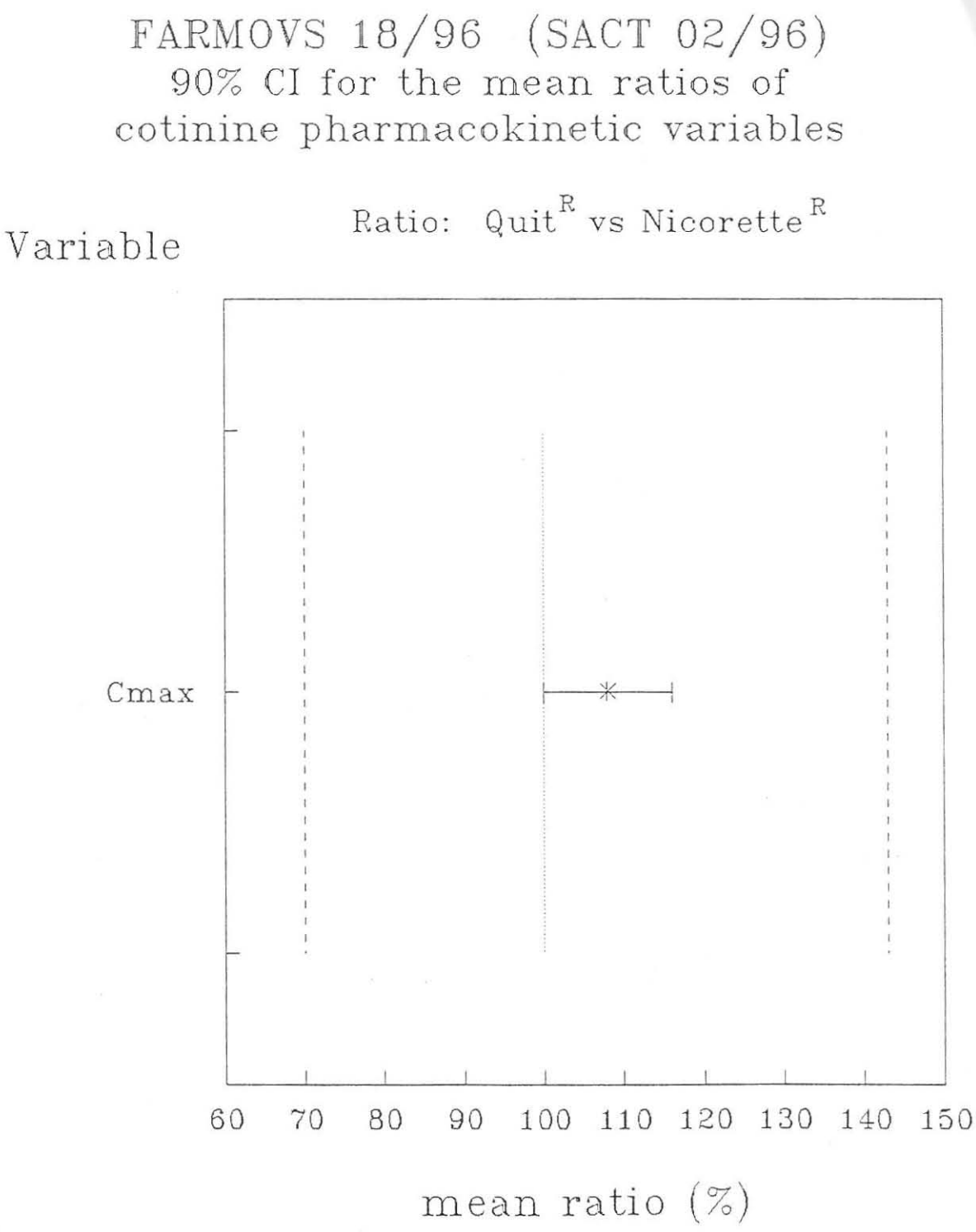


Figure 6.6: Cotinine Pharmaco... e C_{max}



6.4 Summary Tables

Table 6.4
Summary of Pharmacokinetic Data for Nicotine, Nicorette® (Reference) and Quit® (Test).

Table 6.4.1
Summary of Pharmacokinetic Data for Nicotine, Cigarettes, Nicorette® (Reference) and Quit® (Test).

Table 6.5
Summary of Pharmacokinetic Data for Cotinine, Nicorette® (Reference) and Quit® (Test).

Table 6.5.1
Summary of Pharmacokinetic Data for Cotinine, Cigarettes, Nicorette® (Reference) and Quit® (Test).

FARMOVS 18/96

SUMMARY OF PHARMACOKINETIC DATA FOR NICOTINE

(n = 34)

		NICORETTE® (Reference) Dose: 2 mg nicotine chew piece 2-hourly			**QUIT®** (Test) Dose: 1 mg nicotine buccal spray 1-hourly					
VARIABLE	**UNIT**	**GEOMETRIC MEAN**	**SD**	RANGE	**GEOMETRIC MEAN**	**SD**	RANGE	**MEAN RATIO (%)***	**90% CONFIDENCE INTERVAL (%)****	**INTRA-INDIVIDUAL CV (%)**
C_{max} (0-2h)	(ng/ml)	**9.39**	1.37	5.58 - 32.4	**7.54**	1.50	2.66 - 26.2	**81**	74 - 87	19.6
C_{max} (0-1h)	(ng/ml)				**6.56**	1.48	2.66 - 25.7			
C_{max} (1-2h)	(ng/ml)				**7.45**	1.51	2.29 - 26.2			
C_{min} (0-2h)	(ng/ml)	**4.28**	1.53	2.32 - 25.8	**4.70**	1.60	1.59 - 23.0	**111**	102 - 119	18.6
C_{min} (0-1h)	(ng/ml)				**4.74**	1.61	1.59 - 23.0			
C_{min} (1-2h)	(ng/ml)				**5.23**	1.58	1.64 - 23.0			
$T_{max}^{\#}$ (0-2h)	(h)	**0.50**		0.33 - 1.33						
$T_{max}^{\#}$ (0-1h)	(h)				**0.31**		0.0 - 1.00			
$T_{max}^{\#}$ (1-2h)	(h)				**0.33**		0.15 - 1.00			
AUD_{ss}	(ng·h/ml)	**13.7**	1.41	8.61 - 57.9	**12.3**	1.52	4.39 - 49.9	**90**	84 - 97	18.0
%PTF	(%)	**71.8**	1.38	22.7 - 107	**42.2**	1.58	12.5 - 90.8	**59**	51 - 68	35.6
T75%C_{max}	(h)	**0.86**	1.48	0.47 - 2.00	**1.06**	2.12	0.13 - 2.00	**124**	96 - 161	69.9

* : Estimate of "test/reference" mean ratio from analysis of variance of log-transformed data.

** : 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

\# : Medians and ranges.

Table 6.4: Summary of Pharmacokinetic Data for Nicotine, Nicorette® (Reference) and Quit® (Test)

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SUMMARY OF PHARMACOKINETIC DATA FOR NICOTINE

		CIGARETTES Dose: 1 cigarette 1-hourly (n = 33)##			**NICORETTE®** (Reference) Dose: 2 mg nicotine chew piece 2-hourly (n = 34)			**QUIT®** (Test) Dose: 1 mg nicotine buccal spray 1-hourly (n = 34)		
VARIABLE	**UNIT**	**GEOMETRIC MEAN**	**SD**	RANGE	**GEOMETRIC MEAN**	**SD**	RANGE	**GEOMETRIC MEAN**	**SD**	RANGE
C_{max} (0-2h)	(ng/ml)	**35.1**	1.33	18.1 - 60.4	**9.39**	1.37	5.58 - 32.4	**7.54**	1.50	2.66 - 26.2
C_{max} (0-1h)	(ng/ml)	**33.3**	1.34	18.1 - 60.4				**6.56**	1.48	2.66 - 25.7
C_{max} (1-2h)	(ng/ml)	**32.6**	1.33	15.5 - 58.6				**7.45**	1.51	2.29 - 26.2
C_{min} (0-2h)	(ng/ml)	**18.6**	1.49	7.09 - 54.2	**4.28**	1.53	2.32 - 25.8	**4.70**	1.60	1.59 - 23.0
C_{min} (0-1h)	(ng/ml)	**18.7**	1.49	7.09 - 54.2				**4.74**	1.61	1.59 - 23.0
C_{min} (1-2h)	(ng/ml)	**20.0**	1.45	9.02 - 55.1				**5.23**	1.58	1.64 - 23.0
T_{max}# (0-2h)	(h)				**0.50**		0.33 - 1.33			
T_{max}# (0-1h)	(h)	**0.17**		0.17 - 0.50				**0.31**		0.0 - 1.00
T_{max}# (1-2h)	(h)	**0.17**		0.17 - 1.00				**0.33**		0.15 - 1.00
AUD_{ss}	(ng·h/ml)	**51.9**	1.36	26.1 - 114	**13.7**	1.41	8.61 - 57.9	**12.3**	1.52	4.39 - 49.9
%PTF	(%)	**58.3**	1.62	10.8 - 137	**71.8**	1.38	22.7 - 107	**42.2**	1.58	12.5 - 90.8
T75%C_{max}	(h)	**0.73**	2.00	0.19 - 2.00	**0.86**	1.48	0.47 - 2.00	**1.06**	2.12	0.13 - 2.00

: Medians and ranges.

: Excluding subject 30.

Table 6.4.1: Summary of Pharmacokinetic Data for Nicotine, Cigarettes, Nicorette® (Reference) and Quit® (Test)

Table 6.5: Summary of Pharmacokinetic Data for Cotinine, Nicorette® (Reference) and Quit® (Test)

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SUMMARY OF PHARMACOKINETIC DATA FOR COTININE

(n = 34)

		NICORETTE® (Reference) Dose: 2 mg nicotine chew piece 2-hourly			QUIT® (Test) Dose: 1 mg nicotine buccal spray 1-hourly					
VARIABLE	**UNIT**	**GEOMETRIC MEAN**	**SD**	RANGE	**GEOMETRIC MEAN**	**SD**	RANGE	**MEAN RATIO (%)***	**90% CONFIDENCE INTERVAL (%)****	**INTRA-INDIVIDUAL CV (%)**
C_{max} (0-2h)	(ng/ml)	**152**	1.41	54.8 - 369	**163**	1.42	45.8 - 301	**108**	100 - 116	17.7
C_{max} (0-1h)	(ng/ml)				**152**	1.42	45.8 - 284			
C_{max} (1-2h)	(ng/ml)				**158**	1.44	35.9 - 301			
C_{min} (0-2h)	(ng/ml)	**114**	1.39	33.7- 233	**125**	1.44	30.4 - 240	**111**	104 - 118	15.2
C_{min} (0-1h)	(ng/ml)				**128**	1.45	30.8 - 249			
C_{min} (1-2h)	(ng/ml)				**128**	1.44	30.4 - 245			
$T_{max}^{\#}$ (0-2h)	(h)	**1.58**		0.0 - 2.00						
$T_{max}^{\#}$ (0-1h)	(h)				**0.50**		0.0 - 1.00			
$T_{max}^{\#}$ (1-2h)	(h)				**0.83**		0.0 - 1.00			
AUD_{ss}	(ng·h/ml)	**260**	1.38	84.4 - 577	**281**	1.43	71.4 - 518	**109**	102 - 116	16.1
%PTF	(%)	**27.3**	1.56	12.9 - 61.3	**24.7**	1.50	9.14 - 49.5	**91**	82 - 100	23.9
$T75\%C_{max}$	(h)	**1.16**	2.32	0.13 - 2.0	**1.56**	1.49	0.60 - 2.00	**134**	108 - 166	55.9

* : Estimate of "test/reference" mean ratio from analysis of variance of log-transformed data.

** : 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

: Medians and ranges.

FARMOVS 18/96

SUMMARY OF PHARMACOKINETIC DATA FOR COTININE

		CIGARETTES Dose: 1 cigarette 1-hourly (n = 33)##			NICORETTE® (Reference) Dose: 2 mg nicotine chew piece 2-hourly (n = 34)			QUIT® (Test) Dose: 1 mg nicotine buccal spray 1-hourly (n = 34)		
VARIABLE	**UNIT**	**GEOMETRIC MEAN**	**SD**	RANGE	**GEOMETRIC MEAN**	**SD**	RANGE	**GEOMETRIC MEAN**	**SD**	RANGE
C_{max} (0-2h)	(ng/ml)	**369**	1.52	79.3 - 709	**152**	1.41	54.8 - 369	**163**	1.42	45.8 - 301
C_{max} (0-1h)	(ng/ml)	**346**	1.51	79.3 - 709				**152**	1.42	45.8 - 284
C_{max} (1-2h)	(ng/ml)	**358**	1.53	65.3 - 589				**158**	1.44	35.9 - 301
C_{min} (0-2h)	(ng/ml)	**285**	1.53	55.1 -521	**114**	1.39	33.7- 233	**125**	1.44	30.4 - 240
C_{min} (0-1h)	(ng/ml)	**291**	1.52	62.4 - 543				**128**	1.45	30.8 - 249
C_{min} (1-2h)	(ng/ml)	**292**	1.53	55.1 - 534				**128**	1.44	30.4 - 245
T_{max}# (0-2h)	(h)				**1.58**		0.0 - 2.00			
T_{max}# (0-1h)	(h)	**0.50**		0.0 - 1.00				**0.50**		0.0 - 1.00
T_{max}# (1-2h)	(h)	**0.83**		0.0 - 1.00				**0.83**		0.0 - 1.00
AUD_{ss}	(ng·h/ml)	**641**	1.52	130 - 1165	**260**	1.38	84.4 - 577	**281**	1.43	71.4 - 518
%PTF	(%)	**24.1**	1.53	9.51 - 54.9	**27.3**	1.56	12.9 - 61.3	**24.7**	1.50	9.14 - 49.5
T75%C_{max}	(h)	**1.39**	1.89	0.21 - 2.00	**1.16**	2.32	0.13 - 2.0	**1.56**	1.49	0.60 - 2.00

: Medians and ranges.

: Excluding subject 30.

Table 6.5.1: Summary of Pharmacokinetic Data for Cotinine, Cigarettes, Nicorette® (Reference) and Quit® (Test)

6.5 Safety and Tolerance

6.5.1 Symptoms and Signs

A summary of the information on the questionnaires is included in Table 6.5.1.1. A total of 34 volunteers completed a questionnaire. The intensity and frequency of events were similar between the two replacement products. A detailed listing is given in Appendix 16. In addition to these events, 3 volunteers complained of symptoms of influenza (common cold). Two volunteers were withdrawn from the study since they required symptomatic treatment. The third volunteer did not require treatment and completed the study.

Table 6.5.1.1 Adverse Effects As Per Questionnaire

Event:	Number of subjects who recorded the event	
	Quit®	Nicorette®
* Heartburn	16	18
* Bloated feeling	11	11
* Hiccups	13	8
* Sneezing	9	3
* Abnormal dreams	7	5
# Raw/burning sensation of mouth, tongue and/or throat	5	7
# Cough	-	1
# Mucous in throat	-	1
# Nausea	-	1
# Feeling of constriction	1	1
# Numbness of cheek	1	-
# Burping	-	3

* Specified in questionnaire, # Volunteered

6.5.2 Clinical Laboratory Tests (Haematology and Clinical Chemistry)

Some pre- and post-study laboratory values for some subjects were outside the "normal ranges", but these were not considered clinically relevant.

6.6 Volunteer Preference

Subjectively twenty-nine out of the 34 volunteers (two withdrawals) rated Quit®, as prescribed, higher than Nicorette®, as prescribed, with respect to suppression of the craving to smoke. Four volunteers were undecided, whilst one preferred Nicorette®.

Table 6.6: Volunteer Preference

Q = Quit® Nic = Nicorette® Ph = Phase

Subj. No.	Ph 1	Ph 2	Prefer	Subj. No.	Ph 1	Ph 2	Prefer	Subj. No.	Ph 1	Ph 2	Prefer
1	Nic	Q	Q	13	Q	Nic	Q	25	Drop-Out		
2	Q	Nic	Q	14	Nic	Q	Q	26	Nic	Q	Q
3	Nic	Q	Q	15	Nic	Q	Q	27	Q	Nic	Q
4	Q	Nic	Q	16	Q	Nic	Q	28	Q	Nic	Q
5	Q	Nic	Q	17	Q	Nic	Q	29	Nic	Q	Q
6	Nic	Q	Q	18	Nic	Q	Q	30	Nic	Q	Neither
7	Nic	Q	Nic	19	Nic	Q	Neither	31	Q	Nic	Q
8	Nic	Q	Q	20	Q	Nic	Q	32	Nic	Q	Q
9	Q	Nic	Q	21	Q	Nic	Q	33	Nic	Q	Q
10	Nic	Q	Q	22	Q	Nic	Q	34	Drop-Out		
11	Q	Nic	Q	23	Nic	Q	Neither	35	Nic	Q	Neither
12	Q	Nic	Q	24	Nic	Q	Q	36	Q	Nic	Q

7. Discussion

The primary objective of this study was to compare the plasma pharmacokinetics and relative bioavailability of nicotine and cotinine when applied by means of chewing nicotine resin chew pieces (Nicorette®) and spraying a nicotine-in-ethanol solution onto the buccal mucosa (Quit®). The outcome of the study would predict the viability of Quit® as a novel nicotine replacement product.

Secondary objectives included comparison of the occurrence and severity of adverse events associated with nicotine application in the form of Nicorette® and Quit®, and a comparison of the preference rating of the two nicotine replacement products.

The study design included a pharmacokinetic profile of nicotine after application in the form of cigarette smoke. Smokers were chosen as trial volunteers because they would be less prone to experience many of the adverse events associated with nicotine administration to naive subjects, such as nausea, vomiting, headache and palpitations. Habitual smokers would also be able to choose between nicotine replacement products with regard to their ability to suppress the craving to smoke and general acceptability of their mode of application.

The product, named Quit®, comprises 4 canisters of 20 ml each, delivering 70 µl of a peppermint-flavoured ethanol solution, with or without nicotine, by means of a mechanically driven metered dose pump. Quit® 1 delivers 1 mg nicotine per spray and contains ethanol in a concentration of 79.5% v/v. Quit® 2 delivers 0.66 mg nicotine per spray and contains ethanol in a concentration of 79.9% v/v. Quit® 3 delivers 0.33 mg nicotine per spray and contains ethanol in a concentration of 80.3% v/v. Quit® 4 contains only ethanol (80.6% v/v) and

peppermint flavouring. The rationale is that the progressively decreasing nicotine content from Quit® 1 through to Quit® 4 will be helpful to smokers weaning themselves from nicotine.

The dosage schedule for Nicorette® gum was based on the recommendation by the supplier in South Africa, Adcock Ingram Self Medication, that 10 to 12 pieces daily be chewed slowly over 30 minutes, one at a time, when the urge to smoke is felt. We chose to administer equivalent amounts of nicotine over 16 hours. Hence, hourly administration of 1 mg nicotine in the form of cigarette smoke inhaled or buccal administration of Quit® 1, and 2-hourly administration of 2 mg nicotine in the form of 2 mg nicotine chew pieces (Nicorette®). The pharmacokinetic profiles spanned a 2-hour period from 15:30 to 17:30 at steady state, i.e. on the third day of each regimen. This model was taken to represent a legitimate approach to describe and compare the rate and extent of absorption and formation of nicotine and cotinine, respectively.

When nicotine is placed in the mouth, the amount that is actually absorbed via the buccal mucosa is determined by the pH of the saliva, because nicotine is a weak organic base that is best absorbed in the non-ionic form. The pKa value of nicotine is 8 when in aqueous solution at 25°C. At a typical salivary pH of 7.0, only 19% of orally held nicotine is present in the non-ionic form. A wide variety of commonly consumed foods and beverages, including coffee and carbonated beverages, are more acidic than typical whole-mouth saliva. They should be avoided during or immediately before nicotine polacrilex use. Solid foods should be similarly avoided, because they may be acidic (Henningfield *et al.*, 1990). These possible effects of foods and beverages were duly considered and implemented in the protocol design.

The extent to which nicotine was absorbed and cotinine was formed following multiple doses of Quit® (1 mg hourly) and Nicorette® (2 mg two-hourly), as deduced from the AUD_{ss} of plasma nicotine and cotinine concentration versus time profiles and the cumulative urinary excretion of these analytes, was comparable to the degree that the two replacement products, as tested, can be deemed bioequivalent.

Ten minute sampling intervals precluded accurate determination of T_{max} for nicotine. Nevertheless, maximum plasma nicotine concentrations were achieved in about 10 minutes after smoking cigarettes, compared to 19 minutes and 30 minutes after buccal administration in

the form of Quit® and Nicorette®, respectively. The values for cigarettes and Nicorette® are in close agreement with those reported by Russell *et al.* (1976) namely 7.5 minutes and 30 minutes, respectively.

Cigarette smoking produced plasma nicotine concentrations comparable to those found in similar studies. The mean C_{max} values obtained in this study were 35 ng/ml compared to 32 ng/ml reported by Benowitz *et al.* (1987a) and the mean C_{min} values were 18.6 ng/ml compared to 18.3 ng/ml reported by (Mc Nabb *et al.*, 1982). The mean plasma cotinine concentration of between 285 ng/ml and 369 ng/ml correlated very well with the values of between 250 ng/ml and 340 ng/ml reported by (Benowitz *et al.*, 1987a).

In this study, as could be expected, plasma nicotine concentrations were lower after Quit® than after Nicorette® administration during the first hour, and lower after Nicorette® administration during the second hour. Cotinine, which has an elimination half-life of 15 hours (Benowitz *et al.*, 1983a), remained at steady plasma concentrations throughout the profile period (15:30 to 17:30).

The fact that plasma nicotine versus time profiles for Nicorette® and Quit® differed in shape is consistent with the difference in delivery and dosage regimens of nicotine (2 mg every two hours versus 1 mg every hour).

However, these differences are unlikely to affect the efficacy of Quit® as a nicotine replacement product. On the contrary, more rapid absorption of nicotine following administration in the form of Quit® could possibly enhance the ability of this product to effectively suppress the craving to smoke (Benowitz, 1991c). Our urine data seem to support this hypothesis, since more rapid absorption of nicotine might be associated with higher conversion to cotinine and higher renal clearance of both nicotine and cotinine.

Two notable exceptions observed during this study were worthy of mention. Subject 3 appeared not to effectively metabolise nicotine to cotinine in any of the treatment phases. Benowitz *et al.* (1995) described an individual with deficient C-oxidation of nicotine who converted only 8 percent of nicotine to cotinine. Subject 3 conceivably belongs to this rare category. Subject 30 proved to be a "puffer" exhibiting only very low plasma nicotine and

cotinine concentrations whilst smoking cigarettes and concentrations similar to those found in other subjects whilst receiving Nicorette® and Quit®.

At steady state, chewing 2 mg nicotine gum (Nicorette®) two-hourly resulted in mean C_{max} and C_{min} plasma nicotine concentrations of 9.4 ng/ml and 4.3 ng/ml, respectively. These findings are corroborated by published data. Russell *et al.* (1976) reported a nicotine C_{max} value of 8.5 ng/ml after chewing one 2 mg piece of Nicorette®. In another study (Mc Nabb *et al.*, 1982) the mean peak plasma nicotine concentration at steady state while chewing 2 mg nicotine gum hourly was 11.8 ng/ml, compared to average steady state blood nicotine concentrations of 7.9 ng/ml for chewing 2 mg nicotine gum hourly.

It is commonly recognised that compulsive smoking is due, in part, to physical dependence on nicotine. Thus, the rationale for the use of nicotine gum is based on three hypothesised consequences of nicotine dependence (Hughes and Miller, 1984):

1) Smokers smoke to obtain the psychoactive effects of nicotine.

2) When smokers quit, they experience withdrawal symptoms that are due to nicotine deprivation.

3) Gradual reduction of nicotine minimises withdrawal symptoms. Accordingly, nicotine gum is presumed to help smokers because it relieves their withdrawal symptoms. When a smoker has conquered the habit part of the smoking, he slowly tapers the gum.

Most ex-smokers use less than ten pieces of 2 mg nicotine gum per day during abstinence; thus, the levels of nicotine from gum use are usually much lower than those obtained from smoking. However, even this relatively low level of nicotine seems to be sufficient to prevent withdrawal symptoms (Hughes and Miller, 1984).

In this study, the use of nicotine gum and nicotine buccal spray effectively suppressed the craving to smoke at plasma nicotine concentrations about 25 percent of those produced by cigarette smoking. Cotinine is probably behaviourally active in the setting of cigarette abstinence (Keenan *et al.*, 1994), and could have contributed to the overall suppression of

cigarette craving in this study since plasma cotinine concentrations produced by Nicorette® and Quit® were 41 and 44 percent, respectively, of those associated with cigarette smoking.

Regarding the safety and tolerance aspect of this study, it needs to be emphasised that recorded adverse events did not differ in nature and intensity from those known to be associated with the use of nicotine gum. Side-effects reported by some users of nicotine chewing gum are fairly consistent across controlled laboratory studies and clinical trials. Symptoms such as hiccuping and nausea have been reported by 15 to 25 percent of users following acute and chronic administration of nicotine gum (Nemeth-Coslett *et al.*, 1988; Nemeth-Coslett *et al.*, 1987 and West & Russell, 1986). These effects are transient and appear to be related to vigour of chewing, excessive salivation and swallowing of nicotine and air (Nemeth-Coslett, 1989). In this study 24 percent and 38 percent of subjects experienced isolated episodes of transient hiccups associated with Nicorette® and Quit® use, respectively. Other untoward effects which have been reported by users of nicotine gum include blisters in the mouth, jaw fatigue, burning of the tongue and throat and belching. Additionally, it has been reported that a very small percentage (i.e. 5 in 1 000 cases) experience palpitations when chewing the gum (Hughes and Miller, 1984).

In this study, 26 percent of the volunteers reported isolated episodes of transient sneezing when receiving Quit® compared to 9 percent receiving Nicorette®. This higher incidence of sneezing associated with Quit® may possibly be due to access to the nasal passages of some of the nicotine-ethanol solution sprayed into the mouth.

Notwithstanding a higher incidence of hiccups and sneezing associated with Quit®, volunteers overwhelmingly preferred Quit® to Nicorette® in regard to acceptability, tolerability and efficacy (29:1).

Nicotine has been the mainstay of pharmacotherapy for tobacco addiction (Benowitz, 1997). The rationale for promoting nicotine replacement is based on what it seeks to replace, namely tobacco; not that nicotine use is something good, but rather something far less harmful than tobacco (Russell, 1991).

The overall efficacy of nicotine replacement therapy in clinical trials ranges from 10 to 40 percent, depending to a great extent on the intensity of concomitant behavioural therapy

(Silagy *et al.*, 1994). Nicotine replacement therapy could enable about 15 percent of smokers who seek help in stopping smoking to give up the habit (Tang *et al.*, 1994).

The actual dose and frequency of administration of nicotine, when the buccal route is preferred for nicotine replacement therapy, is individually determined. The short-term goal is cessation of tobacco use, while the ultimate goal is nicotine withdrawal. A case has been advanced for selected nicotine replacement products to be made as palatable and acceptable as possible and actively promoted on the open market to enable them to compete with tobacco products (Russell, 1991). One estimate is that the availability of over-the-counter (OTC) nicotine replacement products in the United States of America will increase the number of people who quit smoking in that country, with an additional 450 000 individuals abstinent 10 years after the introduction of the OTC products (Oster *et al.*, 1996). The Quit®-concept appears to be a major step in the right direction.

8. Conclusion

The bioavailability of nicotine represented by the area under the plasma nicotine and cotinine concentrations versus time profiles and urinary excretion of nicotine and cotinine at steady state, was comparable between nicotine polacrilex chewpieces (Nicorette®) and nicotine buccal spray (Quit®).

Applying conventional bioequivalence criteria with respect to C_{max} and AUD_{ss} confirmed that the two products, as tested, are bioequivalent. Nicotine availability in plasma was fourfold greater following cigarette smoking than after application in the form of Nicorette® or Quit®.

Trial subjects rated Quit® preferable to Nicorette® with respect to suppression of the craving to smoke, ease and aesthetics of application. Nicorette® and Quit® were equally well tolerated.

Addendum

The study results served as a basis for the successful submission of an application for registration of Quit® by the South African Medicines Control Council in August 1997, Registration number 29/34/0392. Quit® is now available as a nicotine replacement product from pharmacies in South Africa with Schedule 2 status.

References

Andersson, G., Hansson, E. and Schmiterlöw, CG. 1965. Gastric secretion of ^{14}C nicotine. *Experientia*, **15**:211-213.

Atkinson, H.C., Begg, E.J. and Darlow, B.A. 1988. Drugs in human milk: clinical pharmacokinetic considerations. *Clinical Pharmacokinetics*, **14**:217-240.

Bannon, Y.B., Corish, J., Corrigan, O.I., Devane, J.G., Kavanagh, M. and Mulligan, S. 1989. Transdermal delivery of nicotine in normal human volunteers: a single dose and multiple dose study. *European Journal of Clinical Pharmacology*, **37**:285-290.

Bartecchi, C.E., Mackenzie, T.D. and Schrier, R.W. 1994. The human cost of tobacco use. *The New England Journal of Medicine*, **330**:907-912.

Beckett, A.H., Gorrod, J.W. and Jenner, P. 1971. The analysis of nicotine-1-N-oxide in urine, in the presence of nicotine and cotinine, and its application to the study of *in vivo* nicotine metabolism in man. *Journal of Pharmacy and Pharmacology*, **23**:55-61.

Benowitz, N.L., Jacob III, P., Jones, T. and Rosenberg, J. 1982. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *The Journal of Pharmacology and Experimental Therapeutics*, **221**:368-372.

Benowitz, N.L., Kuyt, F., Jacob III, P., Jones, R.T. and Osman, A. 1983a. Cotinine disposition and effects. *Clinical Pharmacology and Therapeutics*, **34**:604-611.

Benowitz, N.L., Hall, M., Herning, R.I., Jacob III, P., Jones, R.T. and Osman, A. 1983b. Smokers of low - yield cigarettes do not consume less nicotine. *The New England Journal of Medicine*, **309**:139-142.

Benowitz, N.L. and Jacob III, P. 1985. Nicotine renal excretion rate influences nicotine intake during cigarette smoking. *The Journal of Pharmacology and Experimental Therapeutics*, **234**:153-155.

Benowitz, N.L. 1986. Clinical pharmacology of nicotine. *Annual Reviews of Medicine*, **37**:21-32.

Benowitz, N.L., Jacob III, P. and Savanapridi, C. 1987a. Determinants of nicotine intake while chewing nicotine polacrilex gum. *Clinical Pharmacology and Therapeutics*, **41**:467-473.

Benowitz, N.L., Lake, T., Keller, K.H. and Lee, B.L. 1987b. Prolonged absorption with development of tolerance to toxic effects after cutaneous exposure to nicotine. *Clinical Pharmacology and Therapeutics*, **42**:119-120.

Benowitz, N.L., Jacob III, P. and Yu, l. 1989. Daily use of smokeless tobacco: Systemic effects. *Annals of Internal Medicine*, **111**:112-116.

Benowitz, N.L., Jacob III, P., Denaro, C.P. and Jenkins, R. 1991a. Stable isotope studies of nicotine kinetics and bioavailability. *Clinical Pharmacology and Therapeutics*, **49**:270-277.

Benowitz, N.L., Chan, K., Denaro, C.P. and Jacob III, P. 1991b. Stable isotope method for studying transdermal drug absorption: The nicotine patch. *Clinical Pharmacology and Therapeutics*, **50**:286-393.

Benowitz, N.L. 1991c. Pharmacodynamics of nicotine: implications for rational treatment of nicotine addiction. *British Journal of Addiction*, **86**:495-499.

Benowitz, N.L. 1993. Nicotine replacement therapy. What has been accomplished - can we do better? *Drugs*, **54**:157-170.

Benowitz, N.L., Jacob, III P.and Sachs, D.P.L. 1995. Deficient C-oxidation of nicotine. *Clinical Pharmacology and Therapeutics*, **57**:590-594.

Benowitz, N.L. 1996. Pharmacology of nicotine: Addiction and therapeutics. *Annual Review of Pharmacology and Toxicology*, **36**:597-613.

Benowitz, N.L. 1997. Treating tobacco addiction - nicotine or no nicotine? *The New England Journal of Medicine*, **337**:1230-1231.

Busto, U., Bendayan, R. and Sellers, E.M. 1989. Clinical pharmacokinetics of non - opiate abused drugs. *Clinical Pharmacokinetics*, **16**:1-26.

Cryer, P.E., Haymond, M.W., Santiago, J.V. and Shah, S.D. 1976. Norepinephrine and epinephrine release and adrenergic mediation of smoking - associated hemodynamic and metabolic events. *The New England Journal of Medicine*, **295**:573-577.

Curvall, M. and Vala, E.K. 1993. Nicotine and metabolites: analysis and levels in body fluids. In: Nicotine and Related Alkaloids: absorption, distribution, metabolism, excretion. *Chapman and Hall, London (England)*, 146-179.

Department of Health and Human Services. 1988. The health consequences of smoking: nicotine addiction: a report of the Surgeon General. Washington, DC.: *Government Printing Office,(DHHS publication no CDC*, 88-8406).

Diletti, E., Hauschke, D. and Steinijans, V.W. 1991. Sample size determination for bioequivalence assessment by means of confidence intervals. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, **29**:1-8.

Faulkner, J.M. 1933. Nicotine poisoning by absorption through the skin. *Journal of the American Medical Association*, **100**:1664-1665.

Fagerström, K.O., Säwe, U. and Tønnesen, P. 1993. Therapeutic use of nicotine patches: efficacy and safety. *Journal of Drug Development*, **5**:191-205.

Ferno, O., Lichneckert, S.J.A. and Lundren, C.E.G. 1973. A substitute for tobacco smoking. *Psychopharmacologia*, **31**:201-204.

Feyerabend, C. and Russell, M.A.H. 1978. Effect of urinary pH and nicotine excretion rate on plasma nicotine during cigarette smoking and chewing nicotine gum. *British Journal of Clinical Pharmacology*, **5**:293-297.

Feyerabend, C., Ings, R.M.J. and Russell, M.A.H. 1985. Nicotine pharmacokinetics and its application to intake from smoking. *British Journal of Clinical Pharmacology*, **19**:239-247.

Fiore, M.C. 1992. Trends in cigarette smoking in the United States: the epidemiology of tobacco use. *Medical Clinics of North America*, **76**:289-303.

Froggatt, P. Wald, N. 1989. The role of nicotine in the tar reduction progamme. In: N Wald and P Froggatt (Eds): Nicotine, Smoking and the low Tar Programme. *Oxford University Press, Oxford*, 229-235.

Gehlbach, S.H., Williams, W.A., Perry, L.D. and Woodall, J.S. 1974. Green - tobacco sickness an illness of tobacco harvesters. *Journal of the American Medical Association*, **229**:1880-1974.

Gorrod, J.W. and Jenner, P. 1975. The metabolism of tobacco alkaloids. *Essays in Toxicology*, **6**:35-78.

Gorrod, J.W. and Wahren, J. 1993. Sources of inter - individual variability in nicotine pharmacokinetics. In: Nicotine and Related Alkaloids: absorption, distribution, metabolism, excretion. *Chapman and Hall, London (England)*, 219-254.

Gorsline, J. 1993. Nicotine pharmacokinetics of four nicotine transdermal systems. *Health Values*, **17**:20-24

Gries, J., Benowitz, N. and Verotta, D. 1996. Chronopharmacokinetics of nicotine. *Clinical Pharmacology and Therapeutics*, **60**:385-395.

Hall, S.M., Herning, R.I., Jones, R.T., Benowitz, N.L. and Jacob III, P. 1984. Blood cotinine levels as indicators of smoking treatment outcome. *Clinical Pharmacology and Therapeutics*, **35**:810-814.

Henningfield, JE., Radzius, A., Cooper, T.M. and Clayton, R.R. 1990. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *Journal of the American Medical Association*, **264**:1560-1564.

Henningfield, J.E., Cohen, C. and Slade, J.D. 1991. Is nicotine more addictive than cocaine? *British Journal of Addiction*, **86**:565-569.

Henningfield, J.E., Stapleton, J.M., Benowitz, N.L., Grayson, R.F. and London, E.D. 1993. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug and Alcohol Dependence*, **33**:23-29.

Henningfield, J.E., Kozlowski, L.T. and Benowitz, N.L. 1994. A proposal to develop meaningful labelling for cigarettes. *Journal of the American Medical Association*, **272**:312-314.

Henningfield, J.E. 1995. Nicotine medications for smoking cessation. *The New England Journal of Medicine*, **333**:1196-1203.

Hughes, J.R. and Miller, S.A. 1984. Nicotine gum to help stop smoking. *Journal of the American Medical Association*, **252**:2855-2858.

Hughes, J.R., Gulliver, S.B., Fenwick, J.W., Valliere, W.A., Cruser, K., Pepper, S., Shea, P., Solomon, L.J. and Flynn, B.S. 1992. Smoking cessation among self - quitters. *Health Psychology*, **11**:331-334.

Jacob III, P. and Benowitz, N.L. 1993. Pharmacokinetics of (s)-nicotine and metabolites in humans. In: Nicotine and Related Alkaloids: absorption, distribution, metabolism, excretion. *Chapman and Hall, London (England)*, 197-218.

Jarvis, M.J., Hajek, P., Russell, M.A.H., West, R.J. and Feyerabend, C. 1987. Nasal nicotine solution as an aid to cigarette withdrawal: a pilot clinical trial. *British Journal of Addiction*, **82**:983-988.

Johansson, C.J., Olsson, P., Bende, M., Carlsson, T. and Gunnarsson, P.O. 1991. Absolute bioavailability of nicotine applied to different nasal regions. *European Journal of Clinical Pharmacology*, **41**:585-588.

Joseph, A.M., Norman, S.M., Ferry, L.H., Prochazka, A.V., Westerman, E.C., Steele, B.G., Sherman, S.E., Cleveland, M., Antonnucio, D.O., Hartman, N. and McGovern, P.G. 1996. The safety of nicotine transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *The New England Journal of Medicine*, **335**:1792-1798.

Keenan, R.M., Hatsukami, D.K., Pentel, P.R., Thompson, T.N. and Grillo, M.A. 1994. Pharmacodynamic effects of cotinine in abstinent cigarette smokers. *Clinical Pharmacology and Therapeutics*, **55**:581-590.

Klein, A.E. and Gorrod, J.W. 1978. The metabolism of nicotine in cigarette smokers during pregnancy. *European Journal of Drug Metabolism and Pharmacokinetics*, **2**:87-93.

Kozlowski, L.T. and Kleiman, R.M. 1978. Effects of oral pH on cigarette smoking. *Pharmacology Biochemistry and Behaviour*, **9**:477-480.

Kyerematen, G.A., Damiano, M.D., Dvorchik, B.H. and Vesell, E.S. 1982. Smoking - induced changes in nicotine disposition: Application of a new HPLC assay for nicotine and its metabolites. *Clinical Pharmacology and Therapeutics*, **32**:769-780.

Lide, D.R. 1991. CRC handbook of Chemistry and Physics: 1991-1992, 72 nd Edition. Boca Raton, Fla: CRC Press.

Luck, W. and Nau, H. 1984a. Nicotine and cotinine concentrations in serum and milk of nursing smokers. *British Journal of Clinical Pharmacology*, **18**:9-15.

Luck, W. and Nau, H. 1984b. Exposure of the fetus , neonate, and nursed infant to nicotine and cotinine from maternal smoking. *The New England Journal of Medicine*, **311**:672-672.

McNabb, M.E., Ebert, R.V. and McCusker, K. 1982. Plasma nicotine levels produced by chewing nicotine gum. *Journal of the American Medical Association*, **248**:865-868.

Nemeth-Coslett, R., Henningfield, J.E., O'Keeffe, M.K. and Griffiths, R.R. 1987. Nicotine gum: dose - related effects on cigarette smoking and subjective ratings. *Psychopharmacology*, **92**:424-430.

Nemeth-Coslett, R., Benowitz, N.L., Robinson, N. and Henningfield, J.E. 1988. Nicotine gum: chew rate, subjective effects and plasma nicotine. *Pharmacology Biochemistry and Behaviour*, **29**:747-751.

Nemeth-Coslett, R. 1989. Physiologic effects of nicotine polacrilex. *Biomedicine and Pharmacotherapy*, **43**:5-10.

Nyberg, G., Panfilov, V., Sivertsson, K. and Wilhelmsen, L. 1982. Cardiovascular effects of nicotine chewing gum in healthy non - smokers. *European Journal of Clinical Pharmacology*, **23**:303-307.

Oster, G., Delea, T.E. and Huse, D.M. 1996. The benefits and risks of over - the - counter availability of nicotine polacrilex (nicotine gum). *Medical Care*, **34**:389-402.

Palmer, K.J., Buckley, M.M.and Faulds, D. 1992. Transdermal nicotine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy as an aid to smoking cessation. *Drugs*, **44**:498-529.

Rose, J.E., Jarvik, M.E. and Rose, K.D. 1984. Transdermal administration of nicotine. *Drug and Alcohol Dependence*, **13**:209-213.

Rosenberg, J., Benowitz, N.L., Jacob III, P. and Wilson, K.M. 1980. Disposition kinetics and effects of intravenous nicotine. *Clinical Pharmacology and Therapeutics*, **28**:517-522.

Rowland, M. and Tozer, T.N. 1980. Blood to plasma concentration ratio. In: Clinical pharmacokinetics, concepts and applications., *Lea and Febiger,Philadelphia*, 287-288.

Russell, M.A.H., Feyerabend, C. and Cole, P.V. 1976. Plasma nicotine levels after cigarette smoking and chewing nicotine gum. *British Medical Journal*, **1**:1043-1046.

Russell, M.A.H., Jarvis, M.J., Devitt, G. and Feyerabend, C. 1981. Nicotine intake by snuff users. *British Medical Journal*, **283**:814-817.

Russell, M.A.H., Jarvis, M.J., Feyerabend, C. and Ferno, O. 1983. Nasal nicotine solution: a potential aid to giving up smoking? *British Medical Journal*, **286**:683-684.

Russell, M.A.H., Jarvis, M.J., Sutherland, G. and Feyerabend, C. 1987. Nicotine replacement in smoking cessation. Absorption of nicotine vapor from smoke - free cigarettes. *Journal of the American Medical Association*, **257**:3262-3265.

Russell, M.A.H. 1991. The future of nicotine replacement. *British Journal of Addiction*, **86**:653-658.

Schachter, S. 1978. Pharmacological and psychological determinants of smoking. In: Smoking Behaviour, *Churchill Livingstone*, 208-228.

Schievelbein, H. 1982. Nicotine, resorption and fate. *Pharmacology and Therapeutics*, **18**:233-248.

Schneider, N.G., Lunell, E., Olmstead, R.E. and Fagerström, K. 1996. Clinical pharmacokinetics of nasal nicotine delivery. A review and comparison to other nicotine systems. *Clinical Pharmacokinetics*, **1**:65-80.

Seyler, L.E., Pomerleau, O.F., Fertig, J.B., Hunt, D. and Parker, K. 1986. Pituitary hormone response to cigarette smoking. *Pharmacology Biochemistry and Behaviour*, **24**:159-162.

Silagy, C., Mant, D., Flower, G. and Lodge, M. 1994. Meta - analysis on efficacy of nicotine replacement therapies in smoking cessation. *The Lancet*, **343**:139-142.

Sutherland, G., Stapleton, J.A., Russell, M.A., Jarvis, M.J., Hajek, P., Belcher, M. and Feyerabend, C. 1992. Randomised controlled trial of nasal nicotine spray in smoking cessation. *The Lancet*, **340**:324-333.

Svensson, C.K. 1987. Clinical pharmacokinetics of nicotine. *Clinical Pharmacokinetics*, **12**:30-40.

Tang, J.L., Law, M. and Wald, N. 1994. How effective is nicotine replacement therapy in helping people to stop smoking? *British Medical Journal*, **308**:21-26.

Tønnesen, P., Norregaard, J., Mikkelsen, K., Jorgensen, S. and Nilsson, F. 1993. A double - blind trial of a nicotine inhaler for smoking cessation. *Journal of the American Medical Association*, **269**:1268-1271.

Turner, D.M., Armitage, A.K., Briant, R.H. and Dollery, C.T. 1975. Metabolism of nicotine by the isolated perfused dog lung. *Xenobiotica*, **5**:539-551.

West, R.J. and Russell, M.A.H. 1986. Dependence on nicotine chewing gum. *Journal of the American Medical Association*, **256**:3214-3215.

Williamson, D.F., Madans, J., Anda, R.K., Kleinman, J.C.,Giovino, G.A. and Byers, T. 1991. Smoking cessation and severity of weight gain in a national cohort. *The New England Journal of Medicine*, **324**:739-745.

Yoshida, K., Kato, Y. and Imura, H. 1980. Nicotine - induced release of noradrenaline from hypothalamic synaptosomes. *Brain Research*, **182**:361-368.

APPENDICES

APPENDIX 1

Randomisation Schedule for FARMOVS 18/96

APPENDIX 1

RANDOMISATION SCHEDULE

Nicotine replacement therapy: pharmacokinetics, relative bioavailability (Nicorette® and Quit®) and efficacy (Quit®)

(FARMOVS 18/96)

Subject	Regimen II (Days 4-6)	Regimen III (Days 7-9)
1	B	C
2	C	B
3	B	C
4	C	B
5	C	B
6	B	C
7	B	C
8	B	C
9	C	B
10	B	C
11	C	B
12	C	B
13	C	B
14	B	C
15	B	C
16	C	B
17	C	B
18	B	C

Products (Administered from Days 4 to 9)

B: Nicorette® (Adcock Ingram)

One chew piece (equivalent to 2 mg nicotine) to be chewed every second hour for 30 minutes (from 07:30 until 21:30) for 3 days.

C: Quit® (Noble Pharmaceuticals)

One spray to the buccal mucosa (delivering 1 mg nicotine) hourly from 07:30 until 22:30, for 3 days.

APPENDIX 1 (continued)

RANDOMISATION SCHEDULE

Nicotine replacement therapy: pharmacokinetics, relative bioavailability (Nicorette® and Quit®) and efficacy (Quit®)
(FARMOVS 18/96)

Subject	Regimen II	Regimen III
19	B	C
20	C	B
21	C	B
22	C	B
23	B	C
24	B	C
25	C	B
26	B	C
27	C	B
28	C	B
29	B	C
30	B	C
31	C	B
32	B	C
33	B	C
34	C	B
35	B	C
36	C	B

Products (Administered from Days 4 to 9)

B: Nicorette® (Adcock Ingram)
One chew piece (equivalent to 2 mg nicotine) to be chewed every second hour for 30 minutes (from 07:30 until 21:30) for 3 days.

C: Quit® (Noble Pharmaceuticals)
One spray to the buccal mucosa (delivering 1 mg nicotine) hourly from 07:30 until 22:30, for 3 days.

APPENDIX 2

Flow-chart (A) - Daily Procedures for Study Days 1 to 9

APPENDIX 2

FLOW-CHART (A) - Daily Procedures for Study days 1 to 9

TIME BY CLOCK	BLOOD (Trough conc.)	NICOTINE APPLICATIONS			MEALS, SNACKS AND FLUID, ADDITIONAL COMMENTS
		Cigarette Days 1-3	Nicorette Rand. order	Quit Rand. order	
Day 0 20:00	Admission to study site and randomisation. Fasting and non-smoking from 22:30				
07:00					250 ml fluid
07:25	B0				*Days 3, 4, 6, 7, 9 and 10: urine collection (Flow-Chart B),*
07:30		√	* √	* √	Water *ad libitum*, except: * No fluids within 10 minutes of application of Quit, and within 10 minutes of removal of the Nicorette chewing piece.
08:15					Breakfast, 250 ml fluid
08:30		√		* √	
09:30		√	* √	* √	
10:30		√		* √	
11:00					Snack, 250 ml fluid
11:30		√	* √	* √	*Days 3, 6 and 9: urine collection (Flow-chart B)*
12:30		√		* √	
13:00					Lunch, 250 ml fluid
13:30		√	* √	* √	
14:30		√		* √	
15:00					*Days 3, 6 and 9: Insert intravenous cannula (Flow-chart B)*
15:30		√	* √	* √	*Days 3, 6 and 9: urine collection and blood sampling (Flow-chart B)*
16:30		√		* √	*Days 3, 6 and 9: blood sampling (Flow-chart B)*
17:30		√	* √	* √	*Days 3, 6 and 9: blood sampling (Flow-chart B)*
18:30		√		* √	
19:00					Dinner, 250 ml fluid
19:30		√	* √	* √	*Days 3, 6 and 9: urine collection (Flow-chart B)*
20:30		√		* √	
21:00					Snack, 250 ml fluid
21:30		√	* √	* √	
22:30		√		* √	*Days 3, 6 and 9: urine collection (Flow-chart B)*
23:00	Lights off				

APPENDIX 3

Flow-chart (B) - Pharmacokinetic Profiles: Study Days 3, 6 and 9

APPENDIX 3

FLOW-CHART (B) - Pharmacokinetic Profiles: Study days 3, 6 and 9
FLOW-CHART B MUST BE USED IN COMBINATION WITH FLOW-CHART A

TIME BY CLOCK	URINE COLLECTION	BLOOD SAMPLING
07:20	Empty bladder	
07:30	U 1 - Start of collection period	B 0 Trough sample
11:30	U 1 - Collection period ends U 2 - Start of collection period	
15:00		Insert intravenous cannula
15:30	U 2 - Collection period ends U 3 - Start of collection period	B 1 *Draw blood sample just before nicotine application at 15:30*
15:40		B 2
15:50		B 3
16:00		B 4
16:10		B 5
16:20		B 6
16:30		B 7
16:40		B 8
16:50		B 9
17:00		B 10
17:10		B 11
17:20		B 12
17:30		B 13 Remove intravenous cannula
19:30	U 3 - Collection period ends U 4 - Start of collection period	
22:30	U 4 - Collection period ends U 5 - Start of collection period	
07:30	U 5 - Collection period ends *Complete urine collection before nicotine application at 07:30*	**Day 10: Collect blood sample for post-study special investigations**

LABELLING OF SAMPLES:

- Blood and urine samples were marked per STUDY DAY
- All 07:30 blood samples were marked B0 i.e.: DAY 1 B0, DAY 2 B0, DAY 3 B0, etc.
  Profile blood samples were marked from B1 to B13
  i.e.: DAY 3 B1 to B13 DAY 6 B1 To B13 DAY 9 B1 to B13
- Urine samples were marked from U1 to U 5, for Days 3, 6 and 9

APPENDIX 4

Quality Assurance Statement

SACT 02/96: Nicotine Replacement Therapy: Pharmcokinetics, Relative Bioavailability (Nicorette® and Quit®) and Efficacy (Quit®).

This report has been audited by the Quality Assurance Unit of the FARMOVS Research Centre for Clinical Pharmacology and Drug Development. It is considered to be an accurate presentation of the findings as well as a precise account of the procedures and practices employed during the performance of the study.

The following audits were performed:

Pre-study audit	:	07/06/96
Post-study audit (clinical)	:	04/07/96
Post-study audit (analytics)	:	18/09/96
Report	:	30/01/97

The following guidelines were in force:

* In-house SOPs (SACT)
* Declaration of Helsinki
* **Good clinical Practice for Trials on Medicinal Products in the European Community. In: The Rules Governing Medicinal Products in the European Community. Volume III. Addendum, July 1990. Guidelines on the quality, safety and efficacy of medicinal products of human use.**
  Commission of the European Communities, Luxembourg, 1990 57-98
* **Investigation of Bioavailibility and Bioequivalence. In: The Rules Governing Medicinal Products in the European Community. Volume III, Addendum no 2. Guidelines on the quality, safety and efficacy of medicinal products for human use.**
  Commission of the European Communities, Luxembourg, 1992 149 - 164

MR P J BELL
Quality Assurance Auditor (FARMOVS)

11 January 1998
DATE

APPENDIX 5

Urine Volumes

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE VOLUMES (ml)
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	316.000	369.000	370.000	58.000	424.000
2	492.000	415.000	400.000	71.000	448.000
3	218.000	315.000	157.000	.000	677.000
4	261.000	380.000	612.000	256.000	1158.000
5	289.000	164.000	342.000	251.000	818.000
6	197.000	211.000	166.000	109.000	722.000
7	96.000	244.000	415.000	116.000	868.000
8	447.000	770.000	798.000	218.000	895.000
9	585.000	705.000	835.000	585.000	1076.000
10	203.000	256.000	294.000	281.000	425.000
11	198.000	172.000	112.000	92.000	432.000
12	88.000	315.000	367.000	245.000	363.000
13	232.000	199.000	392.000	356.000	391.000
14	190.000	188.000	203.000	365.000	778.000
15	163.000	191.000	205.000	223.000	835.000
16	395.000	536.000	415.000	431.000	847.000
17	291.000	552.000	183.000	190.000	731.000
18	131.000	208.000	117.000	104.000	373.000
19	11.000	118.000	56.000	139.000	222.000
20	232.000	468.000	212.000	205.000	306.000
21	198.000	280.000	292.000	274.000	568.000
22	466.000	669.000	423.000	487.000	851.000
23	191.000	466.000	311.000	583.000	1182.000
24	398.000	382.000	389.000	411.000	858.000
26	379.000	454.000	348.000	441.000	862.000
27	205.000	431.000	454.000	367.000	813.000
28	244.000	343.000	291.000	348.000	460.000
29	240.000	258.000	322.000	271.000	777.000
30	224.000	234.000	49.000	203.000	317.000
31	500.000	377.000	448.000	417.000	375.000
32	.000	332.000	399.000	451.000	825.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE VOLUMES (ml)
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	251.000	465.000	404.000	565.000	528.000
35	291.000	358.000	328.000	412.000	505.000
36	62.000	694.000	375.000	762.000	850.000
MEAN	255.412	368.206	337.765	302.559	663.529
SD	138.756	168.376	174.736	176.124	256.958
GEOM MEAN		332.539	288.605		611.051
GEOM SD		1.592	1.877		1.534
CV%	54.327	45.729	51.733	58.212	38.726
SEM	23.797	28.876	29.967	30.205	44.068
MIN	.000	118.000	49.000	.000	222.000
MAX	585.000	770.000	835.000	762.000	1182.000
MEDIAN	232.000	350.500	345.000	272.500	726.500
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE VOLUMES (ml)
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	190.000	362.000	458.000	243.000	455.000
2	243.000	415.000	300.000	381.000	347.000
3	312.000	350.000	306.000	127.000	211.000
4	464.000	378.000	415.000	.000	1019.000
5	71.000	196.000	257.000	381.000	766.000
6	224.000	395.000	158.000	297.000	570.000
7	331.000	288.000	265.000	119.000	616.000
8	643.000	785.000	752.000	460.000	555.000
9	688.000	928.000	901.000	685.000	1123.000
10	331.000	434.000	459.000	438.000	888.000
11	258.000	434.000	467.000	264.000	434.000
12	287.000	213.000	157.000	155.000	340.000
13	.000	.000	428.000	224.000	549.000
14	.000	283.000	217.000	107.000	456.000
15	184.000	195.000	.000	212.000	440.000
16	442.000	.000	377.000	.000	498.000
17	322.000	254.000	192.000	.000	686.000
18	330.000	191.000	221.000	279.000	298.000
19	233.000	307.000	362.000	.000	182.000
20	35.000	266.000	170.000	83.000	300.000
21	.000	285.000	203.000	104.000	381.000
22	322.000	458.000	860.000	533.000	1713.000
23	180.000	372.000	272.000	290.000	1059.000
24	260.000	382.000	353.000	323.000	693.000
26	226.000	458.000	469.000	450.000	747.000
27	280.000	449.000	328.000	315.000	857.000
28	334.000	252.000	435.000	450.000	583.000
29	.000	439.000	205.000	403.000	860.000
30	.000	222.000	285.000	187.000	145.000
31	313.000	363.000	769.000	497.000	287.000
32	207.000	418.000	424.000	.000	818.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE VOLUMES (ml)
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	418.000	350.000	702.000	359.000	936.000
35	224.000	199.000	417.000	352.000	481.000
36	898.000	843.000	357.000	252.000	632.000
MEAN	272.059	357.765	380.618	263.824	615.441
SD	199.656	194.563	208.513	174.712	323.384
GEOM MEAN					537.483
GEOM SD					1.728
CV%	73.387	54.383	54.783	66.223	52.545
SEM	34.241	33.367	35.760	29.963	55.460
MIN	.000	.000	.000	.000	145.000
MAX	898.000	928.000	901.000	685.000	1713.000
MEDIAN	259.000	356.000	355.000	271.500	562.500
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE VOLUMES (ml)
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	322.000	400.000	337.000	465.000	463.000
2	355.000	179.000	392.000	61.000	437.000
3	250.000	238.000	376.000	90.000	332.000
4	294.000	782.000	466.000	.000	561.000
5	175.000	150.000	149.000	288.000	875.000
6	116.000	209.000	342.000	137.000	447.000
7	212.000	296.000	197.000	280.000	792.000
8	918.000	419.000	667.000	623.000	558.000
9	675.000	772.000	907.000	541.000	740.000
10	250.000	341.000	378.000	464.000	732.000
11	292.000	337.000	897.000	266.000	556.000
12	82.000	338.000	276.000	198.000	221.000
13	107.000	.000	469.000	.000	886.000
14	83.000	182.000	182.000	93.000	576.000
15	332.000	190.000	.000	.000	434.000
16	474.000	643.000	360.000	352.000	581.000
17	343.000	397.000	197.000	329.000	744.000
18	192.000	72.000	166.000	25.000	350.000
19	.000	85.000	124.000	22.000	.000
20	196.000	193.000	389.000	149.000	317.000
21	380.000	335.000	652.000	241.000	791.000
22	751.000	1033.000	1260.000	889.000	655.000
23	212.000	233.000	352.000	.000	887.000
24	374.000	375.000	371.000	299.000	561.000
26	366.000	201.000	449.000	399.000	879.000
27	.000	293.000	269.000	857.000	856.000
28	.000	.000	277.000	190.000	491.000
29	363.000	.000	242.000	.000	339.000
30	.000	244.000	139.000	.000	301.000
31	117.000	613.000	605.000	153.000	695.000
32	277.000	431.000	868.000	.000	844.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE VOLUMES (ml)
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	519.000	503.000	686.000	414.000	407.000
35	184.000	164.000	410.000	243.000	655.000
36	904.000	618.000	285.000	264.000	580.000
MEAN	297.500	331.353	415.765	245.059	574.794
SD	235.311	238.044	268.308	235.334	219.943
GEOM MEAN					
GEOM SD					
CV%	79.096	71.840	64.534	96.031	38.265
SEM	40.356	40.824	46.014	40.359	37.720
MIN	.000	.000	.000	.000	.000
MAX	918.000	1033.000	1260.000	889.000	887.000
MEDIAN	263.500	294.500	365.500	219.500	568.500
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINE VOLUMES (ml)
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	316.000	685.000	1055.000	1113.000	1537.000
2	492.000	907.000	1307.000	1378.000	1826.000
3	218.000	533.000	690.000	690.000	1367.000
4	261.000	641.000	1253.000	1509.000	2667.000
5	289.000	453.000	795.000	1046.000	1864.000
6	197.000	408.000	574.000	683.000	1405.000
7	96.000	340.000	755.000	871.000	1739.000
8	447.000	1217.000	2015.000	2233.000	3128.000
9	585.000	1290.000	2125.000	2710.000	3786.000
10	203.000	459.000	753.000	1034.000	1459.000
11	198.000	370.000	482.000	574.000	1006.000
12	88.000	403.000	770.000	1015.000	1378.000
13	232.000	431.000	823.000	1179.000	1570.000
14	190.000	378.000	581.000	946.000	1724.000
15	163.000	354.000	559.000	782.000	1617.000
16	395.000	931.000	1346.000	1777.000	2624.000
17	291.000	843.000	1026.000	1216.000	1947.000
18	131.000	339.000	456.000	560.000	933.000
19	11.000	129.000	185.000	324.000	546.000
20	232.000	700.000	912.000	1117.000	1423.000
21	198.000	478.000	770.000	1044.000	1612.000
22	466.000	1135.000	1558.000	2045.000	2896.000
23	191.000	657.000	968.000	1551.000	2733.000
24	398.000	780.000	1169.000	1580.000	2438.000
26	379.000	833.000	1181.000	1622.000	2484.000
27	205.000	636.000	1090.000	1457.000	2270.000
28	244.000	587.000	878.000	1226.000	1686.000
29	240.000	498.000	820.000	1091.000	1868.000
30	224.000	458.000	507.000	710.000	1027.000
31	500.000	877.000	1325.000	1742.000	2117.000
32	.000	332.000	731.000	1182.000	2007.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINE VOLUMES (ml)
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	251.000	716.000	1120.000	1685.000	2213.000
35	291.000	649.000	977.000	1389.000	1894.000
36	62.000	756.000	1131.000	1893.000	2743.000
MEAN	255.412	623.618	961.382	1263.941	1927.471
SD	138.756	269.786	411.688	515.243	686.274
GEOM MEAN		566.266	875.000	1158.376	1802.551
GEOM SD		1.593	1.591	1.557	1.474
CV%	54.327	43.261	42.823	40.765	35.605
SEM	23.797	46.268	70.604	88.363	117.695
MIN	.000	129.000	185.000	324.000	546.000
MAX	585.000	1290.000	2125.000	2710.000	3786.000
MEDIAN	232.000	611.500	895.000	1180.500	1845.000
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINE VOLUMES (ml)
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	190.000	552.000	1010.000	1253.000	1708.000
2	243.000	658.000	958.000	1339.000	1686.000
3	312.000	662.000	968.000	1095.000	1306.000
4	464.000	842.000	1257.000	1257.000	2276.000
5	71.000	267.000	524.000	905.000	1671.000
6	224.000	619.000	777.000	1074.000	1644.000
7	331.000	619.000	884.000	1003.000	1619.000
8	643.000	1428.000	2180.000	2640.000	3195.000
9	688.000	1616.000	2517.000	3202.000	4325.000
10	331.000	765.000	1224.000	1662.000	2550.000
11	258.000	692.000	1159.000	1423.000	1857.000
12	287.000	500.000	657.000	812.000	1152.000
13	.000	.000	428.000	652.000	1201.000
14	.000	283.000	500.000	607.000	1063.000
15	184.000	379.000	379.000	591.000	1031.000
16	442.000	442.000	819.000	819.000	1317.000
17	322.000	576.000	768.000	768.000	1454.000
18	330.000	521.000	742.000	1021.000	1319.000
19	233.000	540.000	902.000	902.000	1084.000
20	35.000	301.000	471.000	554.000	854.000
21	.000	285.000	488.000	592.000	973.000
22	322.000	780.000	1640.000	2173.000	3886.000
23	180.000	552.000	824.000	1114.000	2173.000
24	260.000	642.000	995.000	1318.000	2011.000
26	226.000	684.000	1153.000	1603.000	2350.000
27	280.000	729.000	1057.000	1372.000	2229.000
28	334.000	586.000	1021.000	1471.000	2054.000
29	.000	439.000	644.000	1047.000	1907.000
30	.000	222.000	507.000	694.000	839.000
31	313.000	676.000	1445.000	1942.000	2229.000
32	207.000	625.000	1049.000	1049.000	1867.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINE VOLUMES (ml)
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	418.000	768.000	1470.000	1829.000	2765.000
35	224.000	423.000	840.000	1192.000	1673.000
36	898.000	1741.000	2098.000	2350.000	2982.000
MEAN	272.059	629.824	1010.441	1274.265	1889.706
SD	199.656	358.588	504.506	616.757	822.465
GEOM MEAN			907.212	1153.160	1737.683
GEOM SD			1.595	1.562	1.510
CV%	73.387	56.935	49.929	48.401	43.523
SEM	34.241	61.497	86.522	105.773	141.052
MIN	.000	.000	379.000	554.000	839.000
MAX	898.000	1741.000	2517.000	3202.000	4325.000
MEDIAN	259.000	602.500	930.000	1104.500	1697.000
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINE VOLUMES (ml)
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	322.000	722.000	1059.000	1524.000	1987.000
2	355.000	534.000	926.000	987.000	1424.000
3	250.000	488.000	864.000	954.000	1286.000
4	294.000	1076.000	1542.000	1542.000	2103.000
5	175.000	325.000	474.000	762.000	1637.000
6	116.000	325.000	667.000	804.000	1251.000
7	212.000	508.000	705.000	985.000	1777.000
8	918.000	1337.000	2004.000	2627.000	3185.000
9	675.000	1447.000	2354.000	2895.000	3635.000
10	250.000	591.000	969.000	1433.000	2165.000
11	292.000	629.000	1526.000	1792.000	2348.000
12	82.000	420.000	696.000	894.000	1115.000
13	107.000	107.000	576.000	576.000	1462.000
14	83.000	265.000	447.000	540.000	1116.000
15	332.000	522.000	522.000	522.000	956.000
16	474.000	1117.000	1477.000	1829.000	2410.000
17	343.000	740.000	937.000	1266.000	2010.000
18	192.000	264.000	430.000	455.000	805.000
19	.000	85.000	209.000	231.000	231.000
20	196.000	389.000	778.000	927.000	1244.000
21	380.000	715.000	1367.000	1608.000	2399.000
22	751.000	1784.000	3044.000	3933.000	4588.000
23	212.000	445.000	797.000	797.000	1684.000
24	374.000	749.000	1120.000	1419.000	1980.000
26	366.000	567.000	1016.000	1415.000	2294.000
27	.000	293.000	562.000	1419.000	2275.000
28	.000	.000	277.000	467.000	958.000
29	363.000	363.000	605.000	605.000	944.000
30	.000	244.000	383.000	383.000	684.000
31	117.000	730.000	1335.000	1488.000	2183.000
32	277.000	708.000	1576.000	1576.000	2420.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINE VOLUMES (ml)
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	519.000	1022.000	1708.000	2122.000	2529.000
35	184.000	348.000	758.000	1001.000	1656.000
36	904.000	1522.000	1807.000	2071.000	2651.000
MEAN	297.500	628.853	1044.618	1289.676	1864.471
SD	235.311	425.489	631.492	787.823	879.414
GEOM MEAN			878.701	1080.001	1644.623
GEOM SD			1.843	1.867	1.745
CV%	79.096	67.661	60.452	61.087	47.167
SEM	40.356	72.971	108.300	135.111	150.818
MIN	.000	.000	209.000	231.000	231.000
MAX	918.000	1784.000	3044.000	3933.000	4588.000
MEDIAN	263.500	528.000	895.000	1133.500	1878.500
n	34	34	34	34	34

APPENDIX 6

Urine Nicotine and Cotinine Concentrations

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 20.7 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	1387.840	1136.600	1245.110	792.450	1562.730
2	1540.460	1505.090	3381.370	5290.370	3130.660
3	2919.950	4169.800	4998.680	N.S.R.	8042.480
4	2023.100	1712.270	1916.500	1968.690	1813.350
5	834.500	122.260	1296.660	308.130	1493.690
6	4508.790	3604.350	4076.850	3867.880	3543.540
7	8177.690	7433.490	7013.610	5101.200	2843.710
8	1422.060	617.650	604.680	425.770	491.400
9	1398.950	922.590	2299.240	716.230	2040.340
10	1785.670	364.740	365.760	230.310	971.160
11	3518.550	8095.230	12819.760	4421.400	3391.520
12	2692.210	1848.860	3844.560	1546.230	3328.040
13	6502.400	198.070	1909.400	390.050	990.040
14	3608.150	968.460	2775.170	1522.460	761.250
15	5414.310	1714.240	461.490	3047.750	1526.250
16	2508.790	590.290	335.580	2903.200	1575.510
17	2020.810	1649.470	1342.290	1847.840	318.360
18	1549.430	753.160	248.600	315.630	1187.720
19	4579.640	1835.600	1714.820	73.500	196.930
20	1302.650	971.490	2780.040	1255.990	1325.640
21	7487.080	5588.740	9550.220	4577.520	3478.030
22	1691.080	1688.850	739.570	943.930	981.990
23	909.880	555.450	223.030	501.510	329.150
24	1630.080	2557.080	6565.130	1354.330	1480.210
26	4653.920	1248.300	2473.000	1414.740	2279.100
27	3382.710	3615.550	2767.530	1680.540	1283.670
28	1314.070	1764.360	2368.360	1519.900	2859.290
29	2693.310	311.900	189.050	2317.340	1320.390
30	215.540	168.040	499.050	884.190	158.800
31	1252.180	393.400	1392.420	1710.110	1626.980
32	N.S.R.	4865.430	5050.760	2319.290	2381.490

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 20.7 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	1297.270	1395.050	4385.610	1269.800	3220.320
35	1584.330	3780.300	5759.480	4103.960	3335.090
36	7576.490	1400.270	1701.860	1567.970	1523.620
MEAN	2890.421	2045.483	2914.566	1884.552	1964.484
SD	2118.905	2006.750	2843.169	1487.186	1495.042
GEOM MEAN	2236.287	1278.394	1762.583	1292.862	1460.386
GEOM SD	2.144	2.876	3.067	2.710	2.383
CV%	73.308	98.106	97.550	78.915	76.104
SEM	368.854	344.155	487.599	258.886	256.398
MIN	215.540	122.260	189.050	73.500	158.800
MAX	8177.690	8095.230	12819.760	5290.370	8042.480
MEDIAN	2020.810	1452.680	2107.870	1522.460	1544.490
n	33	34	34	33	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 20.7 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	227.770	182.930	285.850	431.270	405.340
2	97.330	113.830	313.300	410.390	622.160
3	1630.290	1467.560	1694.270	604.990	3261.690
4	120.290	722.490	1323.110	N.S.R.	364.670
5	28.490	67.240	666.700	393.050	102.530
6	769.600	404.370	952.380	1745.720	513.960
7	1467.370	1745.030	2792.540	2163.390	518.780
8	166.030	81.740	103.150	170.740	195.200
9	205.280	449.720	504.080	102.340	140.700
10	111.400	60.760	79.410	224.550	28.860
11	309.070	74.450	589.310	407.400	593.060
12	300.110	429.980	454.600	878.310	515.270
13	N.S.R.	N.S.R.	61.800	69.980	175.520
14	N.S.R.	282.910	136.840	700.530	179.700
15	38.650	126.490	N.S.R.	80.830	233.950
16	313.780	N.S.R.	382.670	N.S.R.	724.060
17	42.460	72.280	25.450	N.S.R.	59.590
18	105.520	79.090	30.620	90.250	241.460
19	348.590	67.000	154.090	N.S.R.	102.660
20	608.940	407.590	249.070	1969.500	696.590
21	N.S.R.	314.480	1875.210	2580.220	422.450
22	130.420	167.380	426.200	196.450	148.600
23	49.960	117.510	70.880	140.180	59.010
24	288.040	186.750	415.700	228.450	229.510
26	757.270	151.690	142.820	230.370	219.040
27	657.320	634.500	1052.980	379.540	157.720
28	308.020	256.840	235.150	180.740	235.270
29	N.S.R.	134.530	63.440	164.230	41.660
30	N.S.R.	255.930	90.080	932.480	756.160
31	214.000	117.620	396.780	102.550	102.160
32	182.150	496.130	133.220	N.S.R.	50.710

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 20.7 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	90.530	135.860	160.590	110.090	130.590
35	451.300	995.950	356.930	237.320	342.970
36	40.310	232.450	607.790	29.730	77.060
MEAN	346.907	344.784	509.909	550.193	372.019
SD	394.526	397.071	618.016	686.993	554.567
GEOM MEAN	204.677	218.744	275.495	296.573	219.792
GEOM SD	2.925	2.521	3.232	3.068	2.728
CV%	113.727	115.165	121.201	124.864	149.069
SEM	73.262	70.193	107.583	127.571	95.107
MIN	28.490	60.760	25.450	29.730	28.860
MAX	1630.290	1745.030	2792.540	2580.220	3261.690
MEDIAN	214.000	184.840	313.300	230.370	224.275
n	29	32	33	29	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 20.7 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	92.010	205.640	361.910	386.110	148.160
2	392.850	643.860	205.320	2097.030	729.380
3	1413.440	1258.160	858.720	1051.100	4786.710
4	317.220	303.330	865.490	N.S.R.	563.640
5	134.530	114.630	513.140	665.750	103.620
6	879.590	653.370	1411.910	314.510	517.810
7	794.710	114.570	673.890	729.420	316.470
8	44.480	80.970	190.020	37.880	124.140
9	172.240	300.390	358.950	347.460	425.640
10	136.670	43.100	31.410	62.160	88.700
11	191.030	227.670	184.680	470.060	691.640
12	730.770	209.990	950.430	1102.600	1228.750
13	1094.060	N.S.R.	34.530	N.S.R.	187.220
14	376.740	358.380	301.820	1507.180	257.140
15	233.410	383.340	N.S.R.	N.S.R.	287.490
16	63.450	57.980	43.290	40.610	315.320
17	222.480	178.560	296.930	296.590	43.420
18	49.490	170.260	177.510	136.790	98.870
19	N.S.R.	971.850	826.460	42.970	N.S.R.
20	104.660	497.080	170.100	416.640	284.510
21	999.280	973.380	522.560	1164.250	659.450
22	212.780	170.350	88.330	185.560	158.700
23	37.450	191.130	95.830	N.S.R.	60.500
24	218.620	141.640	694.280	610.130	510.460
26	479.340	703.120	246.550	279.700	310.790
27	N.S.R.	77.370	40.060	164.840	86.560
28	N.S.R.	N.S.R.	1238.440	2100.090	678.240
29	703.980	N.S.R.	1078.530	N.S.R.	169.620
30	N.S.R.	285.480	167.340	N.S.R.	527.250
31	106.290	87.580	207.640	406.040	253.430
32	286.390	59.770	290.030	N.S.R.	197.420

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 20.7 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	205.660	339.390	495.560	93.100	206.040
35	459.610	335.880	386.070	532.110	437.020
36	230.090	420.220	262.740	1121.810	287.490
MEAN	379.444	340.595	432.438	606.018	477.018
SD	355.478	302.510	369.921	585.754	814.654
GEOM MEAN	247.076	237.539	281.689	354.771	281.958
GEOM SD	2.677	2.425	2.842	3.250	2.555
CV%	93.684	88.818	85.543	96.656	170.780
SEM	64.901	54.332	64.395	112.728	141.813
MIN	37.450	43.100	31.410	37.880	43.420
MAX	1413.440	1258.160	1411.910	2100.090	4786.710
MEDIAN	226.285	227.670	296.930	406.040	287.490
n	30	31	33	27	33

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE COTININE CONCENTRATIONS (ng/ml)
LLOQ = 21.1 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	2019.500	2386.150	2849.210	3205.010	3221.890
2	2715.680	2833.510	3601.460	4050.740	3243.880
3	529.490	468.720	520.530	N.S.R.	599.510
4	3250.310	3216.400	3132.270	3354.120	2389.960
5	2085.880	1683.820	2309.260	1871.670	1670.540
6	4694.480	4535.430	4754.880	5403.230	4576.980
7	7212.610	7244.040	4860.690	5323.560	3148.640
8	841.630	603.580	672.010	1162.530	861.670
9	975.200	873.460	1083.860	798.260	1269.020
10	1518.470	1447.430	1286.120	1760.600	1483.580
11	3241.840	3482.550	4001.860	3451.170	3262.000
12	1270.650	1221.270	1165.800	1117.590	1481.580
13	2066.010	2199.540	2527.880	2103.230	1198.120
14	2282.780	2659.060	2857.720	2891.550	1893.790
15	1913.800	1634.680	1713.600	2283.450	1331.600
16	2672.270	2912.640	2519.730	3145.910	2371.790
17	3029.890	1723.780	2716.760	2885.790	2290.020
18	1333.970	1331.770	1205.090	1456.890	814.890
19	2308.970	2110.530	2204.660	1991.700	1406.810
20	2063.310	1410.200	1630.910	1964.880	2557.850
21	2483.770	2190.720	3267.540	2909.360	3453.180
22	2449.350	1772.440	2412.310	2418.220	2505.120
23	2695.910	2283.090	2899.220	2389.870	1673.150
24	2931.810	2317.080	3557.900	2725.940	2812.190
26	4029.020	1969.080	3572.900	1876.080	2164.500
27	2654.960	2639.230	2553.470	1426.860	2091.410
28	2141.010	1680.810	2278.360	1286.390	2295.390
29	2874.720	4261.340	3995.460	4805.570	2786.600
30	188.860	222.870	222.650	267.310	211.860
31	2134.870	2640.320	2584.820	2813.040	3006.070
32	N.S.R.	2880.360	2984.960	1713.870	2408.390

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE COTININE CONCENTRATIONS (ng/ml)
LLOQ = 21.1 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	4574.970	4571.520	5575.730	3975.850	4861.410
35	2747.420	2876.650	3782.170	2425.780	3084.560
36	2841.360	1637.470	2128.370	1894.710	2312.930
MEAN	2508.326	2350.634	2630.299	2519.719	2257.085
SD	1314.705	1358.683	1254.392	1222.651	1045.010
GEOM MEAN	2133.502	1966.761	2234.597	2196.636	1959.222
GEOM SD	1.942	1.954	1.961	1.803	1.852
CV%	52.414	57.801	47.690	48.523	46.299
SEM	228.861	233.012	215.126	212.836	179.218
MIN	188.860	222.870	222.650	267.310	211.860
MAX	7212.610	7244.040	5575.730	5403.230	4861.410
MEDIAN	2449.350	2195.130	2569.145	2389.870	2304.160
n	33	34	34	33	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE COTININE CONCENTRATIONS (ng/ml)
LLOQ = 21.1 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	1270.840	1028.900	1110.810	1018.410	1211.520
2	1125.610	1204.220	1539.500	588.400	912.250
3	277.070	299.680	306.730	305.250	301.650
4	748.420	1168.320	1194.030	N.S.R.	986.710
5	822.370	863.940	997.610	580.210	690.050
6	1985.870	1638.400	1368.510	1845.420	1234.190
7	3181.110	2252.480	2954.960	3360.230	1511.700
8	403.130	348.140	344.730	541.770	575.780
9	405.000	352.050	405.970	427.450	474.470
10	804.570	714.400	511.940	847.750	536.500
11	1016.820	585.620	837.730	829.050	1070.100
12	1092.690	1231.150	1139.450	1105.310	1513.230
13	N.S.R.	N.S.R.	781.950	906.230	996.410
14	N.S.R.	1095.520	1013.910	1456.710	1084.640
15	352.850	686.270	N.S.R.	834.520	652.190
16	814.490	N.S.R.	1018.090	N.S.R.	2629.960
17	845.730	899.980	684.810	N.S.R.	938.720
18	752.060	743.540	946.790	842.320	1193.020
19	823.970	654.990	609.560	N.S.R.	823.160
20	1144.600	1056.620	1343.410	1509.370	1741.110
21	N.S.R.	1176.860	1788.200	1408.930	1737.030
22	320.300	373.620	625.860	275.090	617.730
23	1131.900	1097.710	944.080	909.360	756.770
24	1115.680	710.210	1140.830	914.700	986.430
26	1448.690	669.410	948.480	486.360	789.630
27	538.340	591.740	737.610	676.380	713.700
28	475.390	533.990	777.600	636.080	827.910
29	N.S.R.	803.410	933.690	957.420	738.440
30	N.S.R.	676.010	566.540	907.110	1101.180
31	577.550	790.540	598.020	618.290	953.830
32	830.370	746.710	692.230	N.S.R.	745.820

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE COTININE CONCENTRATIONS (ng/ml)
LLOQ = 21.1 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	934.750	1200.510	881.920	880.110	873.340
35	978.290	965.490	746.230	621.950	979.820
36	66.930	199.820	502.330	482.620	487.270
MEAN	906.393	855.008	939.215	923.200	981.949
SD	591.440	412.859	494.469	593.528	447.789
GEOM MEAN	741.438	761.531	842.628	800.695	899.176
GEOM SD	2.033	1.665	1.594	1.686	1.528
CV%	65.252	48.287	52.647	64.290	45.602
SEM	109.828	72.984	86.076	110.215	76.795
MIN	66.930	199.820	306.730	275.090	301.650
MAX	3181.110	2252.480	2954.960	3360.230	2629.960
MEDIAN	823.970	768.625	881.920	842.320	925.485
n	29	32	33	29	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
URINE COTININE CONCENTRATIONS (ng/ml)
LLOQ = 21.1 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
1	983.800	804.350	940.810	823.140	813.800
2	1566.300	1592.920	1519.290	2184.330	1755.120
3	315.040	296.380	267.470	296.230	381.000
4	1174.210	1112.640	1430.230	N.S.R.	1647.650
5	1321.500	1309.550	1400.280	1333.550	1039.690
6	1774.240	1603.290	1785.220	1933.400	1728.300
7	2053.360	1485.170	1701.780	2031.040	1004.190
8	248.040	370.200	324.760	483.290	665.980
9	605.230	657.920	561.810	670.150	821.320
10	853.820	789.600	900.040	648.850	881.750
11	1436.300	1097.800	779.370	938.800	1205.840
12	1536.170	1360.420	1365.800	1428.700	1735.170
13	1215.210	N.S.R.	1164.090	N.S.R.	1035.670
14	971.380	1105.160	1177.600	1489.660	1238.050
15	740.390	594.590	N.S.R.	N.S.R.	895.240
16	948.760	703.110	1075.470	1234.860	945.470
17	1035.740	945.880	1279.330	1397.610	950.950
18	584.710	803.960	951.460	950.510	1114.520
19	N.S.R.	1289.050	1050.880	1172.700	N.S.R.
20	635.150	916.510	1141.660	1508.270	1737.770
21	1382.700	936.450	952.630	1371.230	894.580
22	742.920	486.990	635.890	875.490	764.000
23	844.790	954.980	741.600	N.S.R.	742.410
24	1010.760	657.560	1337.980	1276.350	1462.440
26	1014.400	1034.230	851.170	406.350	579.850
27	N.S.R.	976.130	864.820	778.050	741.770
28	N.S.R.	N.S.R.	1164.300	1364.300	1093.210
29	1554.660	N.S.R.	1648.300	N.S.R.	1957.550
30	N.S.R.	991.790	966.970	N.S.R.	1448.280
31	1143.690	860.870	732.020	1192.420	904.110
32	440.960	277.520	505.180	N.S.R.	659.320

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

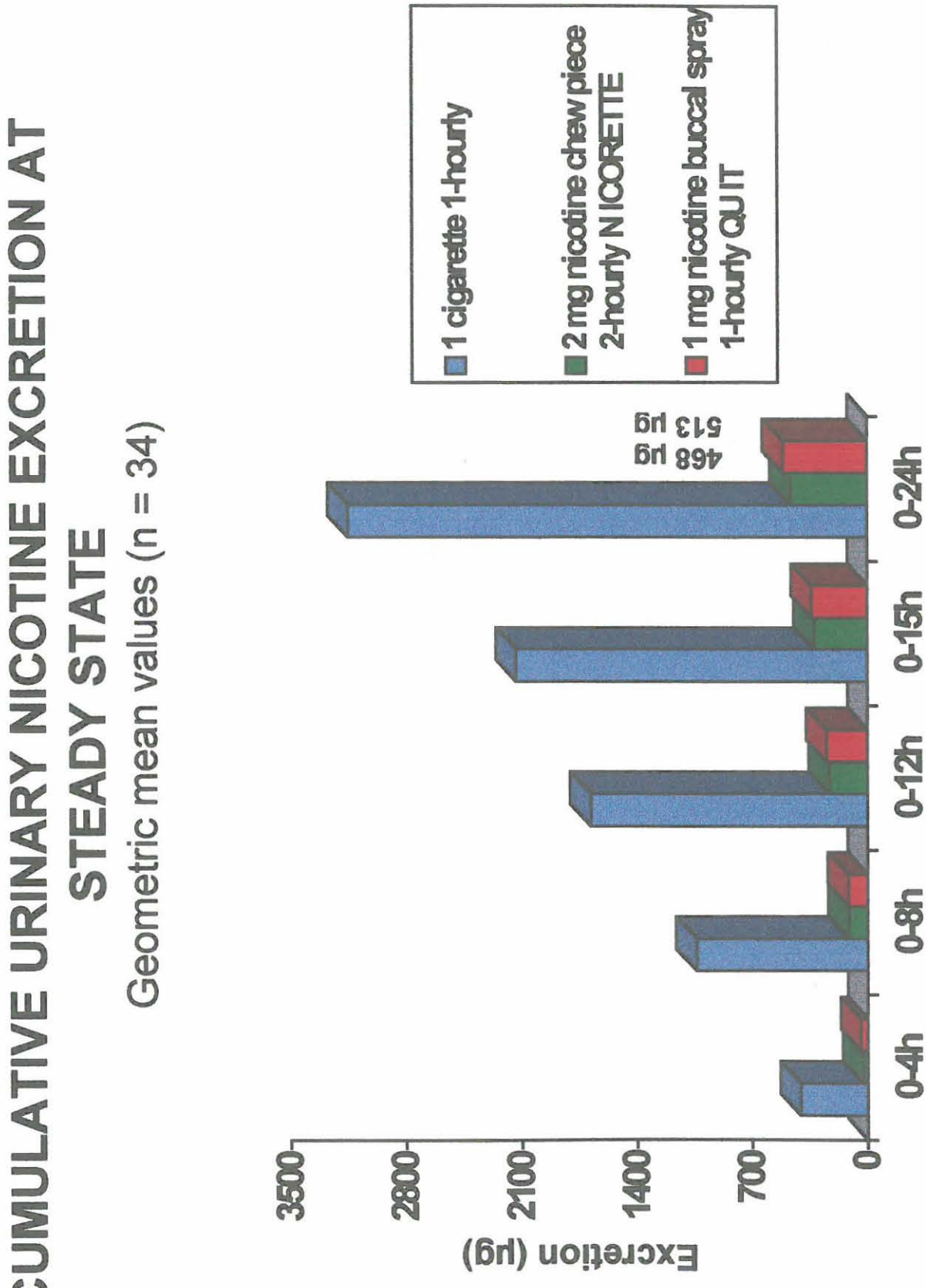
FARMOVS 18/96 (SACT 02/96)
URINE COTININE CONCENTRATIONS (ng/ml)
LLOQ = 21.1 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	4 - 8 h	8 - 12 h	12 - 15 h	15 - 24 h
33	1312.420	1579.930	1340.740	1313.900	1888.410
35	1290.670	819.630	979.130	1256.230	1104.310
36	378.280	474.030	838.370	1055.390	1047.080
MEAN	1037.187	931.891	1041.711	1163.511	1117.721
SD	442.652	370.448	374.096	466.224	414.526
GEOM MEAN	929.251	850.499	963.439	1058.698	1044.462
GEOM SD	1.673	1.588	1.543	1.609	1.462
CV%	42.678	39.752	35.912	40.070	37.087
SEM	80.817	66.534	65.122	89.725	72.160
MIN	248.040	277.520	267.470	296.230	381.000
MAX	2053.360	1603.290	1785.220	2184.330	1957.550
MEDIAN	1012.580	936.450	979.130	1234.860	1035.670
n	30	31	33	27	33

APPENDIX 7

Cumulative Urinary Nicotine Excretion

Figure 7: Cumulative Urinary Nicotine Excretion at Steady State



PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY NICOTINE EXCRETION (ug)
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	438.557	857.963	1318.654	1364.616	2027.213
2	757.906	1382.519	2735.067	3110.683	4513.219
3	636.549	1950.036	2734.829	2734.829	8179.588
4	528.029	1178.692	2351.590	2855.574	4955.434
5	241.171	261.221	704.679	782.019	2003.858
6	888.232	1648.750	2325.507	2747.105	5305.541
7	785.058	2598.830	5509.478	6101.217	8569.558
8	635.661	1111.251	1593.786	1686.604	2126.407
9	818.386	1468.812	3388.677	3807.672	6003.078
10	362.491	455.864	563.398	628.115	1040.858
11	696.673	2089.052	3524.866	3931.635	5396.771
12	236.914	819.305	2230.259	2609.085	3817.164
13	1508.557	1547.973	2296.458	2435.315	2822.421
14	685.548	867.619	1430.979	1986.676	2578.929
15	882.533	1209.952	1304.558	1984.206	3258.625
16	990.972	1307.367	1446.633	2697.912	4032.369
17	588.056	1498.563	1744.202	2095.292	2328.013
18	202.975	359.633	388.719	421.544	864.564
19	50.376	266.977	363.007	373.223	416.942
20	302.215	756.872	1346.241	1603.719	2009.364
21	1482.442	3047.289	5835.953	7090.193	9065.715
22	788.043	1917.884	2230.722	2690.416	3526.089
23	173.787	432.627	501.989	794.369	1183.425
24	648.772	1625.576	4179.412	4736.042	6006.062
26	1763.836	2330.564	3191.168	3815.068	5779.652
27	693.456	2251.758	3508.216	4124.975	5168.599
28	320.633	925.809	1615.001	2143.927	3459.200
29	646.394	726.865	787.739	1415.738	2441.681
30	48.281	87.602	112.056	291.546	341.886
31	626.090	774.402	1398.206	2111.322	2721.439
32	.000	1615.323	3630.576	4676.576	6641.306

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY NICOTINE EXCRETION (ug)
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	325.615	974.313	2746.099	3463.536	5163.865
35	461.040	1814.387	3703.497	5394.328	7078.549
36	469.742	1441.530	2079.727	3274.521	4569.598
MEAN	608.382	1282.446	2200.646	2705.282	3982.264
SD	403.769	710.426	1403.768	1642.901	2328.940
GEOM MEAN		1038.767	1682.542	2131.035	3150.676
GEOM SD		2.137	2.359	2.208	2.218
CV%	66.368	55.396	63.789	60.729	58.483
SEM	69.246	121.837	240.744	281.755	399.410
MIN	.000	87.602	112.056	291.546	341.886
MAX	1763.836	3047.289	5835.953	7090.193	9065.715
MEDIAN	630.875	1258.659	2154.993	2649.750	3671.626
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY NICOTINE EXCRETION (ug)
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	43.276	109.497	240.416	345.215	529.645
2	23.651	70.891	164.881	321.239	537.129
3	508.650	1022.297	1540.743	1617.577	2305.793
4	55.815	328.916	878.006	878.006	1249.605
5	2.023	15.202	186.544	336.296	414.834
6	172.390	332.117	482.593	1001.071	1294.029
7	485.699	988.268	1728.291	1985.735	2305.303
8	106.757	170.923	248.492	327.032	435.368
9	141.233	558.573	1012.749	1082.852	1240.858
10	36.873	63.243	99.692	198.045	223.673
11	79.740	112.051	387.259	494.813	752.201
12	86.132	177.717	249.090	385.228	560.419
13	.000	.000	26.450	42.126	138.486
14	.000	80.064	109.758	184.715	266.658
15	7.112	31.777	31.777	48.913	151.851
16	138.691	138.691	282.957	282.957	643.539
17	13.672	32.031	36.918	36.918	77.796
18	34.822	49.928	56.695	81.875	153.830
19	81.221	101.790	157.571	157.571	176.255
20	21.313	129.732	172.074	335.542	544.519
21	.000	89.627	470.294	738.637	899.591
22	41.995	118.655	485.187	589.895	844.447
23	8.993	52.707	71.986	112.638	175.130
24	74.890	146.229	292.971	366.760	525.811
26	171.143	240.617	307.600	411.266	574.889
27	184.050	468.940	814.318	933.873	1069.039
28	102.879	167.602	269.893	351.226	488.388
29	.000	59.059	72.064	138.249	174.076
30	.000	56.816	82.489	256.863	366.506
31	66.982	109.678	414.802	465.769	495.089
32	37.705	245.087	301.573	301.573	343.053

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY NICOTINE EXCRETION (ug)
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	37.842	85.393	198.127	237.649	359.881
35	101.091	299.285	448.125	531.662	696.630
36	36.198	232.154	449.135	456.627	505.329
MEAN	85.378	202.516	375.633	471.659	632.931
SD	117.596	239.413	398.642	434.368	535.715
GEOM MEAN			232.529	321.162	468.068
GEOM SD			2.842	2.594	2.235
CV%	137.736	118.219	106.125	92.094	84.640
SEM	20.168	41.059	68.367	74.494	91.874
MIN	.000	.000	26.450	36.918	77.796
MAX	508.650	1022.297	1728.291	1985.735	2305.793
MEDIAN	42.635	115.353	259.492	340.755	515.570
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY NICOTINE EXCRETION (ug)
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	29.627	111.883	233.847	413.388	481.986
2	139.462	254.713	335.198	463.117	781.856
3	353.360	652.802	975.681	1070.280	2659.468
4	93.263	330.467	733.785	733.785	1049.987
5	23.543	40.737	117.195	308.931	399.599
6	102.032	238.587	721.460	764.548	996.009
7	168.479	202.391	335.148	539.385	790.029
8	40.833	74.759	201.502	225.102	294.372
9	116.262	348.163	673.731	861.707	1176.680
10	34.167	48.865	60.738	89.580	154.508
11	55.781	132.506	298.164	423.199	807.751
12	59.923	130.900	393.218	611.533	883.087
13	117.064	117.064	133.259	133.259	299.136
14	31.269	96.495	151.426	291.594	439.706
15	77.492	150.327	150.327	150.327	275.097
16	30.075	67.356	82.941	97.236	280.436
17	76.311	147.199	205.694	303.272	335.577
18	9.502	21.761	51.227	54.647	89.252
19	.000	82.607	185.088	186.034	186.034
20	20.513	116.450	182.619	244.698	334.888
21	379.726	705.809	1046.518	1327.102	1848.727
22	159.798	335.769	447.065	612.028	715.977
23	7.939	52.473	86.205	86.205	139.868
24	81.764	134.879	392.457	574.886	861.254
26	175.438	316.766	427.467	539.067	812.251
27	.000	22.669	33.446	174.713	248.809
28	.000	.000	343.048	742.065	1075.081
29	255.545	255.545	516.549	516.549	574.050
30	.000	69.657	92.917	92.917	251.620
31	12.436	66.122	191.745	253.869	430.003
32	79.330	105.091	356.837	356.837	523.459

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY NICOTINE EXCRETION (ug)
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	106.738	277.451	617.405	655.948	739.807
35	84.568	139.653	297.941	427.244	713.492
36	208.001	467.697	542.578	838.736	1005.480
MEAN	92.066	185.753	341.601	445.994	666.333
SD	94.843	167.804	259.539	305.746	516.953
GEOM MEAN			250.250	338.978	513.392
GEOM SD			2.360	2.261	2.127
CV%	103.017	90.337	75.977	68.554	77.582
SEM	16.266	28.778	44.511	52.435	88.657
MIN	.000	.000	33.446	54.647	89.252
MAX	379.726	705.809	1046.518	1327.102	2659.468
MEDIAN	76.901	131.703	298.052	418.294	548.755
n	34	34	34	34	34

APPENDIX 8

Cumulative Urinary Cotinine Excretion

CUMULATIVE URINARY COTININE EXCRETION AT STEADY STATE

Geometric mean values (n = 34)

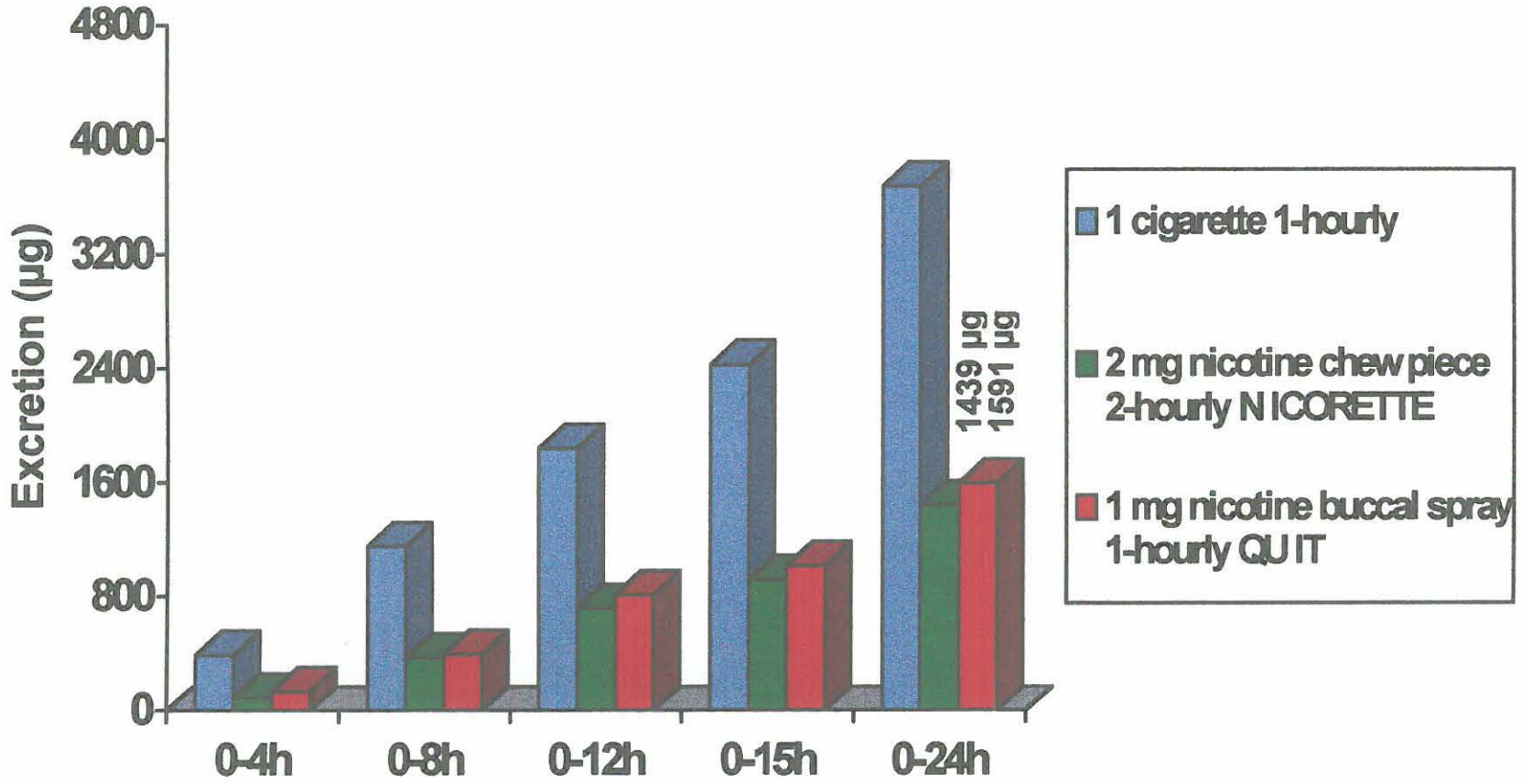


Figure 8: Cumulative Urinary Cotinine Excretion at Steady State

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY COTININE EXCRETION (ug)
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	638.162	1518.651	2572.859	2758.750	4124.831
2	1336.115	2512.021	3952.605	4240.208	5693.466
3	115.429	263.076	344.799	344.799	750.667
4	848.331	2070.563	3987.512	4846.167	7613.741
5	602.819	878.966	1668.733	2138.522	3505.024
6	924.813	1881.788	2671.098	3260.051	6564.630
7	692.411	2459.956	4477.143	5094.676	7827.695
8	376.209	840.965	1377.229	1630.661	2401.855
9	570.492	1186.281	2091.304	2558.286	3923.752
10	308.249	678.792	1056.911	1551.639	2182.161
11	641.884	1240.883	1689.091	2006.599	3415.783
12	111.817	496.517	924.366	1198.175	1735.989
13	479.314	917.023	1907.952	2656.702	3125.167
14	433.728	933.631	1513.749	2569.164	4042.533
15	311.949	624.173	975.461	1484.671	2596.557
16	1055.547	2616.722	3662.410	5018.297	7027.203
17	881.698	1833.224	2330.392	2878.692	4552.696
18	174.750	451.758	592.754	744.270	1048.224
19	25.399	274.441	397.902	674.748	987.060
20	478.688	1138.661	1484.414	1887.215	2669.917
21	491.786	1105.188	2059.310	2856.475	4817.881
22	1141.397	2327.159	3347.567	4525.240	6657.097
23	514.919	1578.839	2480.496	3873.791	5851.454
24	1166.860	2051.985	3436.008	4556.369	6969.228
26	1526.999	2420.961	3664.330	4491.681	6357.480
27	544.267	1681.775	2841.050	3364.708	5065.024
28	522.406	1098.924	1761.927	2209.591	3265.470
29	689.933	1789.358	3075.896	4378.206	6543.395
30	42.305	94.456	105.366	159.630	226.790
31	1067.435	2062.836	3220.835	4393.873	5521.149
32	.000	956.280	2147.279	2920.234	4907.155

PROGRAM: S T A T S (V 1.3)

Division of Biometry
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University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY COTININE EXCRETION (ug)
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	1148.318	3274.074	5526.669	7773.024	10339.850
35	799.499	1829.340	3069.892	4069.313	5627.016
36	176.164	1312.568	2110.707	3554.476	5520.467
MEAN	612.944	1423.583	2309.589	3019.674	4513.483
SD	396.256	780.221	1270.743	1639.719	2324.491
GEOM MEAN		1152.520	1837.644	2421.895	3665.683
GEOM SD		2.147	2.278	2.242	2.197
CV%	64.648	54.807	55.020	54.301	51.501
SEM	67.957	133.807	217.931	281.209	398.647
MIN	.000	94.456	105.366	159.630	226.790
MAX	1526.999	3274.074	5526.669	7773.024	10339.850
MEDIAN	557.380	1276.726	2128.993	2867.583	4685.288
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
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University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY COTININE EXCRETION (ug)
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	241.460	613.921	1122.672	1370.146	1921.388
2	273.523	773.275	1235.125	1459.305	1775.856
3	86.446	191.334	285.193	323.960	387.608
4	347.267	788.892	1284.414	1284.414	2289.872
5	58.388	227.721	484.106	705.166	1233.745
6	444.835	1092.003	1308.228	1856.317	2559.806
7	1052.947	1701.662	2484.726	2884.594	3815.801
8	259.213	532.503	791.740	1040.954	1360.512
9	278.640	605.342	971.121	1263.925	1796.754
10	266.313	576.362	811.343	1182.657	1659.069
11	262.340	516.499	907.719	1126.588	1591.011
12	313.602	575.837	754.731	926.054	1440.552
13	.000	.000	334.675	537.670	1084.699
14	.000	310.032	530.051	685.919	1180.515
15	64.924	198.747	198.747	375.665	662.629
16	360.005	360.005	743.825	743.825	2053.545
17	272.325	500.920	632.403	632.403	1276.365
18	248.180	390.196	599.437	834.444	1189.964
19	191.985	393.067	613.728	613.728	763.543
20	40.061	321.122	549.502	674.779	1197.112
21	.000	335.405	698.410	844.938	1506.747
22	103.137	274.255	812.494	959.117	2017.289
23	203.742	612.090	868.880	1132.594	1934.014
24	290.077	561.377	964.090	1259.538	1943.134
26	327.404	633.994	1078.831	1297.693	1887.547
27	150.735	416.426	658.363	871.422	1483.063
28	158.780	293.346	631.602	917.838	1400.509
29	.000	352.697	544.103	929.944	1565.002
30	.000	150.074	311.538	481.168	640.839
31	180.773	467.739	927.617	1234.907	1508.656
32	171.887	484.011	777.517	777.517	1387.598

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY COTININE EXCRETION (ug)
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	390.725	810.904	1430.012	1745.971	2563.417
35	219.137	411.269	722.447	941.374	1412.667
36	60.103	228.551	407.883	529.503	837.458
MEAN	215.263	491.223	808.155	1013.119	1568.479
SD	194.201	306.198	422.693	490.704	648.188
GEOM MEAN			717.587	916.473	1438.524
GEOM SD			1.654	1.575	1.556
CV%	90.216	62.334	52.303	48.435	41.326
SEM	33.305	52.513	72.491	84.155	111.163
MIN	.000	.000	198.747	323.960	387.608
MAX	1052.947	1701.662	2484.726	2884.594	3815.801
MEDIAN	211.439	442.083	749.278	927.999	1494.905
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY COTININE EXCRETION (ug)
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
1	316.784	638.524	955.577	1338.337	1715.126
2	556.036	841.169	1436.731	1569.975	2336.962
3	78.760	149.298	249.867	276.528	403.020
4	345.218	1215.302	1881.789	1881.789	2806.121
5	231.262	427.695	636.337	1020.399	1930.128
6	205.812	540.899	1151.445	1416.321	2188.871
7	435.312	874.923	1210.173	1778.865	2574.183
8	227.701	382.815	599.429	900.519	1272.136
9	408.530	916.444	1426.006	1788.557	2396.334
10	213.455	482.709	822.924	1123.990	1769.431
11	419.400	789.358	1488.453	1738.174	2408.621
12	125.966	585.788	962.749	1245.631	1629.104
13	130.027	130.027	675.986	675.986	1593.589
14	80.625	281.764	496.087	634.625	1347.742
15	245.809	358.782	358.782	358.782	747.316
16	449.712	901.812	1288.981	1723.652	2272.970
17	355.259	730.773	982.801	1442.615	2150.122
18	112.264	170.149	328.092	351.855	741.937
19	.000	109.569	239.878	265.678	265.678
20	124.489	301.376	745.482	970.214	1521.087
21	525.426	839.137	1460.251	1790.718	2498.331
22	557.933	1060.994	1862.215	2640.526	3140.946
23	179.095	401.606	662.649	662.649	1321.167
24	378.024	624.609	1121.000	1502.628	2323.057
26	371.270	579.151	961.326	1123.460	1633.148
27	.000	286.006	518.643	1185.432	1820.387
28	.000	.000	322.511	581.728	1118.494
29	564.342	564.342	963.230	963.230	1626.840
30	.000	241.997	376.406	376.406	812.338
31	133.812	661.525	1104.397	1286.837	1915.194
32	122.146	241.757	680.253	680.253	1236.719

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
CUMULATIVE URINARY COTININE EXCRETION (ug)
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0 - 4 h	0 - 8 h	0 - 12 h	0 - 15 h	0 - 24 h
33	681.146	1475.851	2395.598	2939.553	3708.136
35	237.483	371.903	773.346	1078.610	1801.933
36	341.965	634.916	873.851	1152.474	1759.780
MEAN	269.267	553.323	941.566	1190.206	1787.851
SD	185.891	336.056	506.671	631.160	750.145
GEOM MEAN			808.913	1014.249	1591.276
GEOM SD			1.795	1.851	1.735
CV%	69.036	60.734	53.812	53.030	41.958
SEM	31.880	57.633	86.893	108.243	128.649
MIN	.000	.000	239.878	265.678	265.678
MAX	681.146	1475.851	2395.598	2939.553	3708.136
MEDIAN	234.372	552.620	914.714	1138.232	1764.605
n	34	34	34	34	34

APPENDIX 9

Plasma Nicotine Concentrations

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

* BLQ VALUES IN DATA WERE SUBSTITUTED WITH HALF THE LLOQ VALUE

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
1	9.050	10.340	9.100	28.370
2	2.710	3.930	4.620	21.490
3	17.280	27.550	27.910	57.000
4	4.440	5.800	4.710	27.720
5	4.290	2.130	4.290	17.770
6	2.690	4.590	3.690	19.040
7	2.060	3.650	4.230	23.200
8	1.430	1.190	1.030	11.110
9	1.580	2.340	2.390	17.290
10	2.270	1.980	1.760	9.590
11	1.670	3.390	2.850	23.680
12	BLQ	1.950	1.810	11.330
13	2.860	4.960	7.000	23.480
14	3.510	4.810	5.920	17.220
15	1.330	3.280	4.880	20.030
16	2.470	3.510	7.380	26.870
17	3.770	7.860	11.860	22.490
18	.920	1.670	2.300	7.090
19	.730	1.810	2.600	10.410
20	3.890	3.370	3.700	15.840
21	3.120	4.890	5.360	23.840
22	2.990	3.720	5.390	27.270
23	3.060	2.500	3.430	20.100
24	5.320	5.210	6.400	28.740
26	2.280	4.120	3.610	18.120
27	2.460	2.200	1.730	16.850
28	1.600	2.550	2.390	15.490
29	1.610	4.170	3.240	20.760
30	BLQ	BLQ	BLQ	1.050
31	.840	1.620	1.180	15.770
32	2.130	2.350	1.750	10.290

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

* BLQ VALUES IN DATA WERE SUBSTITUTED WITH HALF THE LLOQ VALUE

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
33	3.000	3.160	2.730	25.240
35	1.580	2.670	2.530	21.130
36	1.400	2.250	2.300	21.170
MEAN	2.970*	4.172*	4.600*	19.907
SD	3.019	4.558	4.775	9.259
GEOM MEAN	2.181	3.160	3.387	17.403
GEOM SD	2.217	2.053	2.193	1.886
CV%	101.654	109.263	103.806	46.512
SEM	.518	.782	.819	1.588
MIN	BLQ	BLQ	BLQ	1.050
MAX	17.280	27.550	27.910	57.000
MEDIAN	2.370	3.325	3.520	20.065
n	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

* BLQ VALUES IN DATA WERE SUBSTITUTED WITH HALF THE LLOQ VALUE

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
1	14.730	2.720	2.640	9.040
2	1.070	1.050	1.460	6.140
3	19.690	8.630	14.030	25.830
4	2.340	1.690	1.540	7.370
5	1.850	1.420	1.630	3.810
6	5.320	.950	1.400	4.330
7	7.830	1.330	2.060	5.750
8	1.100	BLQ	BLQ	2.370
9	BLQ	.830	.640	3.090
10	3.660	.800	1.170	3.600
11	1.210	1.200	1.170	4.630
12	.880	.770	1.040	4.420
13	1.370	1.300	1.020	5.500
14	3.630	1.190	.980	4.670
15	3.220	.690	.680	3.450
16	1.530	1.170	1.020	4.130
17	2.060	1.250	1.080	3.660
18	1.250	BLQ	BLQ	4.120
19	1.390	BLQ	BLQ	2.930
20	.980	1.030	1.990	4.150
21	2.720	2.270	1.410	5.660
22	1.190	1.270	.980	4.600
23	2.710	1.100	.760	3.470
24	5.490	1.350	1.040	3.670
26	2.720	1.860	1.370	3.440
27	BLQ	BLQ	.820	4.040
28	.880	.970	1.720	4.530
29	2.060	2.770	1.240	3.650
30	BLQ	.870	BLQ	4.400
31	BLQ	BLQ	.830	3.460
32	1.310	1.140	.790	3.390

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

* BLQ VALUES IN DATA WERE SUBSTITUTED WITH HALF THE LLOQ VALUE

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
33	2.890	1.130	1.060	5.370
35	2.470	1.200	.720	3.060
36	BLQ	BLQ	BLQ	2.320
MEAN	2.975*	1.349*	1.467*	4.943
SD	4.016	1.423	2.283	3.931
GEOM MEAN	1.739	1.023	1.024	4.358
GEOM SD	2.785	2.042	2.068	1.529
CV%	134.995	105.532	155.604	79.541
SEM	.689	.244	.391	.674
MIN	BLQ	BLQ	BLQ	2.320
MAX	19.690	8.630	14.030	25.830
MEDIAN	1.690	1.135	1.040	4.125
n	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

* BLQ VALUES IN DATA WERE SUBSTITUTED WITH HALF THE LLOQ VALUE

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
1	3.270	3.410	2.400	5.460
2	5.380	1.240	2.760	9.310
3	17.210	16.070	16.300	25.710
4	7.900	1.820	2.980	10.070
5	3.310	2.910	1.480	6.450
6	.830	.740	1.010	6.070
7	1.070	.720	.870	5.520
8	.690	.650	BLQ	1.590
9	4.030	1.040	1.930	3.880
10	.840	BLQ	.800	3.720
11	5.140	1.170	1.670	5.190
12	2.450	1.170	1.480	6.680
13	3.420	1.570	1.150	5.480
14	1.310	1.490	1.490	4.430
15	.820	1.830	1.070	4.490
16	4.070	1.410	.970	5.250
17	6.020	1.430	1.270	5.310
18	BLQ	BLQ	BLQ	3.490
19	BLQ	BLQ	BLQ	3.240
20	2.710	.780	BLQ	5.730
21	3.650	1.280	1.680	6.550
22	3.060	1.320	2.000	5.300
23	.940	1.120	.860	3.020
24	1.100	1.580	1.520	5.070
26	BLQ	.800	1.570	4.330
27	1.660	1.230	.640	2.710
28	1.960	1.280	1.190	4.110
29	BLQ	2.050	2.260	5.910
30	BLQ	BLQ	BLQ	3.690
31	1.080	.850	.880	3.710
32	BLQ	BLQ	BLQ	2.140

PROGRAM: S T A T S (V 1.3)

Division of Biometry
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University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

* BLQ VALUES IN DATA WERE SUBSTITUTED WITH HALF THE LLOQ VALUE

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
33	.740	.860	1.970	6.560
35	1.490	.740	.720	3.010
36	2.790	.930	.770	3.030
MEAN	2.672*	1.620*	1.694*	5.477
SD	3.191	2.643	2.677	4.004
GEOM MEAN	1.586	1.083	1.117	4.771
GEOM SD	2.886	2.168	2.273	1.626
CV%	119.430	163.124	158.050	73.106
SEM	.547	.453	.459	.687
MIN	BLQ	BLQ	BLQ	1.590
MAX	17.210	16.070	16.300	25.710
MEDIAN	1.575	1.170	1.170	5.130
n	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
1	28.370	41.830	39.790	40.270	33.990	38.250
2	21.490	26.370	35.660	30.050	29.120	25.970
3	57.000	60.350	56.390	58.780	55.490	54.220
4	27.720	38.260	36.230	31.910	34.060	31.130
5	17.770	26.490	22.910	24.010	22.720	23.330
6	19.040	35.000	30.640	27.520	28.810	28.520
7	23.200	32.170	31.280	31.430	31.340	28.830
8	11.110	22.510	18.840	15.840	14.700	14.130
9	17.290	28.250	30.690	25.140	24.240	23.820
10	9.590	20.910	16.990	14.900	14.000	13.230
11	23.680	33.390	33.820	34.640	30.170	29.330
12	11.330	17.190	18.310	17.560	16.230	15.460
13	23.480	29.230	27.800	25.740	22.360	22.110
14	17.220	25.740	24.930	22.010	19.390	20.780
15	20.030	27.740	28.450	25.600	24.000	22.220
16	26.870	59.880	42.160	35.820	33.150	31.150
17	22.490	36.220	30.140	24.920	24.300	21.460
18	7.090	18.080	13.450	13.370	11.540	11.460
19	10.410	21.570	18.120	15.260	12.950	10.560
20	15.840	29.410	24.610	19.680	21.130	18.590
21	23.840	46.520	33.900	31.940	25.970	25.290
22	27.270	32.340	33.130	32.220	28.790	29.890
23	20.100	38.970	29.040	24.860	23.410	22.080
24	28.740	47.260	42.510	33.840	35.470	32.270
26	18.120	44.990	32.720	27.880	24.290	22.040
27	16.850	39.800	28.540	25.040	21.600	19.130
28	15.490	37.090	24.550	20.950	19.020	17.100
29	20.760	24.640	28.440	22.550	22.280	21.340
30	1.050	3.630	2.390	1.990	1.720	1.460
31	15.770	35.690	21.830	19.480	17.460	14.140
32	10.290	39.570	25.960	20.010	19.350	16.930

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
33	25.240	38.220	34.850	33.680	29.440	29.240
35	21.130	39.320	36.520	32.150	26.210	25.730
36	21.170	29.330	31.270	29.840	28.710	27.410
MEAN	19.907	33.175	29.025	26.202	24.336	23.194
SD	9.259	11.493	9.678	9.709	9.181	9.273
GEOM MEAN	17.403	30.547	26.612	23.796	22.003	20.745
GEOM SD	1.886	1.619	1.676	1.712	1.739	1.791
CV%	46.512	34.642	33.342	37.052	37.728	39.981
SEM	1.588	1.971	1.660	1.665	1.575	1.590
MIN	1.050	3.630	2.390	1.990	1.720	1.460
MAX	57.000	60.350	56.390	58.780	55.490	54.220
MEDIAN	20.065	32.865	29.590	25.370	24.120	22.165
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
1	33.830	46.200	39.110	36.700	35.570	35.250
2	25.410	31.500	31.860	32.130	32.650	30.620
3	55.140	56.640	57.020	55.470	56.020	58.190
4	29.560	37.570	38.950	38.750	39.320	33.100
5	20.830	27.070	21.910	20.440	18.330	17.780
6	23.580	48.900	37.140	32.020	32.080	28.410
7	25.110	33.130	34.130	35.340	34.690	32.410
8	13.200	21.100	16.780	14.690	12.670	11.040
9	20.900	30.310	32.030	30.310	27.450	26.780
10	11.320	24.000	17.870	15.230	14.340	15.620
11	27.660	37.580	34.540	30.210	28.490	26.570
12	14.630	20.690	21.620	15.300	16.580	14.190
13	22.230	31.530	31.220	28.960	28.930	23.550
14	18.880	29.570	26.450	26.770	23.760	22.070
15	19.600	29.130	29.480	25.300	24.360	20.390
16	27.290	57.050	44.170	35.310	33.490	33.470
17	21.150	30.020	28.910	25.540	25.180	24.850
18	9.020	15.540	15.150	13.900	13.300	13.520
19	10.040	22.990	16.470	13.610	11.760	13.580
20	15.690	30.320	29.490	25.200	23.130	19.430
21	23.730	37.810	34.780	31.220	29.370	21.820
22	25.870	37.650	39.180	32.930	30.010	28.740
23	20.400	32.390	29.780	25.860	22.960	23.500
24	30.200	49.650	42.550	39.270	33.880	35.760
26	19.110	32.060	29.390	25.900	21.100	22.780
27	18.920	36.400	30.840	24.790	21.690	20.000
28	18.080	24.050	24.200	20.930	20.110	21.600
29	20.680	27.830	28.880	23.650	21.220	22.280
30	1.420	1.690	2.110	1.780	1.690	1.850
31	14.390	27.250	22.920	21.370	20.810	17.880
32	14.840	30.420	24.760	19.570	17.440	14.710

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
33	27.930	31.560	33.230	31.710	30.220	30.420
35	20.730	39.930	37.820	31.510	29.890	27.470
36	22.590	36.150	32.180	33.030	28.850	26.390
MEAN	21.293	32.520	29.909	26.903	25.334	24.001
SD	8.996	10.994	9.999	9.766	9.782	9.711
GEOM MEAN	18.997	29.491	27.291	24.285	22.736	21.589
GEOM SD	1.786	1.783	1.716	1.760	1.774	1.738
CV%	42.250	33.808	33.431	36.302	38.614	40.460
SEM	1.543	1.886	1.715	1.675	1.678	1.665
MIN	1.420	1.690	2.110	1.780	1.690	1.850
MAX	55.140	57.050	57.020	55.470	56.020	58.190
MEDIAN	20.780	31.515	30.310	26.335	24.770	23.140
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	2.0 h
1	34.940
2	29.670
3	58.640
4	33.830
5	18.760
6	28.510
7	27.650
8	11.690
9	24.290
10	12.910
11	25.870
12	13.610
13	24.790
14	21.990
15	19.480
16	30.700
17	24.910
18	9.840
19	11.780
20	19.600
21	22.890
22	27.890
23	21.820
24	33.960
26	23.410
27	17.060
28	16.810
29	21.740
30	1.710
31	16.710
32	14.770

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	2.0 h
33	24.700
35	24.260
36	25.670
MEAN	22.849
SD	9.777
GEOM MEAN	20.378
GEOM SD	1.769
CV%	42.791
SEM	1.677
MIN	1.710
MAX	58.640
MEDIAN	23.150
n	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
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University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
1	9.040	10.450	12.870	12.940	13.100	12.780
2	6.140	9.050	12.220	13.790	13.630	12.850
3	25.830	26.140	29.400	31.110	32.410	29.120
4	7.370	9.750	13.510	12.880	13.280	12.090
5	3.810	6.900	10.910	10.300	9.150	7.730
6	4.330	5.030	7.330	7.940	6.910	6.940
7	5.750	6.720	9.260	9.970	9.880	10.620
8	2.370	2.930	5.070	N.S.R.	5.990	6.070
9	3.090	5.430	9.110	8.540	7.230	6.170
10	3.600	4.590	5.770	7.480	6.490	5.570
11	4.630	5.410	7.810	8.570	6.970	6.900
12	4.420	5.130	7.950	7.130	7.390	6.750
13	5.500	5.500	8.490	9.070	9.310	9.740
14	4.670	5.780	8.910	10.760	11.030	10.880
15	3.450	3.940	5.530	7.830	7.540	7.110
16	4.130	6.060	9.040	9.980	9.860	8.530
17	3.660	4.870	7.840	7.670	7.000	5.710
18	4.120	4.950	7.070	7.340	8.150	8.070
19	2.930	4.500	7.520	9.050	8.100	7.310
20	4.150	9.490	12.100	11.340	9.920	7.850
21	5.660	8.940	12.660	13.090	9.900	8.290
22	4.600	5.650	8.200	9.210	9.870	8.900
23	3.470	5.150	9.400	8.800	8.360	7.290
24	3.670	4.680	8.680	7.980	7.890	6.370
26	3.440	3.650	6.620	7.680	7.660	6.700
27	4.040	4.330	6.610	7.060	7.190	6.660
28	4.530	4.770	6.240	7.380	7.620	7.820
29	3.650	3.270	3.900	5.580	5.220	5.280
30	4.400	4.060	6.430	7.240	8.590	7.750
31	3.460	4.380	7.430	7.920	7.740	7.450
32	3.390	4.370	6.490	9.990	8.380	8.710

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
33	5.370	4.970	7.090	9.290	10.540	10.190
35	3.060	4.020	7.940	8.130	8.280	7.270
36	2.320	4.100	4.920	6.290	5.050	4.700
MEAN	4.943	6.146	8.833	9.677	9.283	8.593
SD	3.931	4.010	4.338	4.344	4.575	4.160
GEOM MEAN	4.358	5.522	8.191	9.141	8.690	8.040
GEOM SD	1.529	1.510	1.441	1.359	1.390	1.395
CV%	79.541	65.249	49.115	44.888	49.286	48.415
SEM	.674	.688	.744	.756	.785	.714
MIN	2.320	2.930	3.900	5.580	5.050	4.700
MAX	25.830	26.140	29.400	31.110	32.410	29.120
MEDIAN	4.125	5.000	7.890	8.570	8.215	7.590
n	34	34	34	33	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
1	11.950	12.560	11.960	10.780	10.000	10.440
2	11.200	10.910	9.420	8.390	8.870	6.790
3	29.950	29.600	30.250	26.960	28.880	27.040
4	11.580	10.420	10.020	9.100	8.030	7.400
5	7.310	6.210	5.940	5.080	5.040	5.450
6	6.490	6.200	5.930	5.510	5.180	4.940
7	8.550	8.780	7.970	7.380	6.980	6.350
8	5.250	4.410	3.700	3.690	4.240	3.540
9	5.650	5.110	5.020	4.480	3.920	3.540
10	4.500	4.120	4.320	4.160	3.880	3.530
11	6.930	6.180	6.260	5.100	5.190	4.910
12	6.610	6.570	6.740	6.980	6.550	5.320
13	8.810	7.890	7.980	7.560	7.380	5.880
14	8.590	8.430	8.220	8.040	7.360	5.880
15	6.390	6.070	5.300	4.820	4.580	3.880
16	7.210	6.240	5.830	5.620	5.720	4.900
17	5.790	5.680	5.310	4.960	4.570	4.030
18	7.240	6.110	5.140	4.380	4.180	4.560
19	6.550	6.210	5.740	4.500	4.610	4.360
20	7.760	7.570	6.930	6.510	5.930	5.110
21	7.350	7.770	8.080	6.630	7.990	5.810
22	8.120	8.030	7.100	6.750	6.480	6.340
23	6.950	6.060	5.610	5.420	5.130	4.740
24	5.910	5.590	5.080	4.470	4.240	5.130
26	6.170	4.960	4.810	4.920	4.410	4.330
27	6.510	6.590	5.510	5.790	4.780	5.000
28	7.760	6.910	8.160	6.830	6.930	6.450
29	5.340	5.090	4.780	4.530	4.040	3.980
30	7.000	7.040	5.770	5.450	4.800	4.260
31	7.000	6.190	5.660	5.330	5.000	4.360
32	7.880	6.510	6.120	5.670	5.640	4.500

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
33	8.150	6.760	6.640	6.690	5.880	4.960
35	6.660	5.130	5.200	4.810	3.730	3.900
36	4.340	4.390	4.130	3.720	3.650	3.690
MEAN	7.925	7.420	7.077	6.500	6.288	5.744
SD	4.262	4.328	4.459	3.950	4.291	4.003
GEOM MEAN	7.374	6.828	6.455	5.955	5.678	5.202
GEOM SD	1.400	1.433	1.455	1.444	1.477	1.455
CV%	53.779	58.322	63.005	60.760	68.243	69.682
SEM	.731	.742	.765	.677	.736	.686
MIN	4.340	4.120	3.700	3.690	3.650	3.530
MAX	29.950	29.600	30.250	26.960	28.880	27.040
MEDIAN	7.000	6.225	5.880	5.480	5.155	4.925
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	2.0 h
1	9.720
2	7.280
3	26.780
4	7.580
5	4.570
6	4.730
7	6.610
8	3.480
9	3.330
10	3.540
11	4.550
12	5.260
13	4.870
14	5.760
15	4.170
16	4.510
17	4.210
18	3.650
19	3.980
20	5.210
21	6.100
22	5.440
23	5.030
24	4.700
26	4.330
27	4.210
28	5.520
29	3.900
30	4.080
31	4.120
32	3.790

PROGRAM: S T A T S (V 1.3)

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FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	2.0 h
33	4.490
35	3.610
36	3.000

MEAN	5.474
SD	4.006
GEOM MEAN	4.914
GEOM SD	1.478
CV%	73.186
SEM	.687
MIN	3.000
MAX	26.780
MEDIAN	4.530
n	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
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University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
1	5.460	8.090	7.200	7.600	7.130	6.510
2	9.310	9.050	8.800	9.160	8.960	9.980
3	25.710	25.220	24.530	24.330	24.940	24.310
4	10.070	10.960	10.540	10.880	10.890	11.280
5	6.450	9.120	8.650	7.730	7.370	7.760
6	6.070	7.750	8.370	7.730	8.360	7.230
7	5.520	7.550	7.270	6.730	6.740	6.090
8	1.590	2.520	2.660	2.360	2.300	1.800
9	3.880	4.550	4.500	4.380	3.970	3.960
10	3.720	5.720	4.930	4.610	4.310	3.620
11	5.190	5.860	6.820	6.150	5.700	5.780
12	6.680	7.120	6.970	7.240	7.420	7.240
13	5.480	5.920	6.810	6.560	6.760	6.660
14	4.430	6.650	6.370	6.040	5.510	5.190
15	4.490	5.210	6.120	5.420	5.200	5.410
16	5.250	5.650	6.580	5.700	5.250	4.970
17	5.310	6.450	6.410	6.150	6.170	6.080
18	3.490	7.890	4.530	4.490	3.970	3.700
19	3.240	4.980	4.980	4.960	3.820	4.190
20	5.730	7.870	7.720	7.220	7.770	6.730
21	6.550	9.530	9.810	9.770	9.290	7.620
22	5.300	5.450	7.250	7.150	6.000	6.040
23	3.020	5.320	4.560	4.380	4.180	3.350
24	5.070	6.440	6.340	5.730	5.690	5.530
26	4.330	5.950	5.690	6.080	5.840	5.730
27	2.710	3.270	4.650	3.850	4.030	3.810
28	4.110	4.290	4.590	4.950	4.980	5.100
29	5.910	6.580	7.380	7.670	6.770	7.220
30	3.690	3.990	4.350	4.480	4.230	4.160
31	3.710	4.110	4.400	4.250	4.260	3.750
32	2.140	4.010	3.430	3.390	3.470	3.500

PROGRAM: S T A T S (V 1.3)

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FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
33	6.560	7.990	8.530	8.420	8.080	8.290
35	3.010	3.870	3.140	3.150	3.280	3.340
36	3.030	4.480	4.790	4.320	4.830	4.270
MEAN	5.477	6.747	6.755	6.560	6.396	6.182
SD	4.004	3.796	3.667	3.688	3.804	3.776
GEOM MEAN	4.771	6.134	6.168	5.953	5.767	5.523
GEOM SD	1.626	1.510	1.499	1.519	1.532	1.571
CV%	73.106	56.256	54.287	56.228	59.477	61.071
SEM	.687	.651	.629	.633	.652	.648
MIN	1.590	2.520	2.660	2.360	2.300	1.800
MAX	25.710	25.220	24.530	24.330	24.940	24.310
MEDIAN	5.130	5.935	6.390	6.060	5.695	5.630
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

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FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
1	7.380	9.500	10.020	9.710	11.570	9.280
2	8.890	8.670	10.980	10.300	8.290	8.270
3	23.040	25.620	25.690	25.260	26.160	24.920
4	10.800	11.580	11.840	11.900	12.060	11.010
5	6.850	8.390	7.490	8.100	8.050	7.400
6	7.150	7.780	8.190	8.130	8.850	8.650
7	5.900	7.820	7.890	7.820	7.700	7.650
8	2.200	2.190	2.170	2.040	2.190	2.290
9	4.220	4.310	4.450	4.490	4.940	4.330
10	3.640	6.460	6.100	6.170	5.360	5.040
11	5.590	5.940	6.020	5.940	6.330	5.600
12	6.950	10.220	6.910	7.020	6.620	5.790
13	6.350	9.430	9.320	8.480	8.370	6.450
14	5.570	8.200	7.300	6.710	6.770	5.110
15	5.470	7.540	7.750	7.090	7.350	5.820
16	5.170	8.220	8.550	8.490	7.220	7.420
17	5.250	6.720	6.140	5.840	6.210	6.590
18	3.570	6.940	5.520	5.090	4.350	4.430
19	3.800	4.810	4.740	5.090	4.560	4.250
20	7.180	8.860	8.850	8.090	8.540	8.340
21	7.900	14.540	14.450	13.640	11.580	10.960
22	5.730	6.380	7.020	6.580	7.290	8.880
23	3.350	5.600	4.850	4.270	3.950	3.690
24	5.630	6.380	6.250	5.950	5.940	6.750
26	5.020	6.800	6.790	7.050	7.020	6.740
27	3.760	5.190	5.880	4.200	4.140	3.890
28	5.240	5.640	6.470	6.500	6.770	6.600
29	6.680	8.710	7.580	8.240	8.020	8.350
30	4.030	4.510	4.760	4.560	4.220	4.380
31	4.090	4.830	4.840	4.590	4.910	4.720
32	3.010	4.210	3.790	3.390	4.000	3.140

PROGRAM: S T A T S (V 1.3)

Division of Biometry
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FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
33	7.420	8.180	7.940	8.920	8.710	8.290
35	3.560	3.930	4.270	5.630	3.960	3.920
36	3.670	6.200	5.560	5.380	4.520	4.590
MEAN	6.002	7.656	7.540	7.372	7.251	6.869
SD	3.532	3.980	4.025	3.957	4.072	3.856
GEOM MEAN	5.412	6.967	6.844	6.672	6.532	6.192
GEOM SD	1.535	1.531	1.534	1.550	1.556	1.553
CV%	58.849	51.987	53.386	53.668	56.154	56.143
SEM	.606	.683	.690	.679	.698	.661
MIN	2.200	2.190	2.170	2.040	2.190	2.290
MAX	23.040	25.620	25.690	25.260	26.160	24.920
MEDIAN	5.520	6.870	6.850	6.645	6.770	6.520
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

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FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	2.0 h
1	8.590
2	8.880
3	25.490
4	10.520
5	7.080
6	7.410
7	7.530
8	1.640
9	3.810
10	5.080
11	5.670
12	5.810
13	8.090
14	5.210
15	6.100
16	6.360
17	6.080
18	3.880
19	3.540
20	7.500
21	10.060
22	6.950
23	3.040
24	6.250
26	6.970
27	3.210
28	5.910
29	7.800
30	4.810
31	4.120
32	2.810

PROGRAM: S T A T S (V 1.3)

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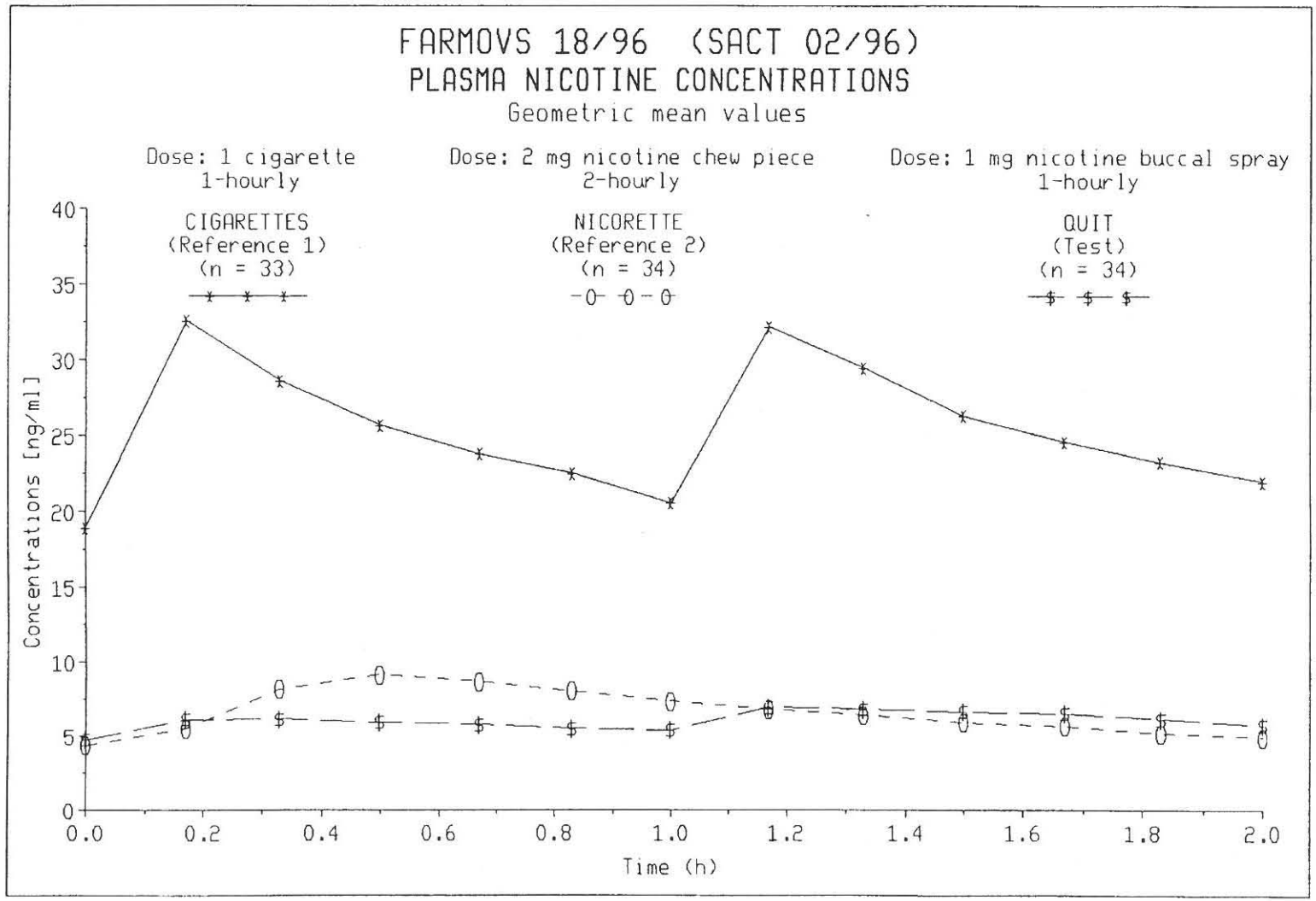
FARMOVS 18/96 (SACT 02/96)
PLASMA NICOTINE CONCENTRATIONS (ng/ml)
LLOQ = 0.636 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

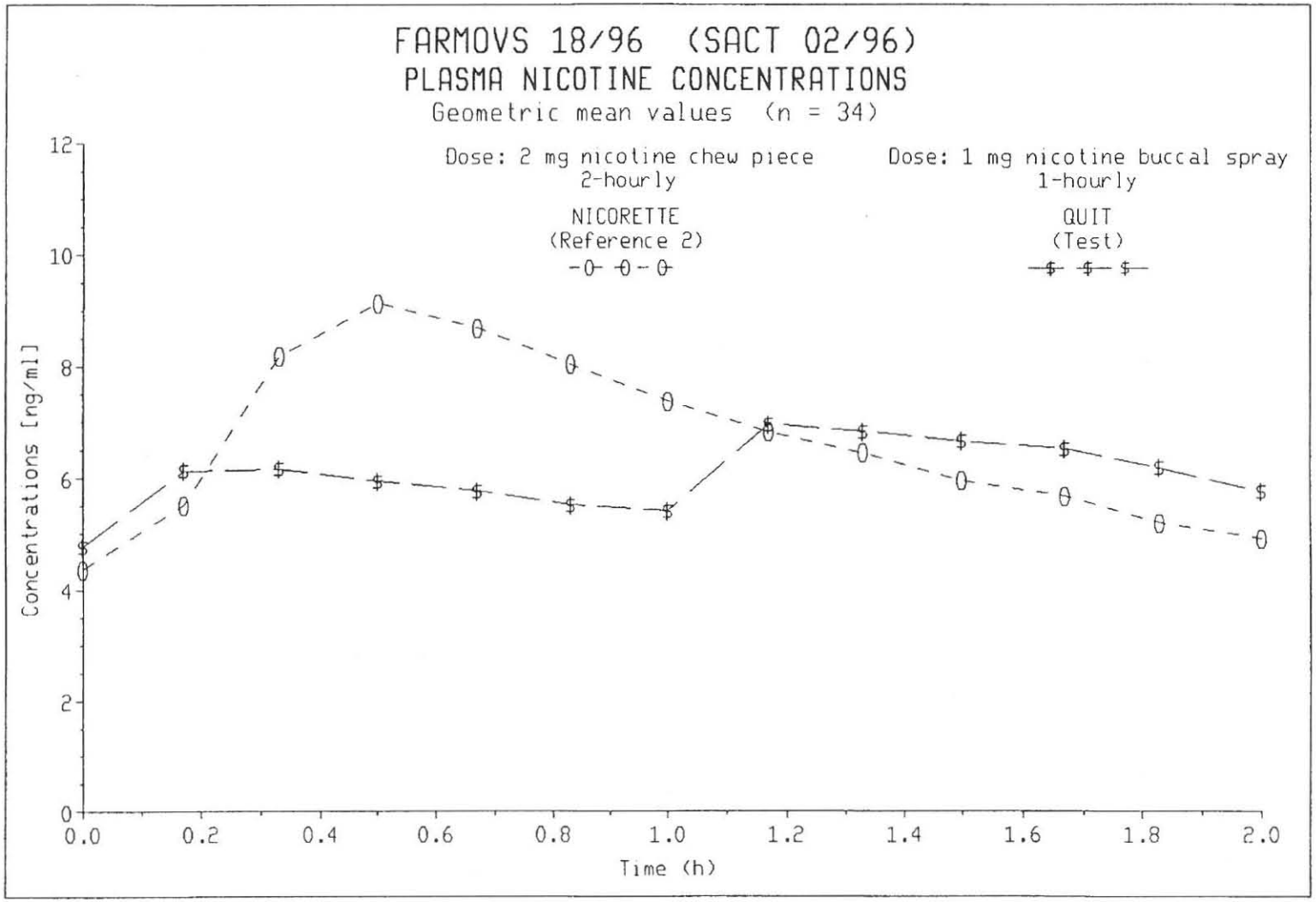
SUBJECT NO.	2.0 h
33	7.720
35	3.510
36	4.020

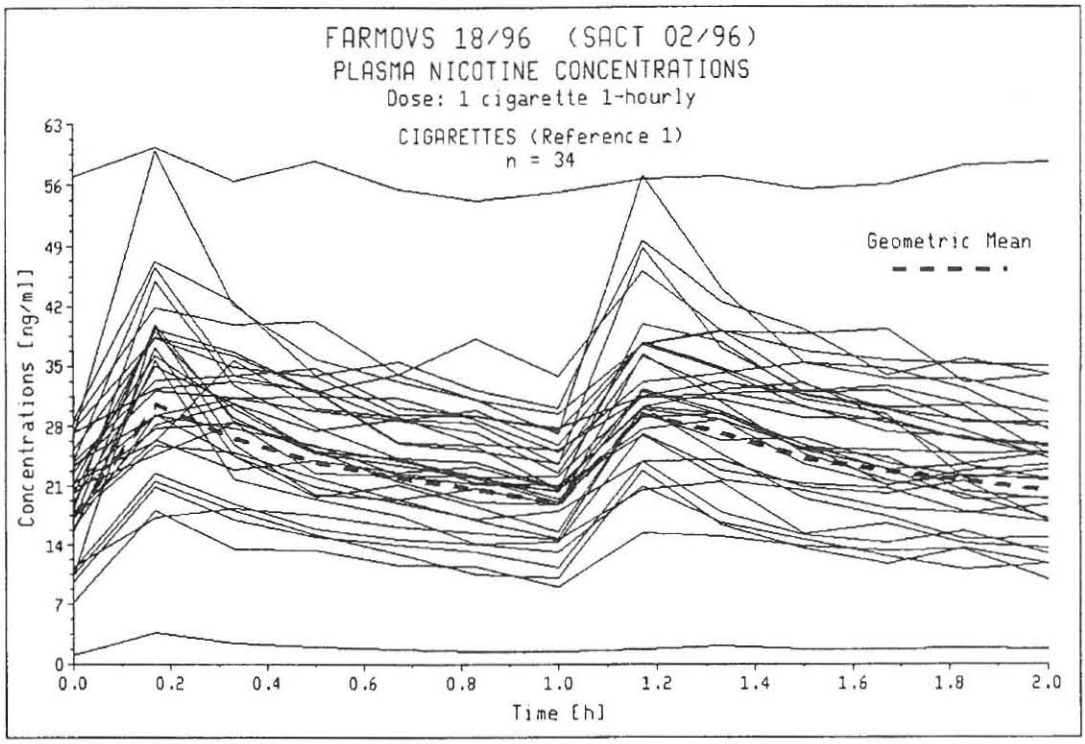
MEAN	6.513
SD	3.973
GEOM MEAN	5.761
GEOM SD	1.627
CV%	61.002
SEM	.681
MIN	1.640
MAX	25.490
MEDIAN	6.090
n	34

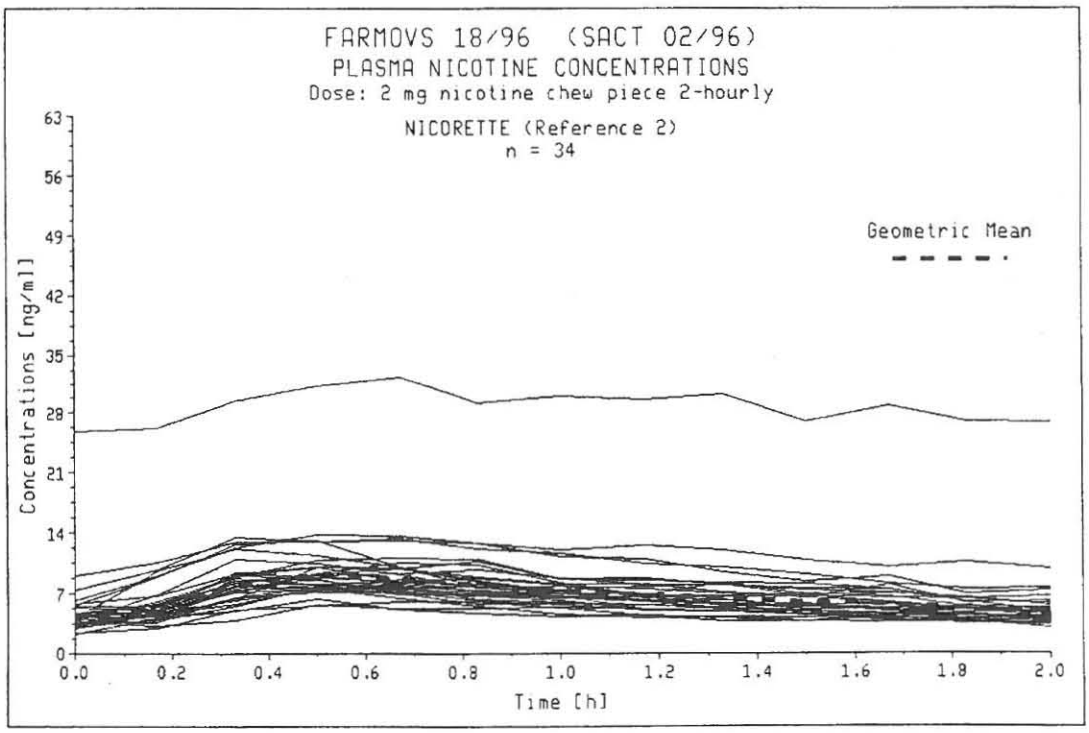
APPENDIX 10

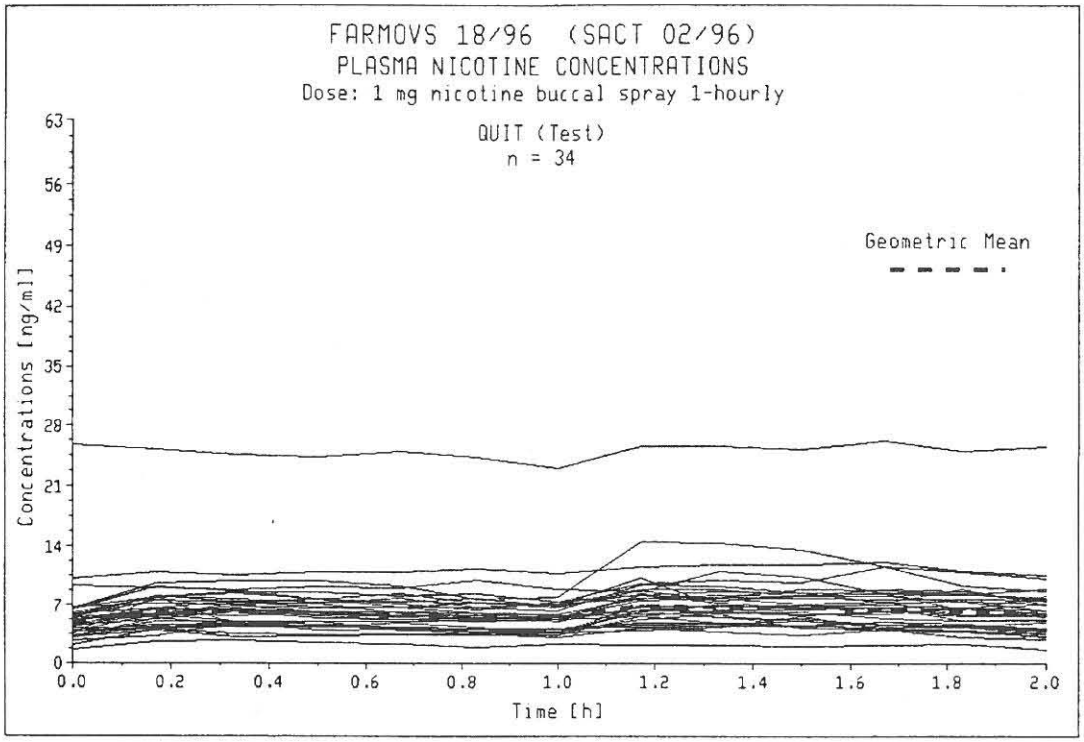
Plasma Nicotine Concentrations *vs* Time Profiles

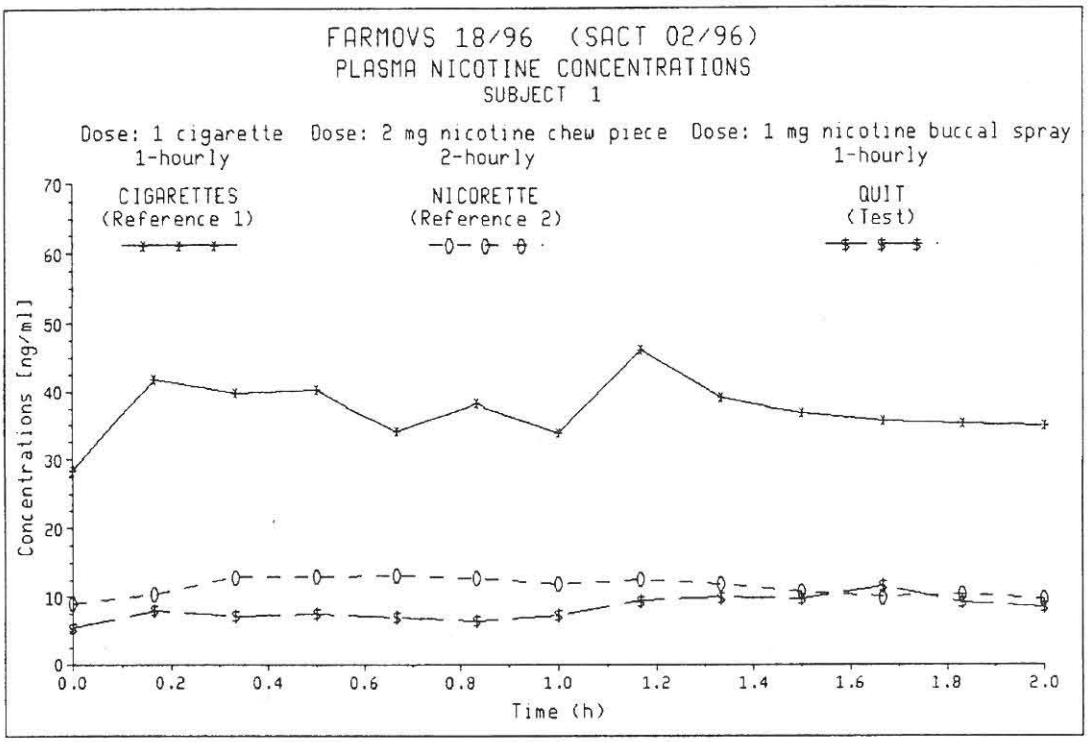


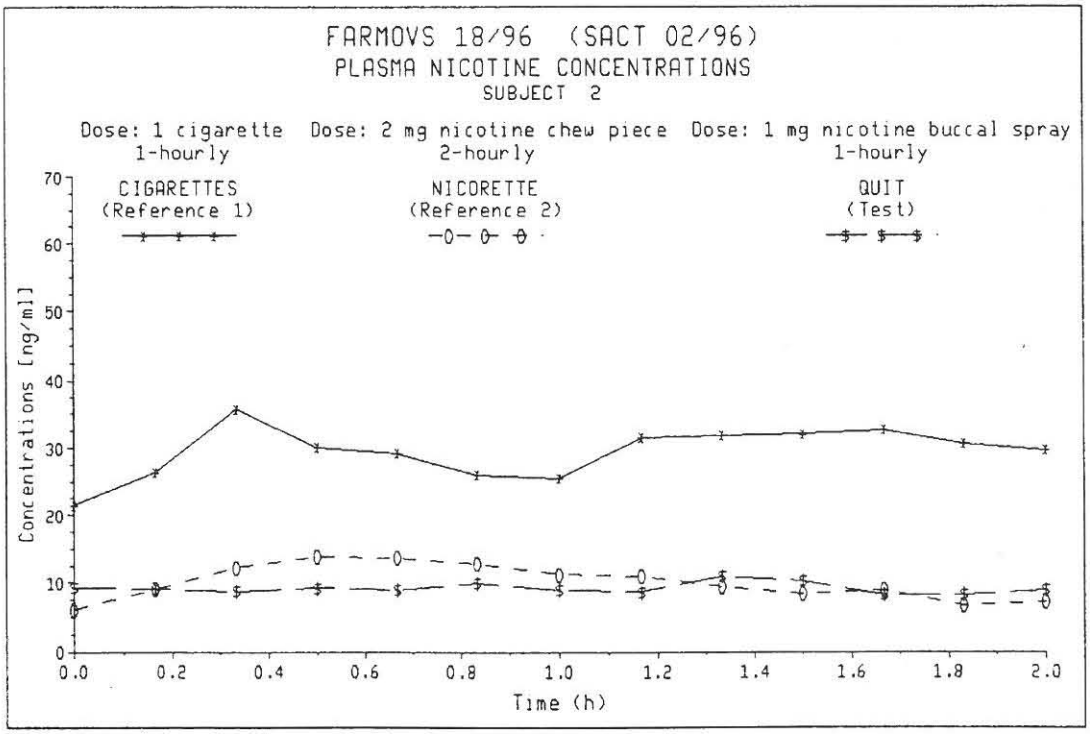


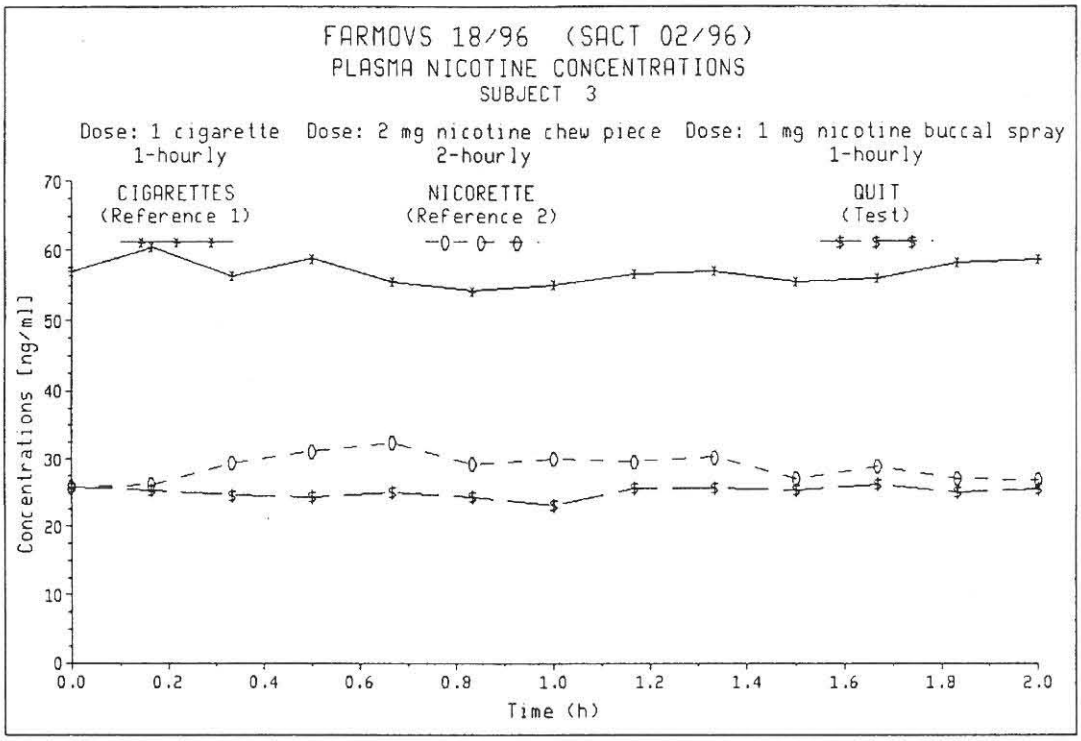


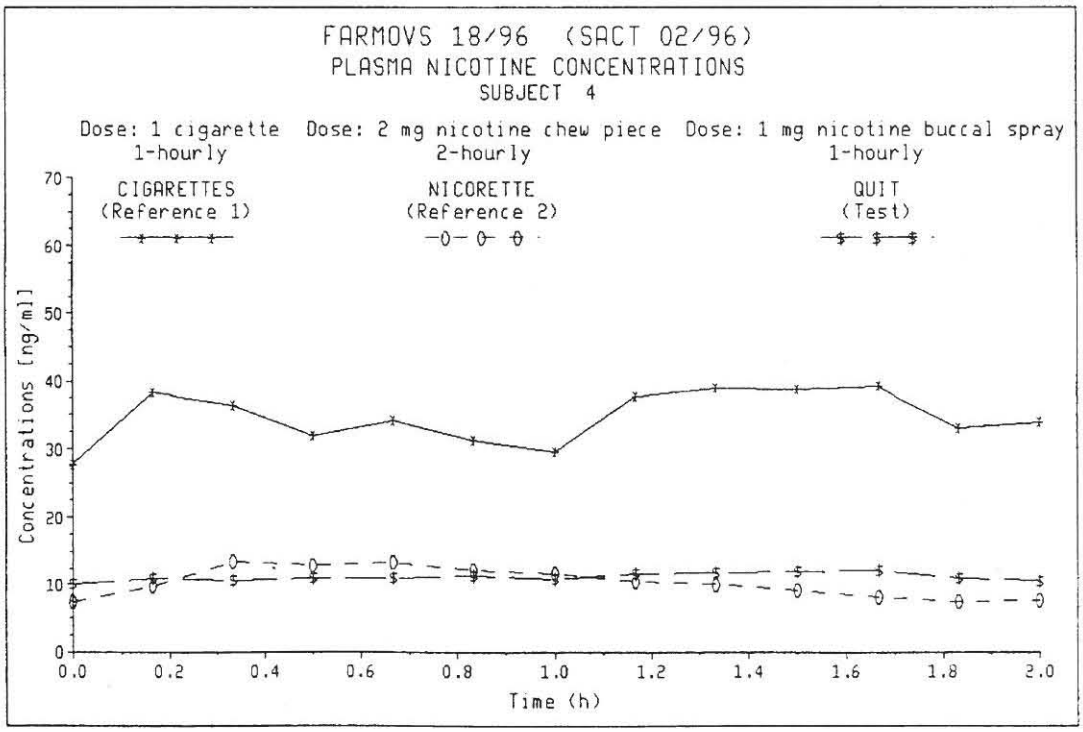


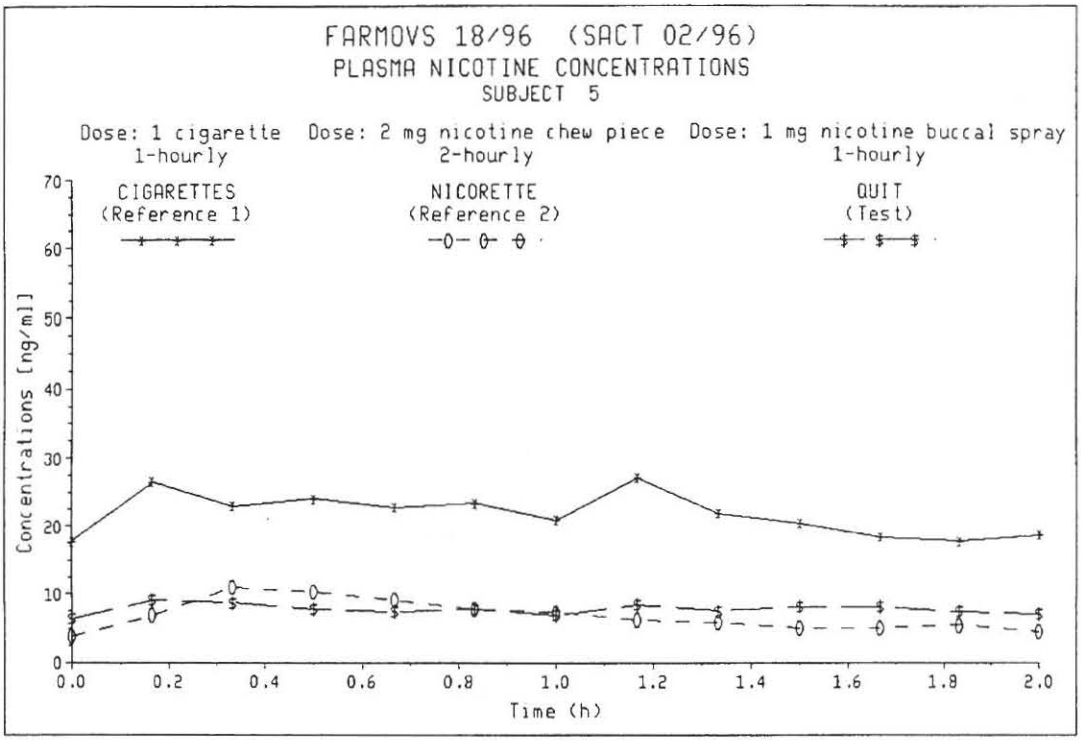


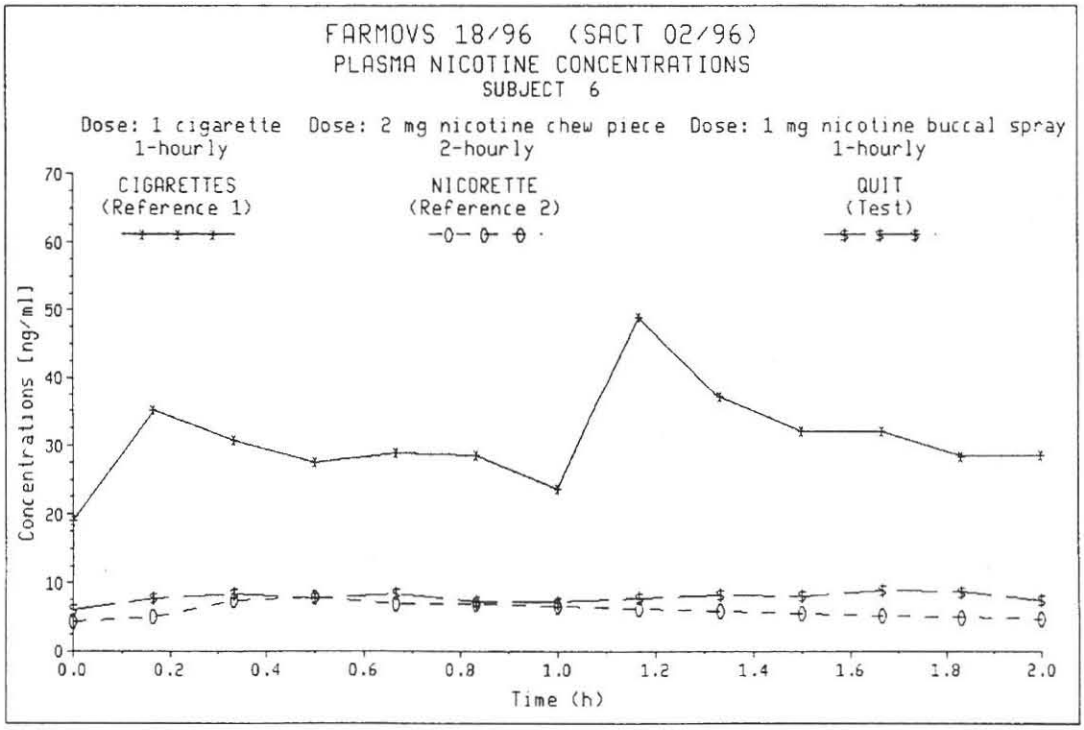


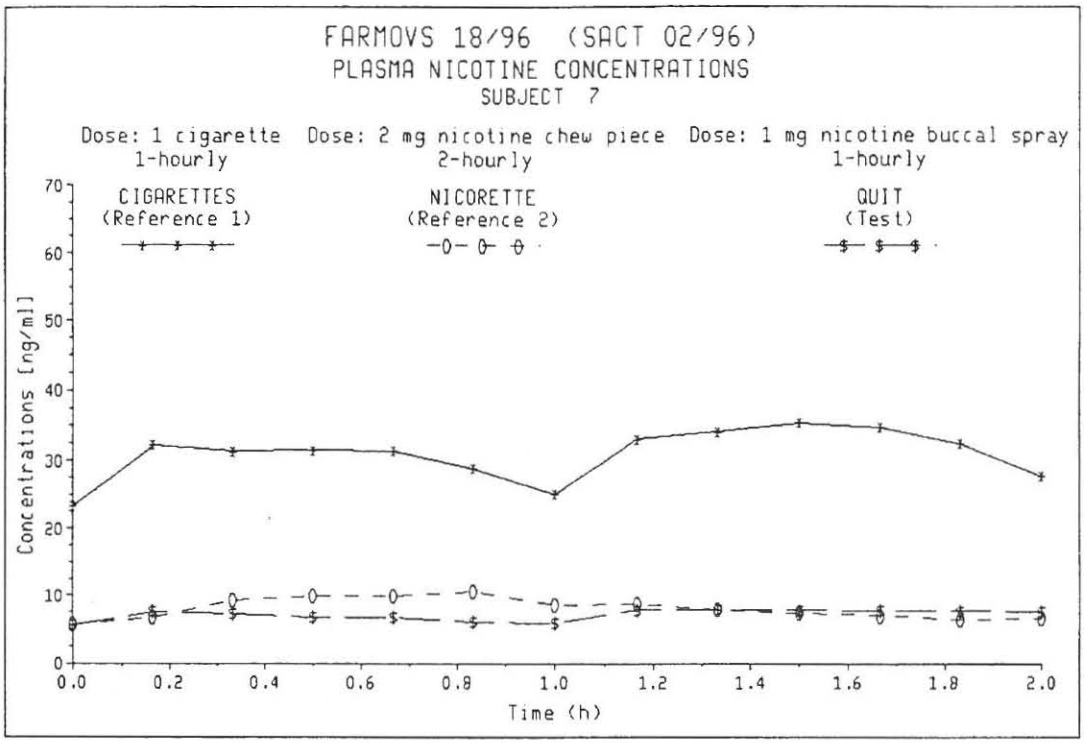


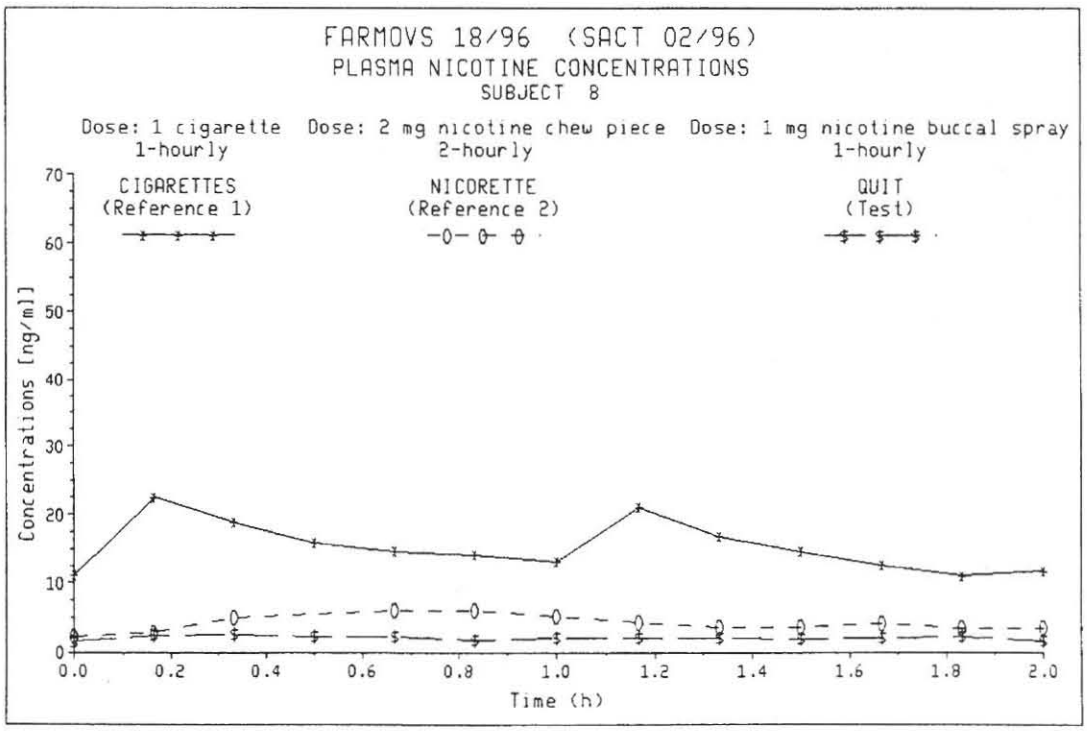


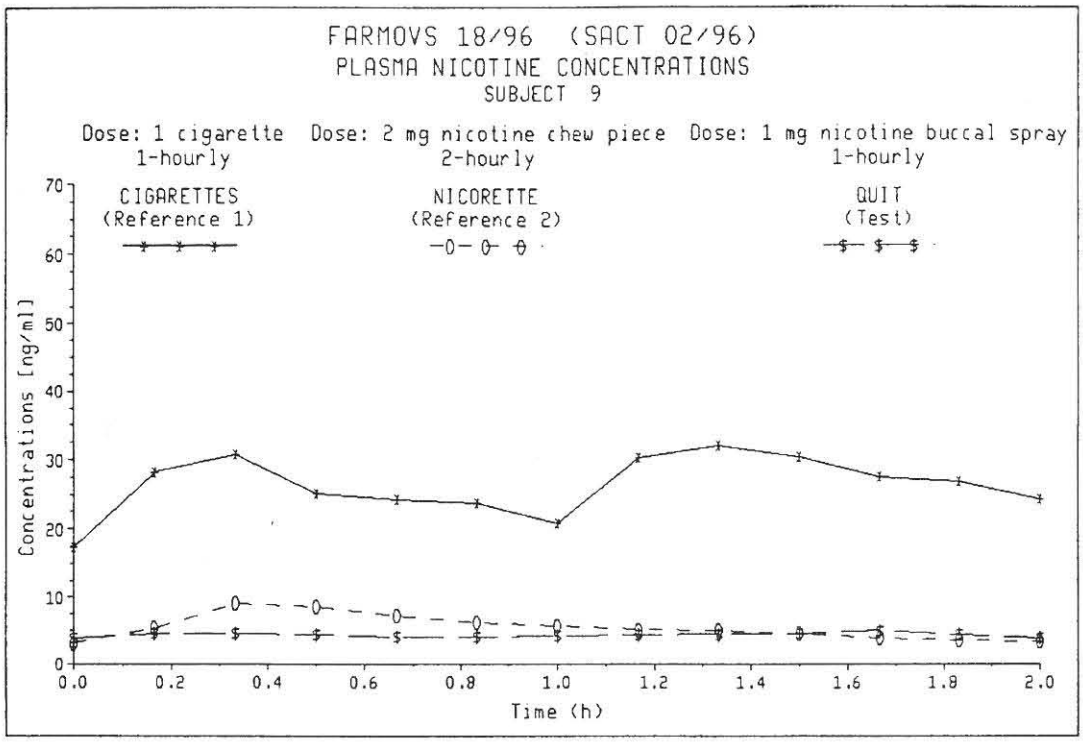


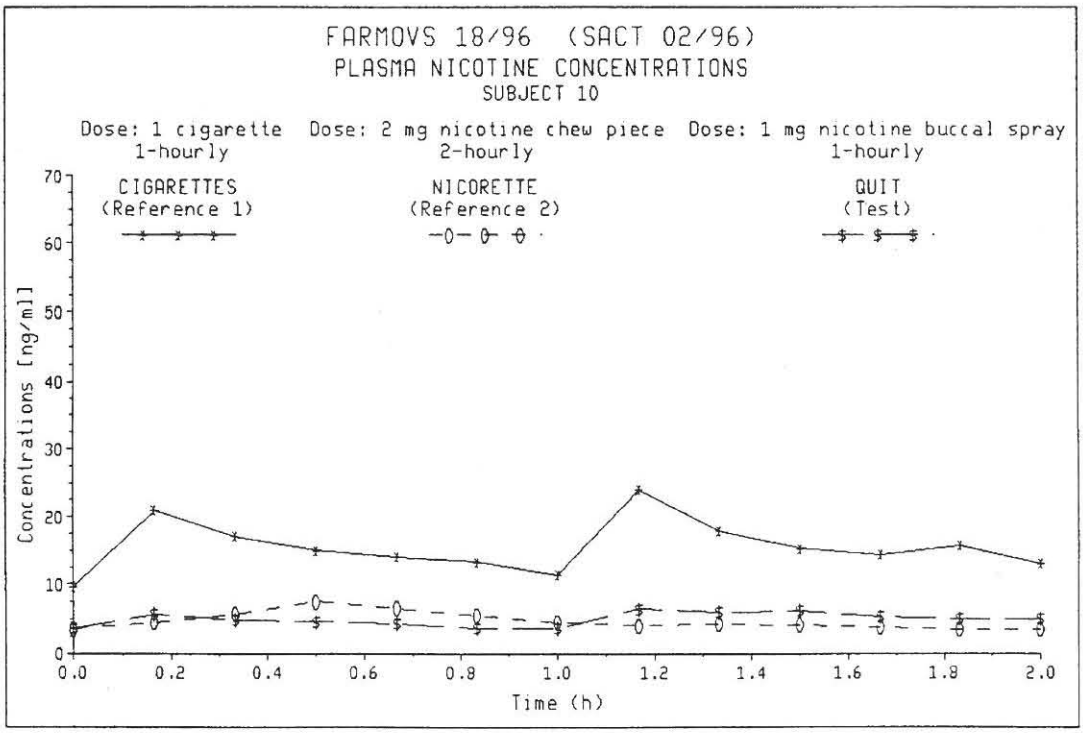


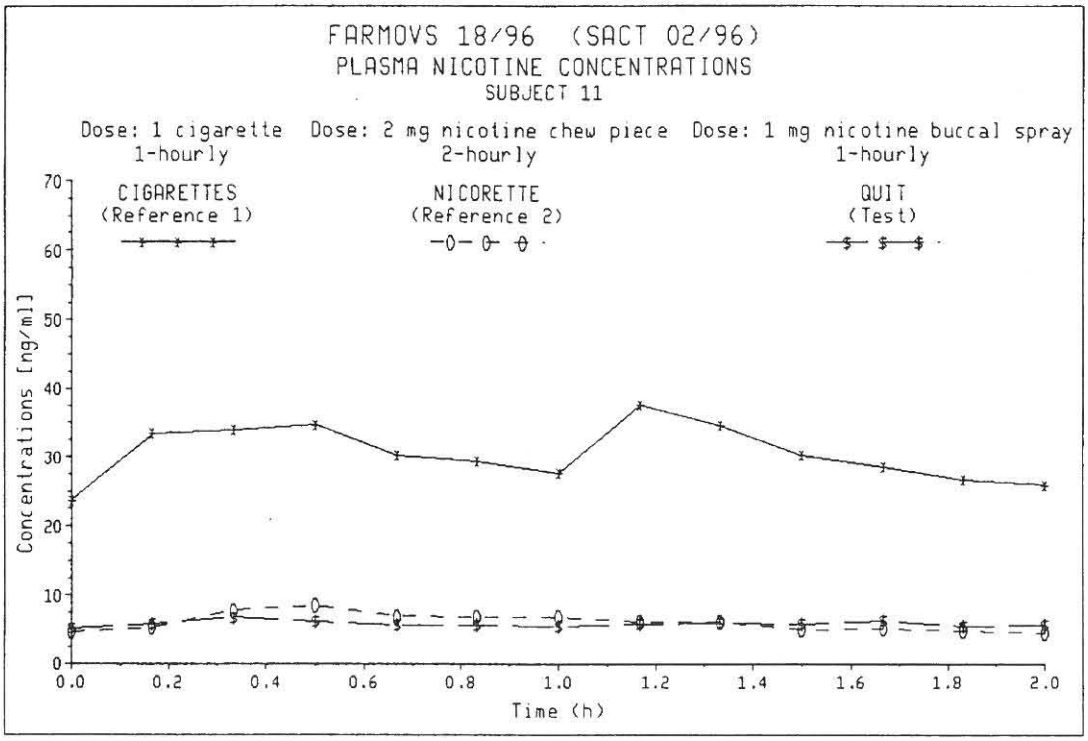


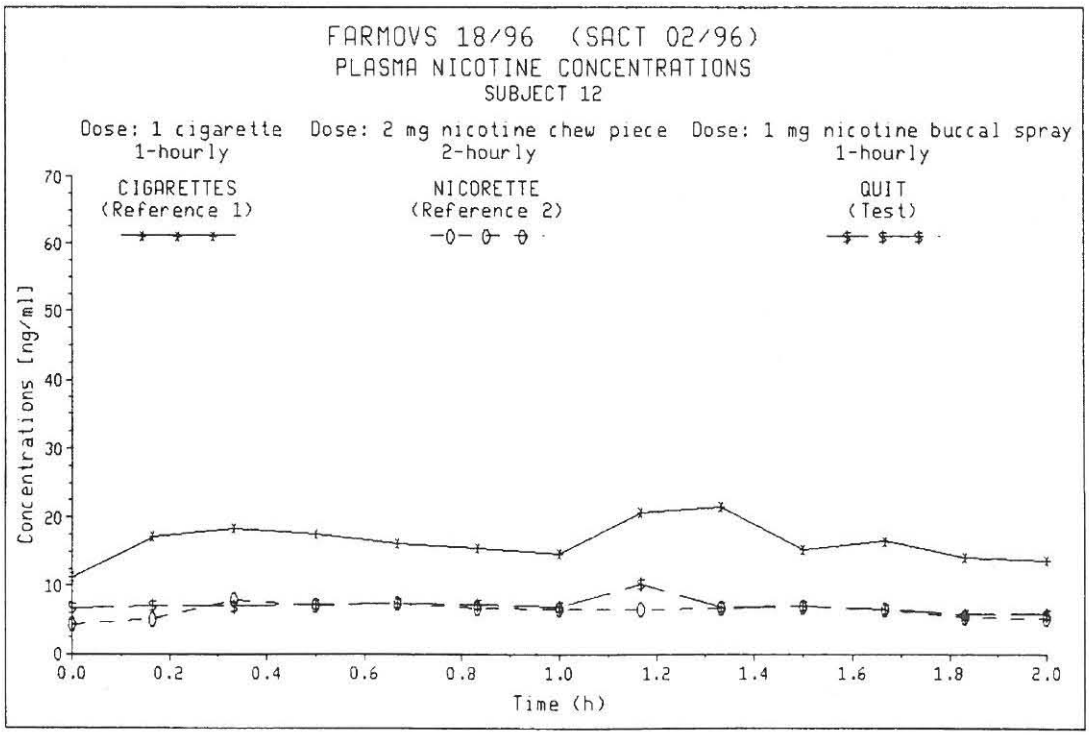


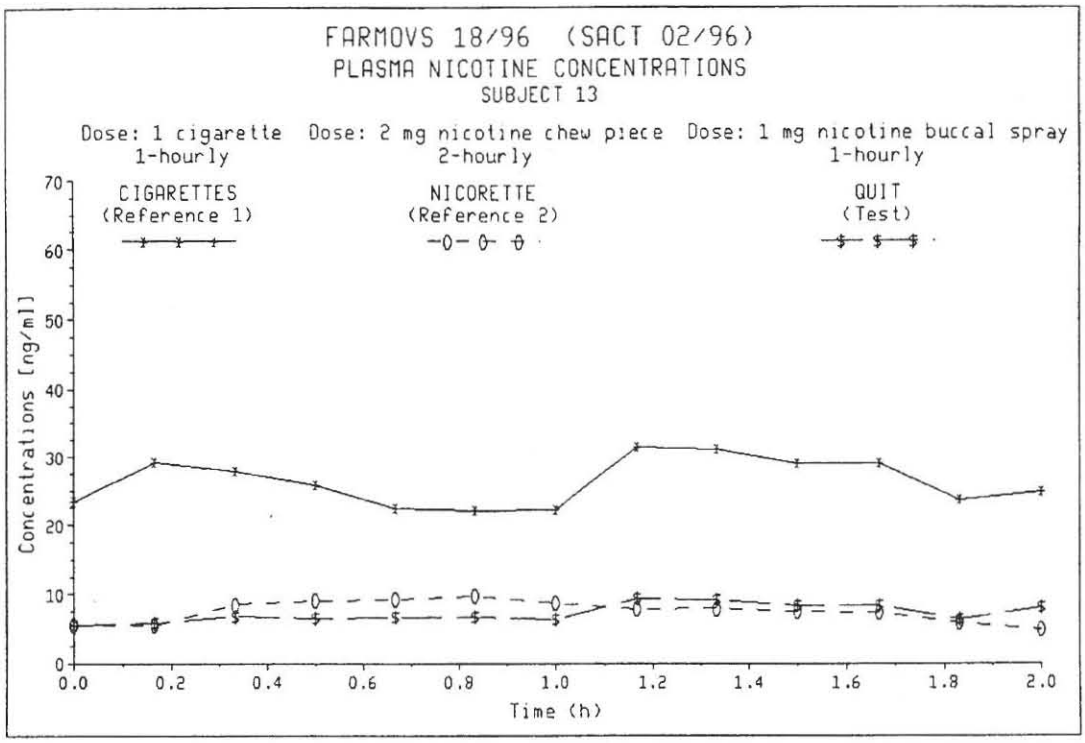


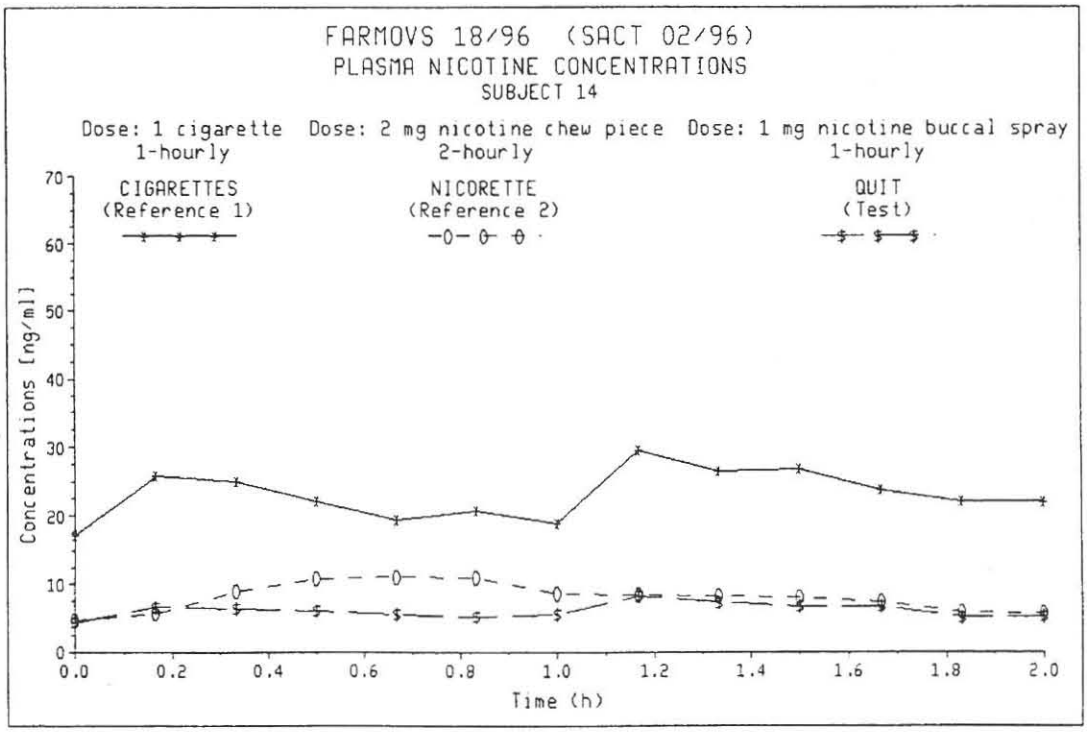


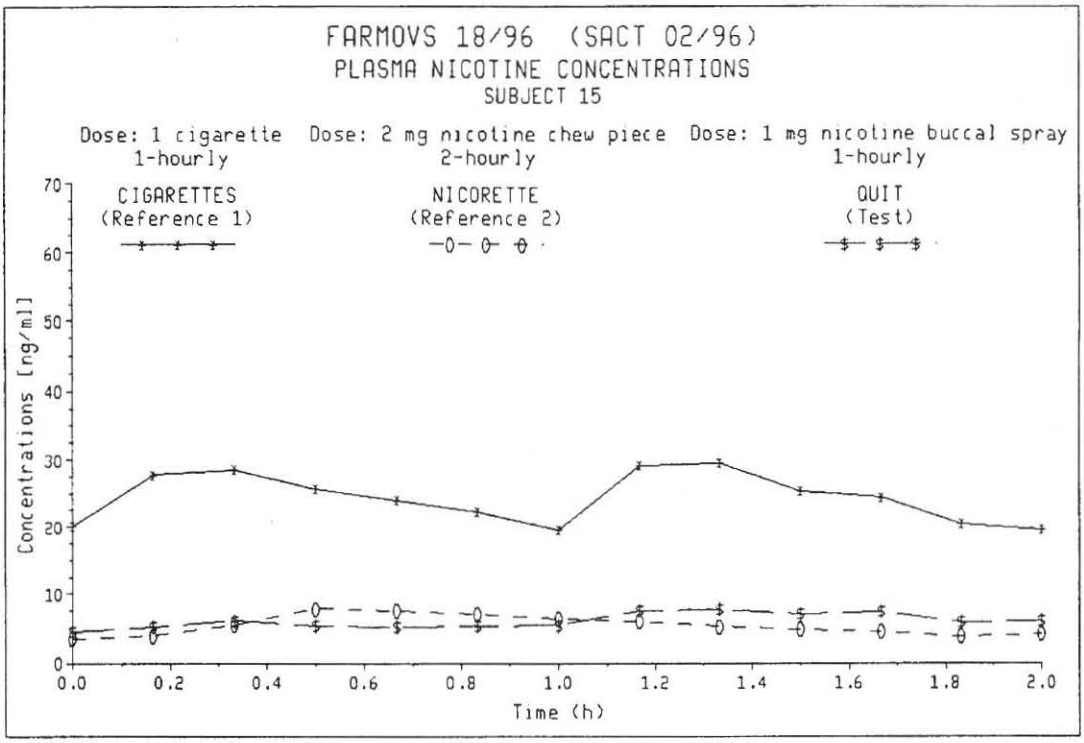


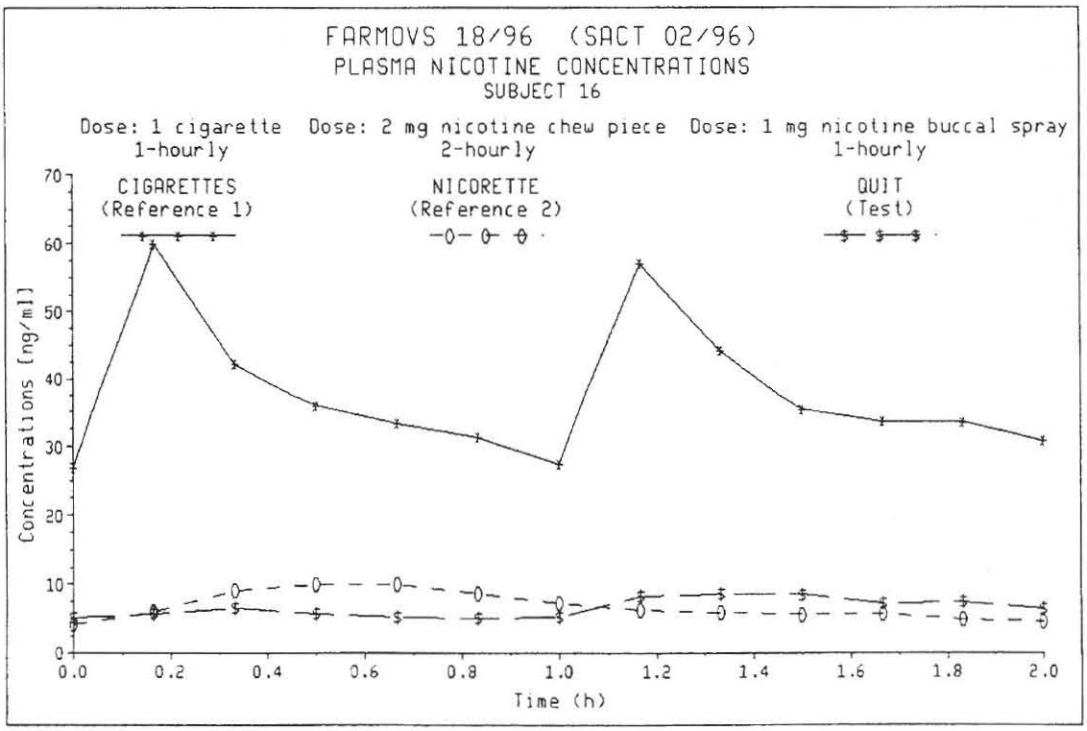


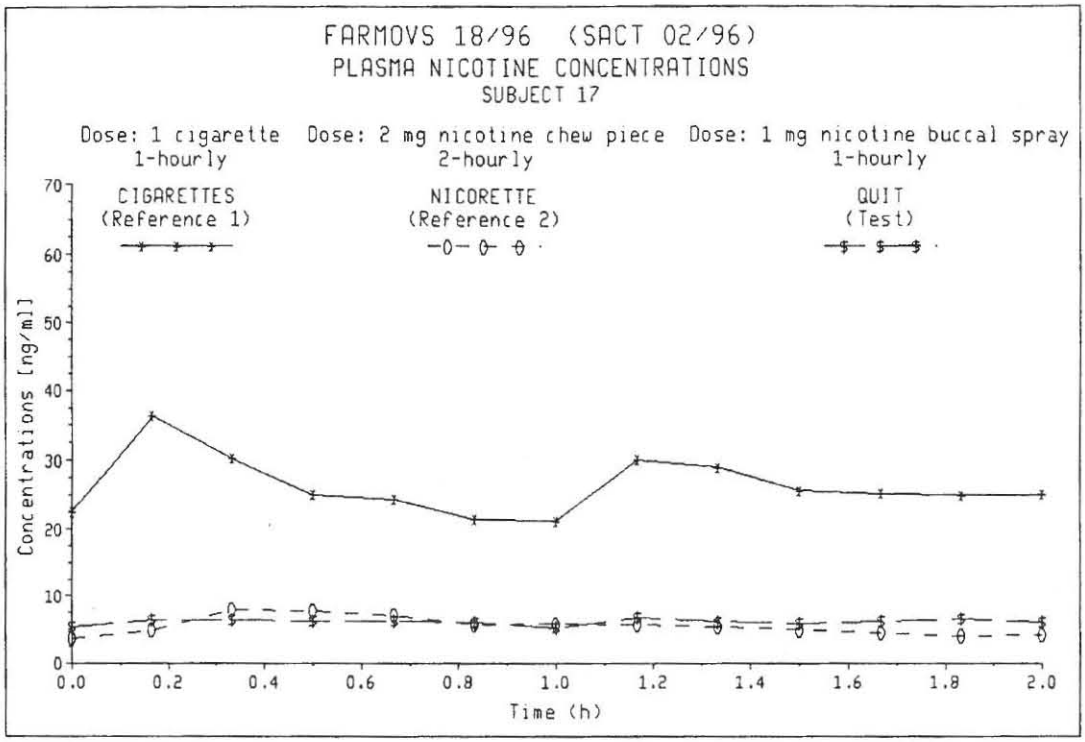


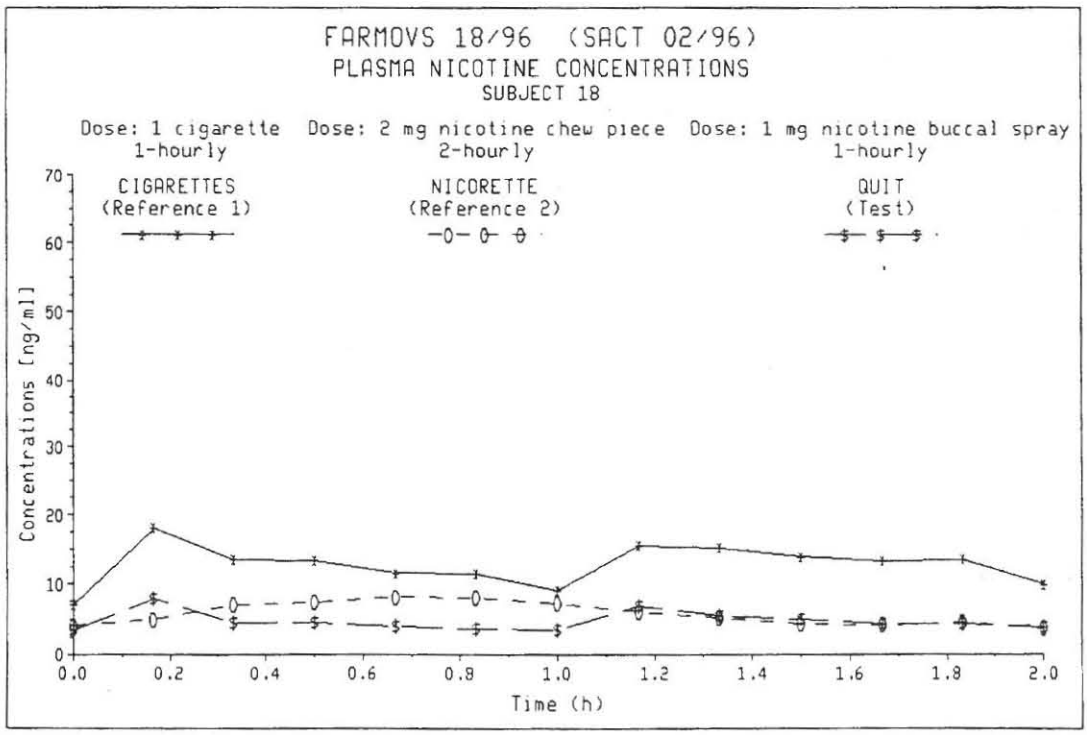


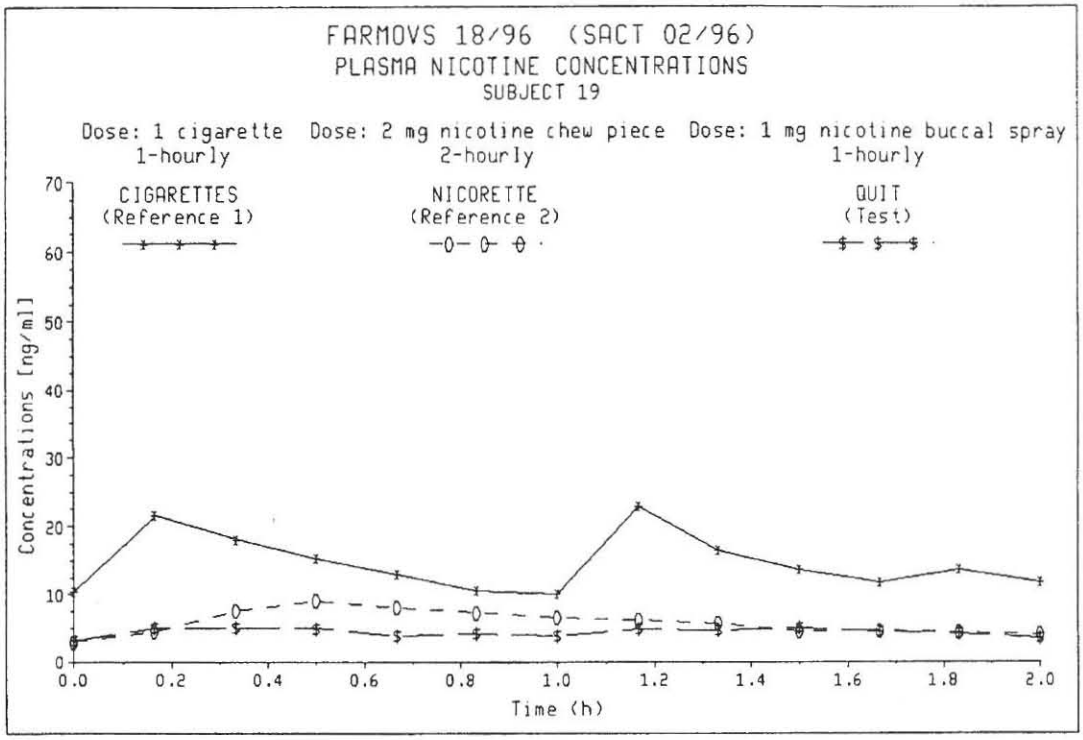


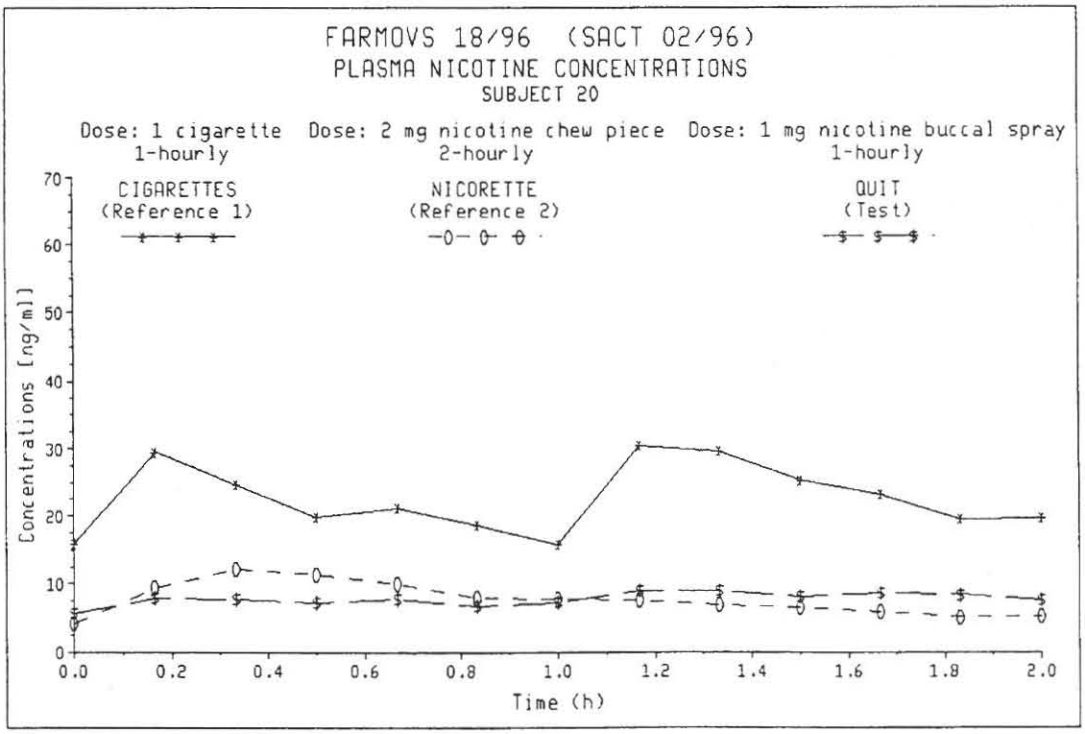


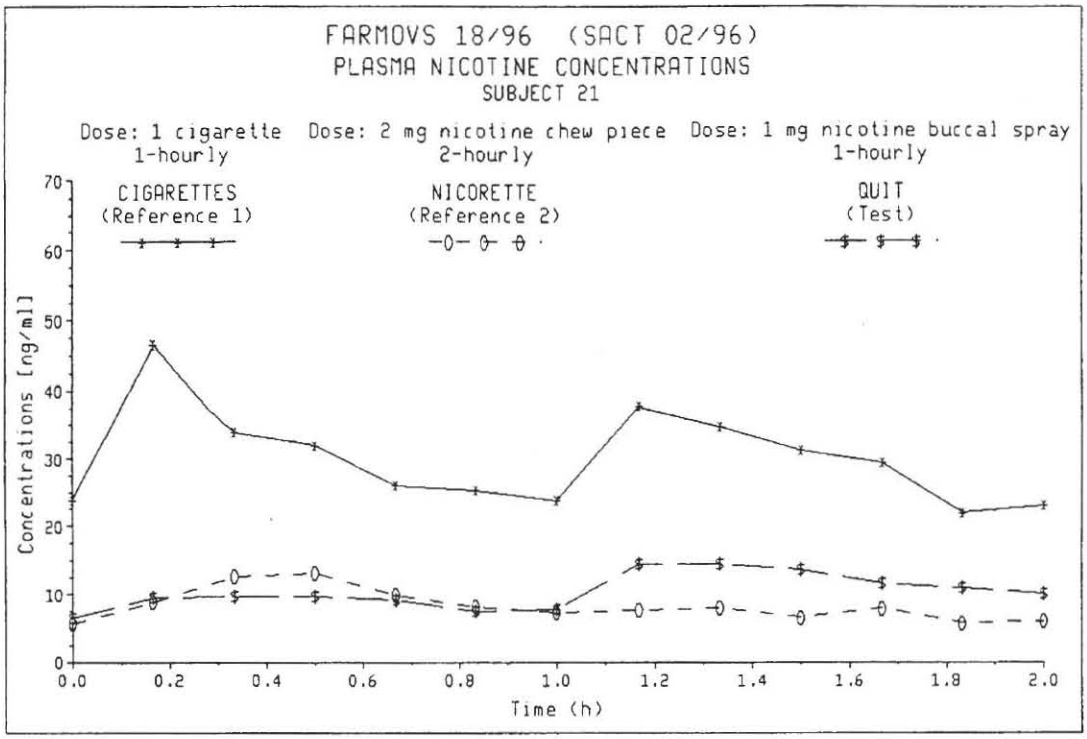


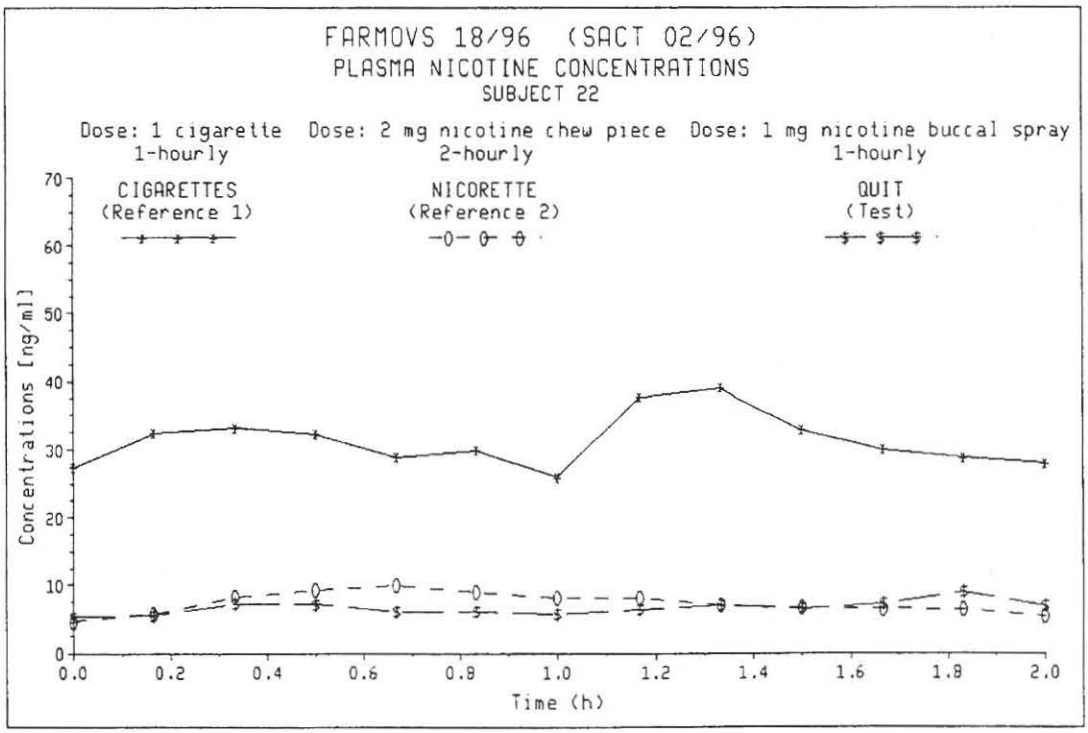


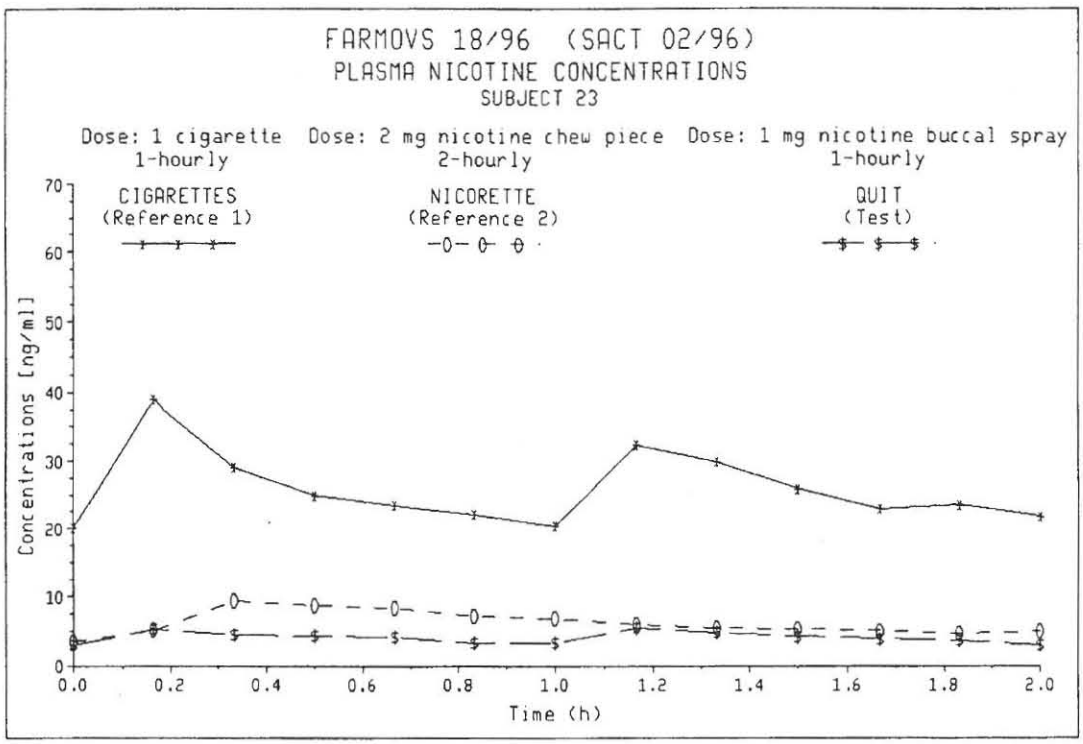


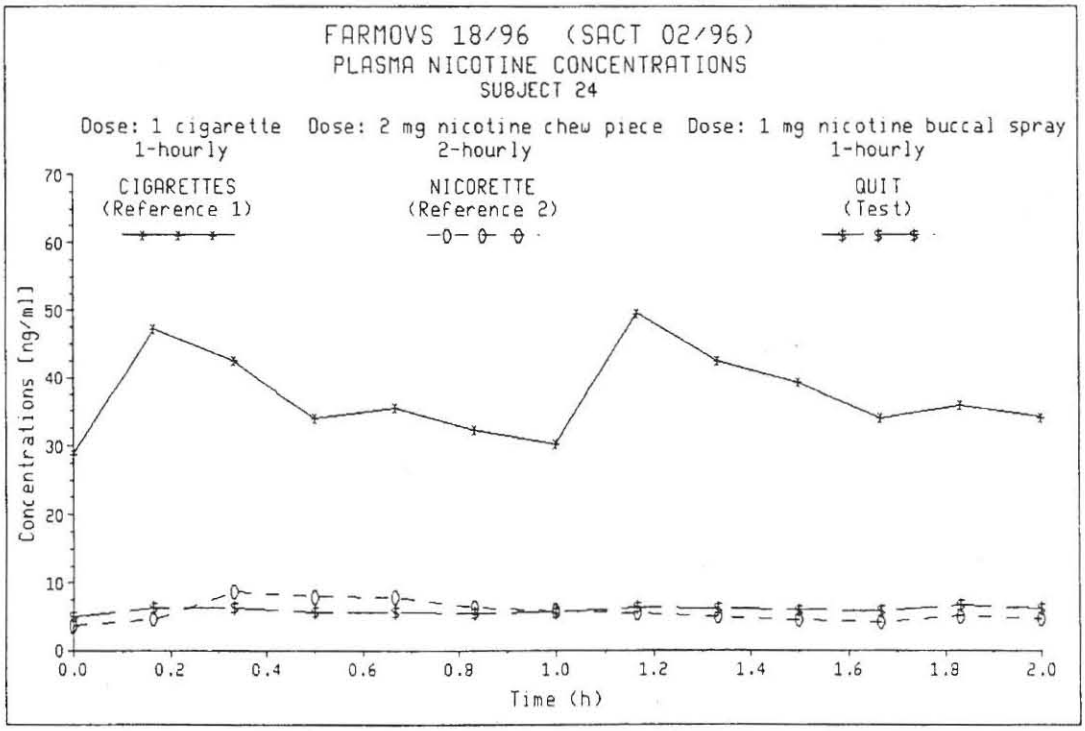


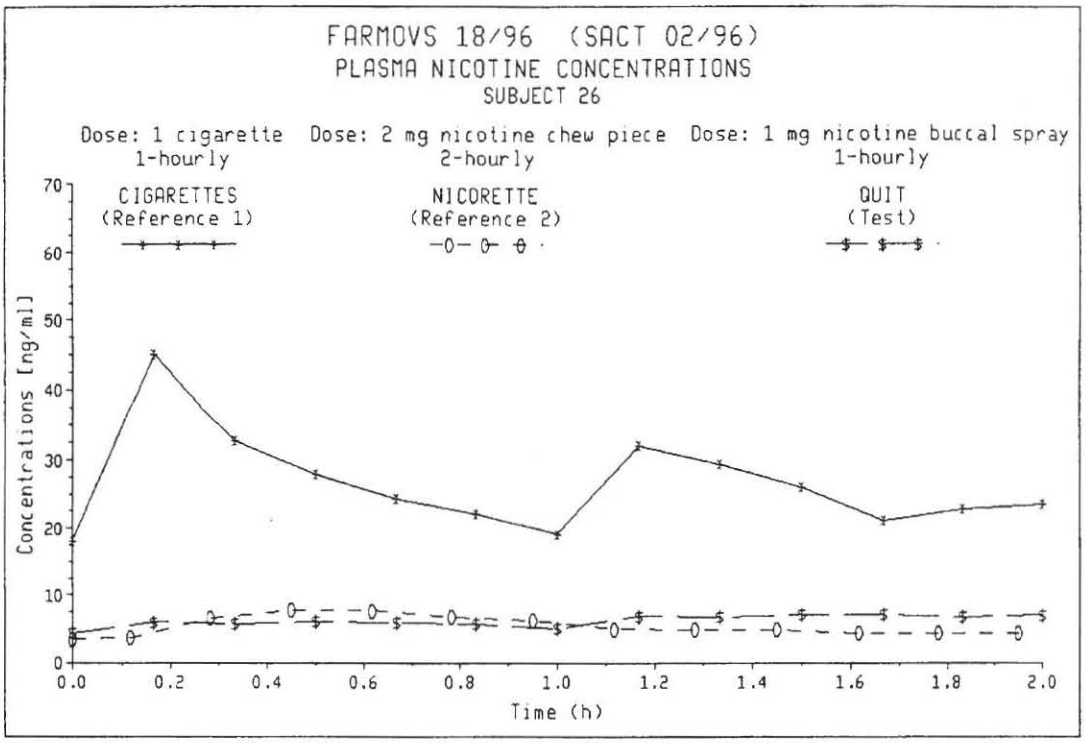


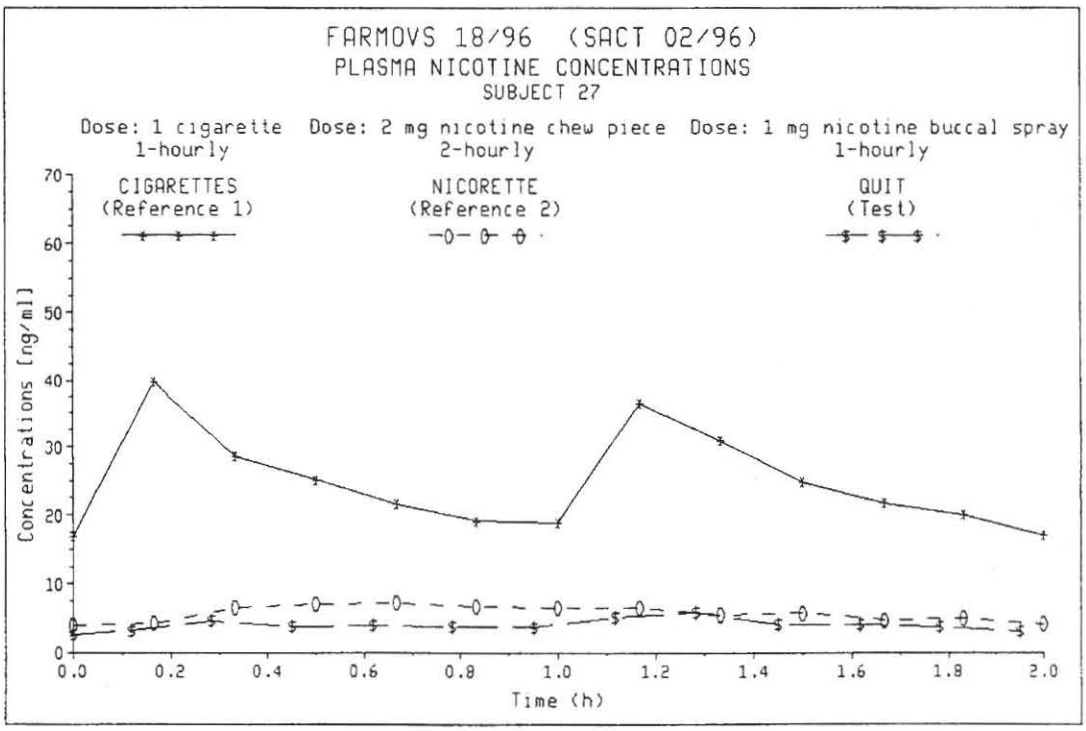


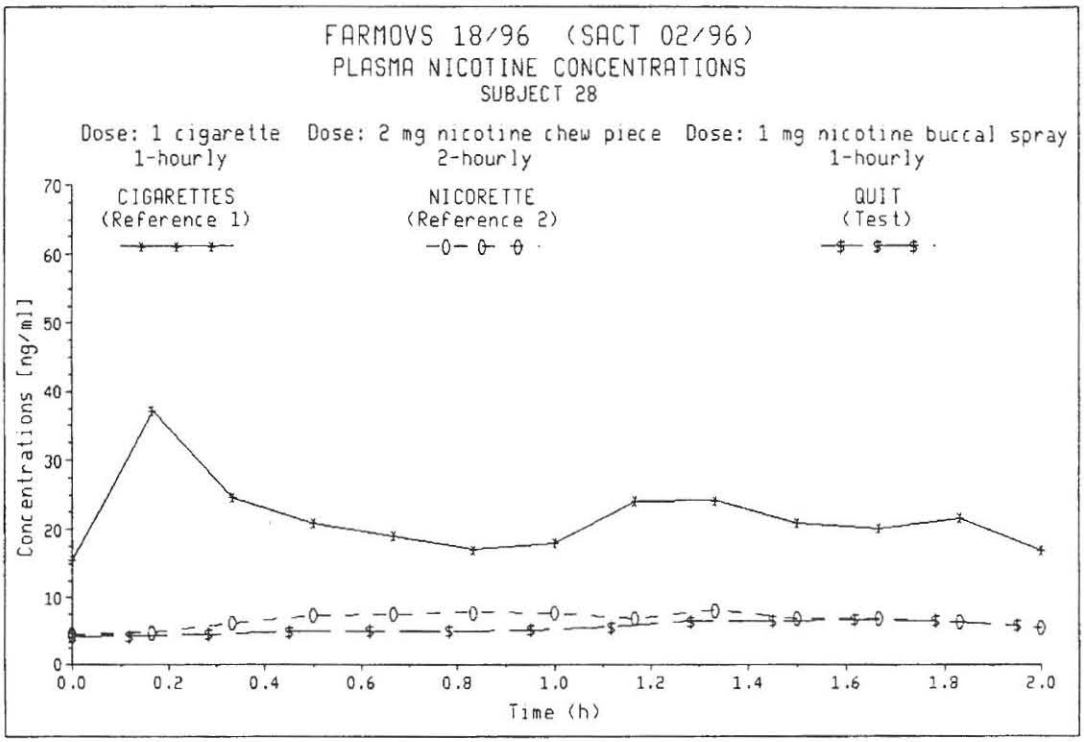


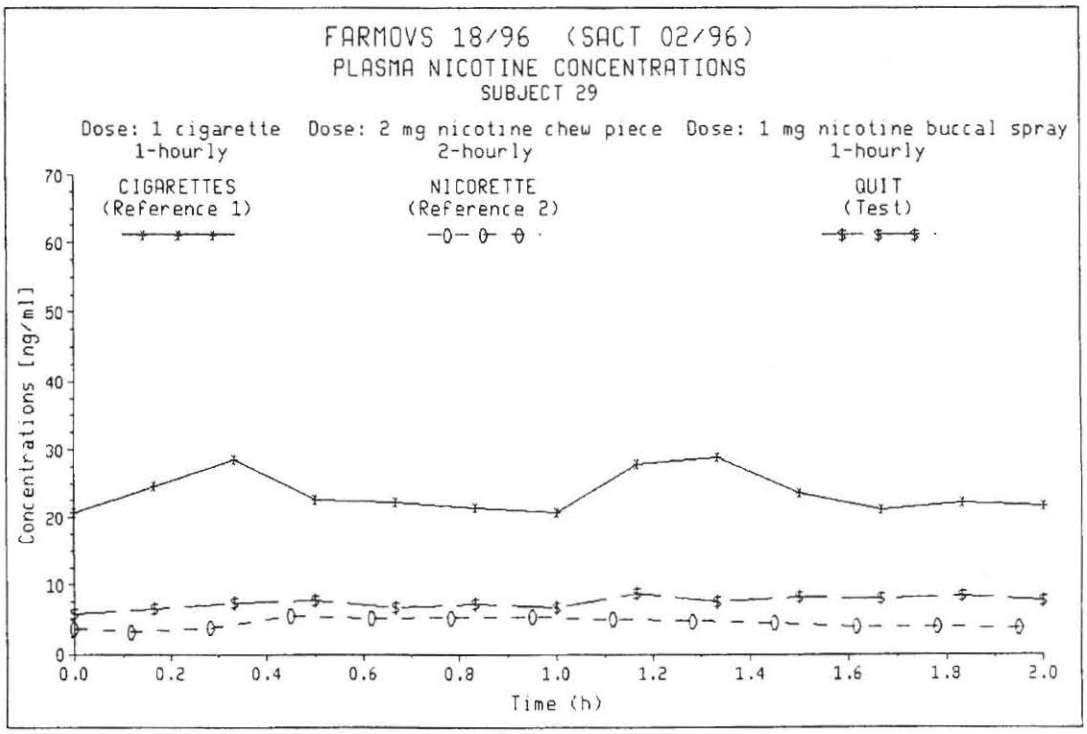


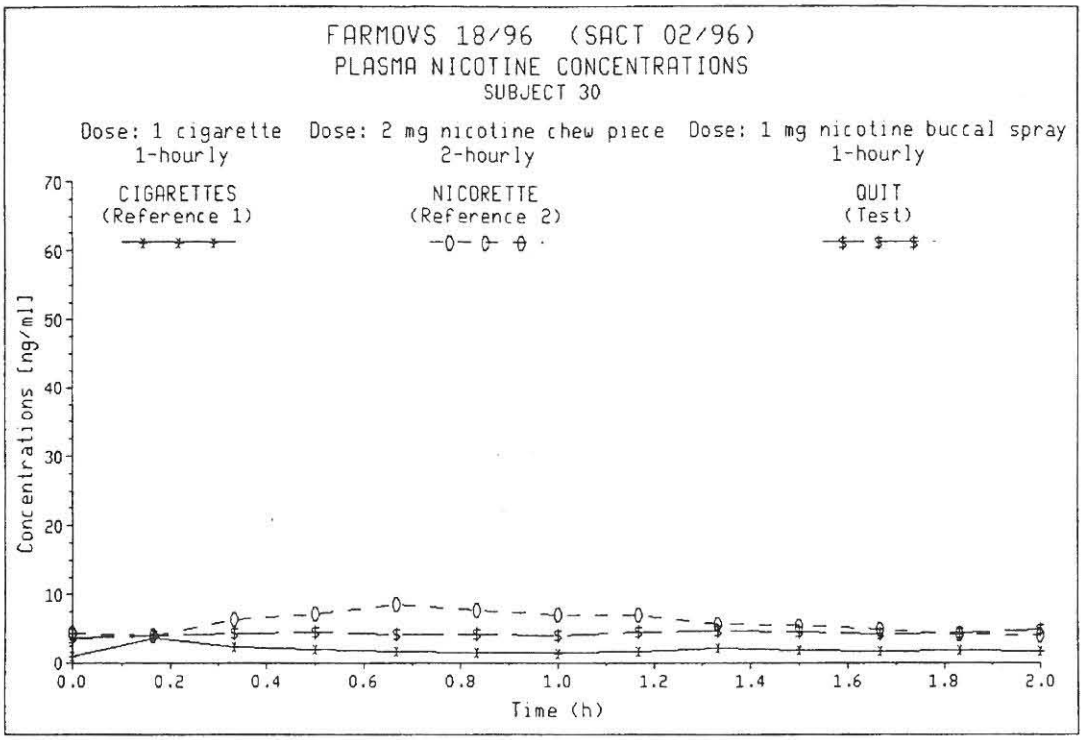


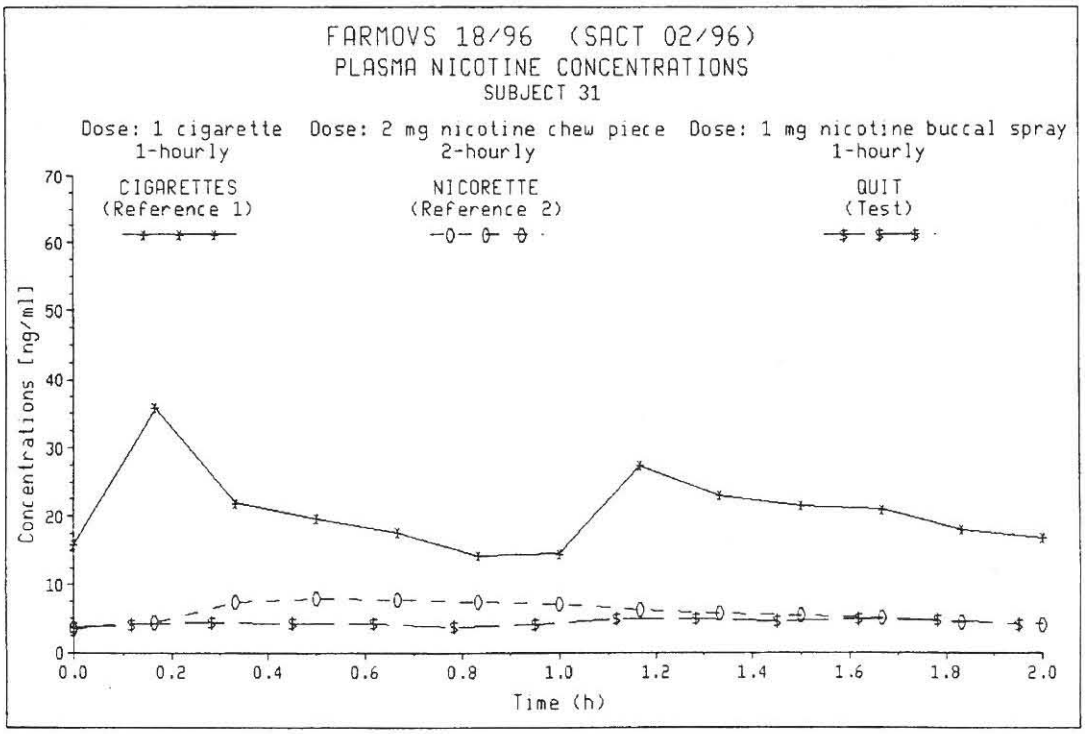


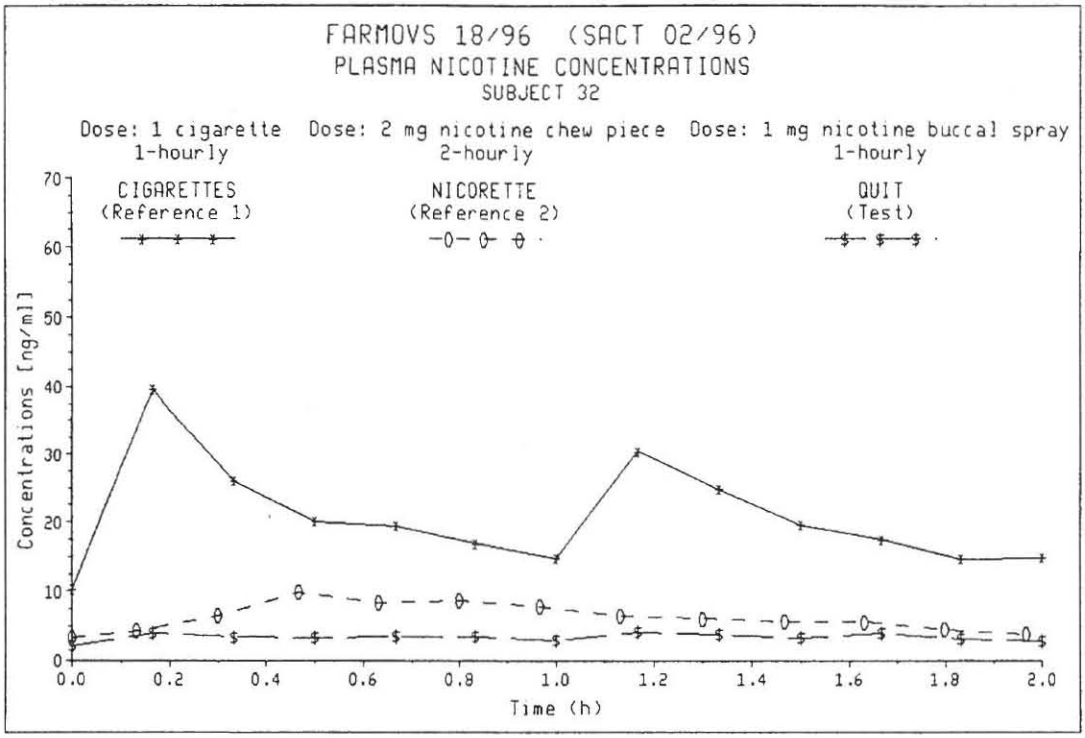


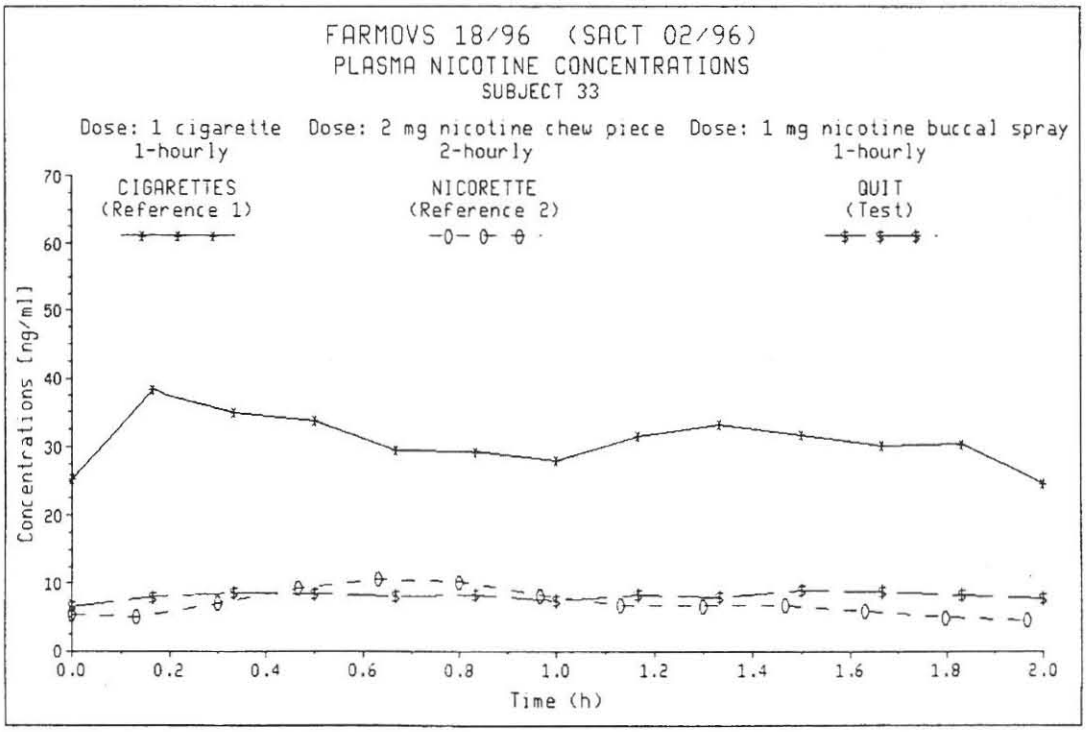


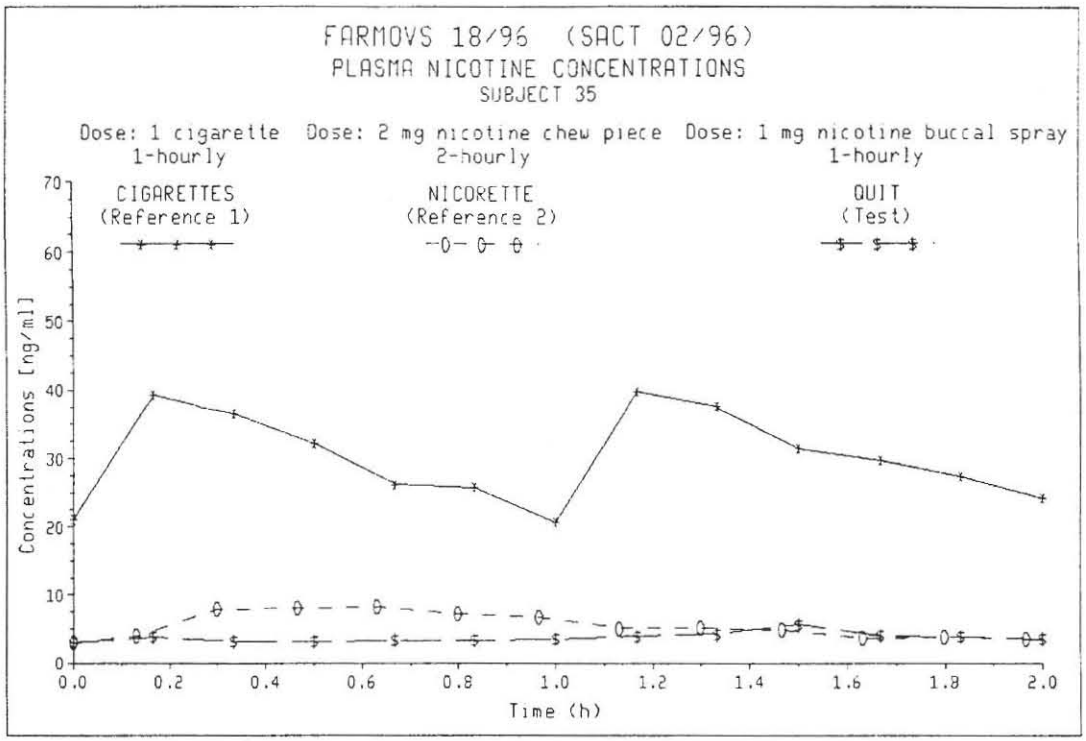


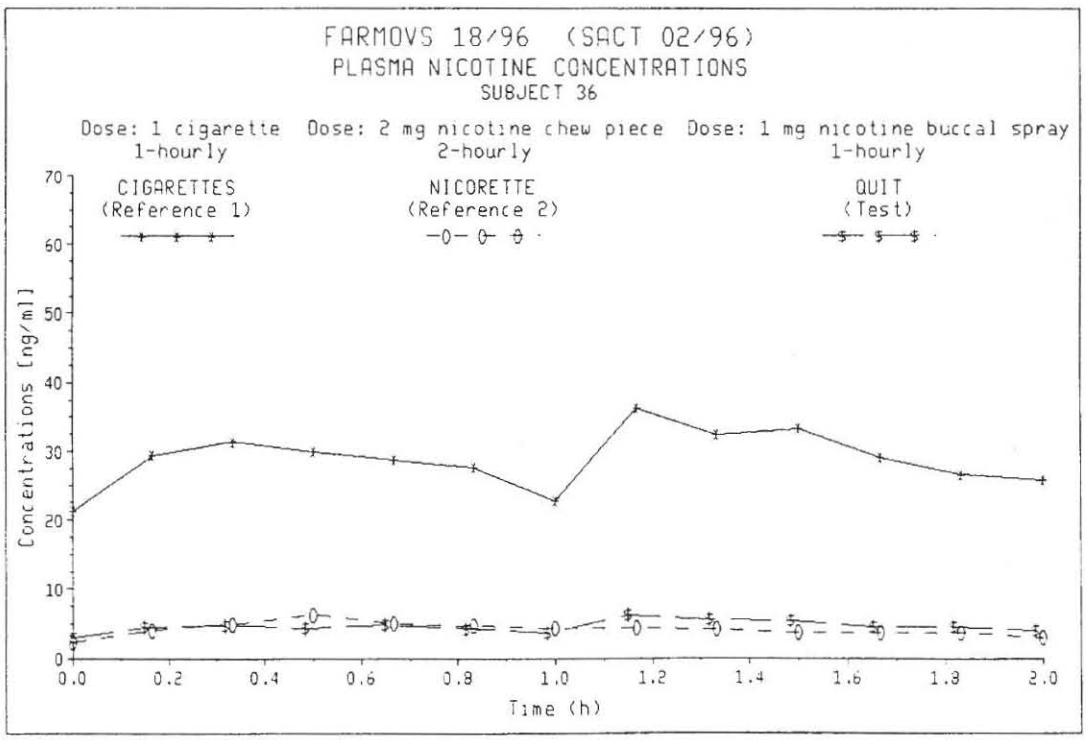












APPENDIX 11

Nicotine Pharmacokinetic Variables

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
1	41.830	46.200	46.200	28.370	33.830	28.370
2	35.660	32.650	35.660	21.490	25.410	21.490
3	60.350	58.640	60.350	54.220	55.140	54.220
4	38.260	39.320	39.320	27.720	29.560	27.720
5	26.490	27.070	27.070	17.770	17.780	17.770
6	35.000	48.900	48.900	19.040	23.580	19.040
7	32.170	35.340	35.340	23.200	25.110	23.200
8	22.510	21.100	22.510	11.110	11.040	11.040
9	30.690	32.030	32.030	17.290	20.900	17.290
10	20.910	24.000	24.000	9.590	11.320	9.590
11	34.640	37.580	37.580	23.680	25.870	23.680
12	18.310	21.620	21.620	11.330	13.610	11.330
13	29.230	31.530	31.530	22.110	22.230	22.110
14	25.740	29.570	29.570	17.220	18.880	17.220
15	28.450	29.480	29.480	19.600	19.480	19.480
16	59.880	57.050	59.880	26.870	27.290	26.870
17	36.220	30.020	36.220	21.150	21.150	21.150
18	18.080	15.540	18.080	7.090	9.020	7.090
19	21.570	22.990	22.990	10.040	10.040	10.040
20	29.410	30.320	30.320	15.690	15.690	15.690
21	46.520	37.810	46.520	23.730	21.820	21.820
22	33.130	39.180	39.180	25.870	25.870	25.870
23	38.970	32.390	38.970	20.100	20.400	20.100
24	47.260	49.650	49.650	28.740	30.200	28.740
26	44.990	32.060	44.990	18.120	19.110	18.120
27	39.800	36.400	39.800	16.850	17.060	16.850
28	37.090	24.200	37.090	15.490	16.810	15.490
29	28.440	28.880	28.880	20.680	20.680	20.680
30	3.630	2.110	3.630	1.050	1.420	1.050
31	35.690	27.250	35.690	14.140	14.390	14.140
32	39.570	30.420	39.570	10.290	14.710	10.290

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
33	38.220	33.230	38.220	25.240	24.700	24.700
35	39.320	39.930	39.930	20.730	20.730	20.730
36	31.270	36.150	36.150	21.170	22.590	21.170
MEAN	33.803	32.959	35.498	19.611	20.806	19.534
SD	11.261	11.096	11.332	8.908	9.038	8.879
GEOM MEAN	31.221	30.059	32.862	17.185	18.515	17.125
GEOM SD	1.612	1.730	1.612	1.878	1.788	1.876
CV%	33.315	33.665	31.925	45.424	43.438	45.458
SEM	1.931	1.903	1.944	1.528	1.550	1.523
MIN	3.630	2.110	3.630	1.050	1.420	1.050
MAX	60.350	58.640	60.350	54.220	55.140	54.220
MEDIAN	34.820	32.045	36.185	19.850	20.705	19.790
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
1	.167	.167	75.403	47.292	.848
2	.333	.667	59.484	47.643	.618
3	.167	1.000	113.588	10.793	2.000
4	.167	.667	69.931	33.175	1.972
5	.167	.167	44.012	42.261	1.462
6	.167	.167	62.723	95.212	.262
7	.167	.500	62.544	38.821	.876
8	.167	.167	31.146	73.652	.609
9	.333	.333	53.447	55.158	.650
10	.167	.167	31.605	91.189	.408
11	.500	.167	61.859	44.941	1.555
12	.333	.333	33.368	61.675	1.036
13	.167	.167	52.963	35.572	1.403
14	.167	.167	46.656	52.941	1.164
15	.333	.333	49.333	40.541	1.512
16	.167	.167	76.941	85.806	.441
17	.167	.167	52.727	57.163	.678
18	.167	.167	26.129	84.122	.709
19	.167	.167	29.663	87.315	.502
20	.167	.167	45.727	63.989	.915
21	.167	.167	60.947	81.054	.433
22	.333	.333	63.051	42.220	1.364
23	.167	.167	52.362	72.075	.483
24	.167	.167	75.660	55.274	.860
26	.167	.167	53.830	99.832	.222
27	.167	.167	50.610	90.694	.475
28	.167	.333	43.966	98.258	.194
29	.333	.333	47.503	34.524	1.352
30	.167	.333	3.851	133.988	.180
31	.167	.167	41.571	103.678	.206
32	.167	.167	42.672	137.231	.207

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
33	.167	.333	62.575	43.212	1.713
35	.167	.167	61.654	62.283	1.062
36	.333	.167	58.191	51.485	1.450
MEAN	.211	.270	52.873	66.326	.877
SD	.085	.188	18.874	29.039	.538
GEOM MEAN	.199	.232	48.096	59.773	.702
GEOM SD	1.385	1.655	1.717	1.639	2.065
CV%	40.258	69.685	35.697	43.783	61.360
SEM	.015	.032	3.237	4.980	.092
MIN	.167	.167	3.851	10.793	.180
MAX	.500	1.000	113.588	137.231	2.000
MEDIAN	.167	.167	52.845	59.419	.778
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Excluding Subject 30
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
1	41.830	46.200	46.200	28.370	33.830	28.370
2	35.660	32.650	35.660	21.490	25.410	21.490
3	60.350	58.640	60.350	54.220	55.140	54.220
4	38.260	39.320	39.320	27.720	29.560	27.720
5	26.490	27.070	27.070	17.770	17.780	17.770
6	35.000	48.900	48.900	19.040	23.580	19.040
7	32.170	35.340	35.340	23.200	25.110	23.200
8	22.510	21.100	22.510	11.110	11.040	11.040
9	30.690	32.030	32.030	17.290	20.900	17.290
10	20.910	24.000	24.000	9.590	11.320	9.590
11	34.640	37.580	37.580	23.680	25.870	23.680
12	18.310	21.620	21.620	11.330	13.610	11.330
13	29.230	31.530	31.530	22.110	22.230	22.110
14	25.740	29.570	29.570	17.220	18.880	17.220
15	28.450	29.480	29.480	19.600	19.480	19.480
16	59.880	57.050	59.880	26.870	27.290	26.870
17	36.220	30.020	36.220	21.150	21.150	21.150
18	18.080	15.540	18.080	7.090	9.020	7.090
19	21.570	22.990	22.990	10.040	10.040	10.040
20	29.410	30.320	30.320	15.690	15.690	15.690
21	46.520	37.810	46.520	23.730	21.820	21.820
22	33.130	39.180	39.180	25.870	25.870	25.870
23	38.970	32.390	38.970	20.100	20.400	20.100
24	47.260	49.650	49.650	28.740	30.200	28.740
26	44.990	32.060	44.990	18.120	19.110	18.120
27	39.800	36.400	39.800	16.850	17.060	16.850
28	37.090	24.200	37.090	15.490	16.810	15.490
29	28.440	28.880	28.880	20.680	20.680	20.680
31	35.690	27.250	35.690	14.140	14.390	14.140
32	39.570	30.420	39.570	10.290	14.710	10.290

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Excluding Subject 30
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
33	38.220	33.230	38.220	25.240	24.700	24.700
35	39.320	39.930	39.930	20.730	20.730	20.730
36	31.270	36.150	36.150	21.170	22.590	21.170
MEAN	34.717	33.894	36.463	20.174	21.394	20.094
SD	10.073	9.814	9.987	8.411	8.493	8.385
GEOM MEAN	33.324	32.578	35.131	18.704	20.013	18.637
GEOM SD	1.341	1.332	1.325	1.488	1.446	1.486
CV%	29.015	28.955	27.389	41.693	39.699	41.730
SEM	1.754	1.708	1.739	1.464	1.478	1.460
MIN	18.080	15.540	18.080	7.090	9.020	7.090
MAX	60.350	58.640	60.350	54.220	55.140	54.220
MEDIAN	35.000	32.060	36.220	20.100	20.730	20.100
n	33	33	33	33	33	33

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Excluding Subject 30
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
1	.167	.167	75.403	47.292	.848
2	.333	.667	59.484	47.643	.618
3	.167	1.000	113.588	10.793	2.000
4	.167	.667	69.931	33.175	1.972
5	.167	.167	44.012	42.261	1.462
6	.167	.167	62.723	95.212	.262
7	.167	.500	62.544	38.821	.876
8	.167	.167	31.146	73.652	.609
9	.333	.333	53.447	55.158	.650
10	.167	.167	31.605	91.189	.408
11	.500	.167	61.859	44.941	1.555
12	.333	.333	33.368	61.675	1.036
13	.167	.167	52.963	35.572	1.403
14	.167	.167	46.656	52.941	1.164
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23	.167	.167	52.362	72.075	.483
24	.167	.167	75.660	55.274	.860
26	.167	.167	53.830	99.832	.222
27	.167	.167	50.610	90.694	.475
28	.167	.333	43.966	98.258	.194
29	.333	.333	47.503	34.524	1.352
31	.167	.167	41.571	103.678	.206
32	.167	.167	42.672	137.231	.207

PROGRAM: S T A T S (V 1.3)

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FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Excluding Subject 30
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
33	.167	.333	62.575	43.212	1.713
35	.167	.167	61.654	62.283	1.062
36	.333	.167	58.191	51.485	1.450
MEAN	.212	.268	54.359	64.275	.898
SD	.086	.191	17.029	26.874	.532
GEOM MEAN	.200	.229	51.921	58.329	.732
GEOM SD	1.390	1.661	1.363	1.617	2.003
CV%	40.455	71.146	31.328	41.811	59.231
SEM	.015	.033	2.964	4.678	.093
MIN	.167	.167	26.129	10.793	.194
MAX	.500	1.000	113.588	137.231	2.000
MEDIAN	.167	.167	52.963	57.163	.848
n	33	33	33	33	33

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (h)	AUDss (ng.h/ml)	%PTF (%)	T75%Cmax (h)
33	10.540	4.490	.633	14.334	84.418	.634
35	8.280	3.060	.633	11.409	91.508	.790
36	6.290	2.320	.500	8.607	92.255	.533
MEAN	9.954	4.859	.553	14.764	74.880	.933
SD	4.483	3.940	.205	8.315	19.506	.392
GEOM MEAN	9.393	4.276	.522	13.674	71.785	.864
GEOM SD	1.366	1.529	1.399	1.411	1.376	1.478
CV%	45.035	81.098	37.138	56.318	26.050	42.081
SEM	.769	.676	.035	1.426	3.345	.067
MIN	5.580	2.320	.333	8.607	22.745	.469
MAX	32.410	25.830	1.333	57.860	107.168	2.000
MEDIAN	8.865	4.050	.500	12.665	76.498	.863
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (h)	AUDss (ng.h/ml)	%PTF (%)	T75%Cmax (h)
33	10.540	4.490	.633	14.334	84.418	.634
35	8.280	3.060	.633	11.409	91.508	.790
36	6.290	2.320	.500	8.607	92.255	.533
MEAN	9.954	4.859	.553	14.764	74.880	.933
SD	4.483	3.940	.205	8.315	19.506	.392
GEOM MEAN	9.393	4.276	.522	13.674	71.785	.864
GEOM SD	1.366	1.529	1.399	1.411	1.376	1.478
CV%	45.035	81.098	37.138	56.318	26.050	42.081
SEM	.769	.676	.035	1.426	3.345	.067
MIN	5.580	2.320	.333	8.607	22.745	.469
MAX	32.410	25.830	1.333	57.860	107.168	2.000
MEDIAN	8.865	4.050	.500	12.665	76.498	.863
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
1	8.090	11.570	11.570	5.460	7.380	5.460
2	9.980	10.980	10.980	8.800	8.270	8.270
3	25.710	26.160	26.160	23.040	23.040	23.040
4	11.280	12.060	12.060	10.070	10.520	10.070
5	9.120	8.390	9.120	6.450	6.850	6.450
6	8.370	8.850	8.850	6.070	7.150	6.070
7	7.550	7.890	7.890	5.520	5.900	5.520
8	2.660	2.290	2.660	1.590	1.640	1.590
9	4.550	4.940	4.940	3.880	3.810	3.810
10	5.720	6.460	6.460	3.620	3.640	3.620
11	6.820	6.330	6.820	5.190	5.590	5.190
12	7.420	10.220	10.220	6.680	5.790	5.790
13	6.810	9.430	9.430	5.480	6.350	5.480
14	6.650	8.200	8.200	4.430	5.110	4.430
15	6.120	7.750	7.750	4.490	5.470	4.490
16	6.580	8.550	8.550	4.970	5.170	4.970
17	6.450	6.720	6.720	5.250	5.250	5.250
18	7.890	6.940	7.890	3.490	3.570	3.490
19	4.980	5.090	5.090	3.240	3.540	3.240
20	7.870	8.860	8.860	5.730	7.180	5.730
21	9.810	14.540	14.540	6.550	7.900	6.550
22	7.250	8.880	8.880	5.300	5.730	5.300
23	5.320	5.600	5.600	3.020	3.040	3.020
24	6.440	6.750	6.750	5.070	5.630	5.070
26	6.080	7.050	7.050	4.330	5.020	4.330
27	4.650	5.880	5.880	2.710	3.210	2.710
28	5.240	6.770	6.770	4.110	5.240	4.110
29	7.670	8.710	8.710	5.910	6.680	5.910
30	4.480	4.810	4.810	3.690	4.030	3.690
31	4.400	4.910	4.910	3.710	4.090	3.710
32	4.010	4.210	4.210	2.140	2.810	2.140

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
33	8.530	8.920	8.920	6.560	7.420	6.560
35	3.870	5.630	5.630	3.010	3.510	3.010
36	4.830	6.200	6.200	3.030	3.670	3.030
MEAN	7.153	8.134	8.208	5.370	5.859	5.326
SD	3.806	4.033	4.009	3.587	3.560	3.567
GEOM MEAN	6.562	7.446	7.542	4.735	5.229	4.704
GEOM SD	1.482	1.514	1.496	1.605	1.581	1.597
CV%	53.205	49.584	48.840	66.798	60.770	66.970
SEM	.653	.692	.688	.615	.611	.612
MIN	2.660	2.290	2.660	1.590	1.640	1.590
MAX	25.710	26.160	26.160	23.040	23.040	23.040
MEDIAN	6.615	7.400	7.820	5.020	5.360	5.020
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
1	.167	.667	16.835	72.587	.877
2	.833	.333	18.408	29.444	2.000
3	.000	.667	49.936	12.496	2.000
4	.833	.667	22.339	17.817	2.000
5	.167	.167	15.612	34.205	1.976
6	.333	.667	15.821	35.144	1.944
7	.167	.333	14.280	33.193	.952
8	.333	.833	4.389	48.760	1.690
9	.167	.667	8.657	26.105	2.000
10	.167	.167	10.059	56.465	.283
11	.333	.667	11.860	27.488	2.000
12	.667	.167	14.290	62.000	.259
13	.333	.167	14.649	53.930	.740
14	.167	.167	12.373	60.941	1.007
15	.333	.333	12.279	53.101	.129
16	.333	.333	13.170	54.365	.985
17	.167	.167	12.283	23.935	2.000
18	.167	.167	9.693	90.788	.343
19	.167	.500	8.928	41.443	1.869
20	.167	.167	15.630	40.052	1.929
21	.333	.167	21.231	75.267	.768
22	.333	.833	13.315	53.773	.523
23	.167	.167	8.421	61.277	1.038
24	.167	.833	12.048	27.889	2.000
26	.500	.500	12.393	43.896	.838
27	.283	.283	8.299	76.397	.482
28	1.000	.617	11.126	47.816	1.248
29	.500	.167	15.009	37.311	1.845
30	.500	1.000	8.653	25.886	2.000
31	.283	.617	8.803	27.265	2.000
32	.167	.167	6.968	59.412	1.668

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
NICOTINE PHARMACOKINETIC VARIABLES
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
33	.333	.500	16.318	28.925	1.985
35	.167	.500	7.552	69.386	.331
36	.650	.150	9.366	67.695	.815
MEAN	.335	.427	13.559	46.366	1.310
SD	.230	.259	7.570	19.158	.680
GEOM MEAN		.349	12.307	42.236	1.064
GEOM SD		1.934	1.522	1.581	2.116
CV%	68.623	60.608	55.831	41.318	51.946
SEM	.039	.044	1.298	3.286	.117
MIN	.000	.150	4.389	12.496	.129
MAX	1.000	1.000	49.936	90.788	2.000
MEDIAN	.308	.333	12.328	45.856	1.458
n	34	34	34	34	34

APPENDIX 12

Plasma Cotinine Concentrations

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
1	315.920	406.880	383.990	424.650
2	318.090	352.020	325.340	371.200
3	43.380	55.840	69.100	78.750
4	430.710	522.610	532.980	466.280
5	188.790	139.840	262.240	287.400
6	379.760	561.230	544.490	543.190
7	776.910	711.980	738.460	709.110
8	223.170	173.940	176.080	202.040
9	302.660	258.860	289.780	302.290
10	265.650	206.320	207.540	225.990
11	218.710	361.840	332.510	358.420
12	36.670	150.840	151.940	162.800
13	246.470	270.360	319.410	310.940
14	333.020	312.240	330.070	327.420
15	104.830	214.000	269.710	281.140
16	261.940	412.280	406.620	386.830
17	345.910	419.090	425.780	377.320
18	127.570	150.220	169.760	152.990
19	191.060	198.440	194.200	237.580
20	219.920	225.890	212.440	198.400
21	333.460	337.570	307.470	344.800
22	285.060	306.950	323.980	333.230
23	353.320	338.520	380.610	398.480
24	461.950	439.910	431.670	394.970
26	428.980	448.550	412.500	432.930
27	262.910	298.630	310.480	349.790
28	299.860	287.090	248.770	281.300
29	267.530	353.380	364.970	361.240
30	19.410	36.660	29.990	25.910
31	145.330	296.710	317.150	370.450
32	312.480	291.100	271.550	279.630

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
33	526.410	453.990	464.550	489.810
35	488.580	517.410	505.500	565.690
36	329.130	427.730	402.930	345.350
MEAN	289.575	321.733	326.899	334.656
SD	150.012	145.756	140.812	135.534
GEOM MEAN	238.243	280.320	287.999	296.438
GEOM SD	2.138	1.838	1.813	1.818
CV%	51.804	45.304	43.075	40.499
SEM	25.727	24.997	24.149	23.244
MIN	19.410	36.660	29.990	25.910
MAX	776.910	711.980	738.460	709.110
MEDIAN	292.460	309.595	321.695	345.075
n	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
1	374.690	229.610	190.200	172.910
2	202.400	136.290	163.830	197.670
3	71.460	42.900	46.580	46.190
4	258.550	224.860	190.000	208.560
5	154.620	129.330	147.620	121.690
6	614.180	348.980	265.020	199.390
7	737.890	487.960	436.600	369.490
8	169.620	63.810	68.450	78.880
9	149.390	128.110	109.470	119.610
10	252.120	147.850	116.120	101.890
11	140.120	126.000	128.180	113.970
12	147.830	133.180	159.320	150.780
13	143.820	145.110	142.720	148.580
14	303.580	163.230	127.060	131.440
15	279.190	136.660	99.430	107.620
16	199.950	169.320	165.590	125.490
17	218.320	149.190	132.490	140.830
18	166.350	91.450	118.040	102.380
19	217.860	107.460	87.100	83.010
20	122.590	105.990	120.090	121.160
21	154.750	173.710	146.360	129.750
22	137.270	144.930	126.140	126.430
23	375.790	181.810	136.310	118.930
24	455.340	229.700	159.480	121.960
26	389.130	219.970	170.210	131.760
27	109.100	93.250	107.550	117.400
28	115.670	99.230	117.610	107.990
29	325.070	211.090	169.820	139.530
30	20.990	86.970	89.550	119.560
31	132.920	110.680	126.200	125.790
32	245.960	149.670	131.070	130.090

PROGRAM: S T A T S (V 1.3)

Division of Biometry
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University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
33	484.060	245.070	184.050	167.790
35	434.940	240.630	154.210	144.270
36	97.930	55.900	53.430	62.720
MEAN	247.160	162.056	143.703	134.868
SD	158.789	85.917	66.807	54.078
GEOM MEAN	202.270	144.071	132.269	126.641
GEOM SD	1.981	1.638	1.505	1.427
CV%	64.245	53.017	46.490	40.097
SEM	27.232	14.735	11.457	9.274
MIN	20.990	42.900	46.580	46.190
MAX	737.890	487.960	436.600	369.490
MEDIAN	201.175	145.020	131.780	125.640
n	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
1	157.790	150.240	142.750	120.340
2	395.470	230.200	176.890	284.050
3	46.900	39.780	44.580	45.830
4	494.330	335.360	258.580	247.610
5	229.430	199.430	145.940	176.310
6	201.000	204.590	204.570	197.040
7	305.270	241.860	250.910	205.470
8	58.520	55.640	61.510	76.190
9	312.110	190.640	164.040	159.030
10	89.520	105.780	107.710	120.340
11	384.560	216.190	172.930	157.430
12	176.740	159.540	172.800	165.840
13	306.480	207.300	147.990	150.610
14	131.930	141.190	155.840	148.830
15	109.470	150.490	147.990	145.300
16	433.260	239.700	179.380	169.980
17	440.560	261.910	185.690	170.520
18	126.450	101.600	86.570	103.650
19	99.850	109.890	113.860	139.580
20	207.120	139.440	102.260	104.690
21	323.920	221.410	163.160	134.990
22	333.860	170.450	164.260	145.810
23	138.720	129.810	113.610	111.480
24	122.650	167.120	182.290	171.120
26	106.470	107.010	100.820	107.090
27	273.290	188.510	135.320	128.870
28	259.610	159.820	123.460	122.710
29	128.130	198.160	211.370	195.460
30	78.660	103.060	139.100	134.560
31	278.580	178.570	142.600	157.590
32	98.670	80.770	92.320	91.230

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
TROUGH PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Day 1	Day 2	Day 3	Day 3 0.0 h
33	134.210	177.460	258.600	265.670
35	98.020	136.040	148.800	149.730
36	447.630	208.250	123.170	124.990
MEAN	221.446	167.859	150.637	150.881
SD	129.189	61.559	50.259	49.873
GEOM MEAN	184.633	155.008	141.671	142.751
GEOM SD	1.886	1.548	1.455	1.419
CV%	58.339	36.673	33.364	33.054
SEM	22.156	10.557	8.619	8.553
MIN	46.900	39.780	44.580	45.830
MAX	494.330	335.360	258.600	284.050
MEDIAN	188.870	168.785	147.990	147.320
n	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
1	424.650	435.850	404.050	439.520	378.700	466.220
2	371.200	344.990	515.590	446.860	399.970	460.520
3	78.750	74.610	70.980	71.160	79.310	62.410
4	466.280	479.640	478.030	425.720	513.730	521.100
5	287.400	286.290	262.670	299.760	301.320	312.580
6	543.190	502.410	490.770	474.590	450.350	473.260
7	709.110	651.870	613.460	657.360	694.610	599.770
8	202.040	214.850	214.210	199.390	207.240	200.050
9	302.290	314.420	318.370	298.700	280.170	281.880
10	225.990	229.990	227.940	217.740	213.430	216.000
11	358.420	374.280	377.940	388.470	364.000	376.510
12	162.800	176.800	183.770	170.340	163.180	165.320
13	310.940	341.800	325.300	318.710	315.370	320.050
14	327.420	342.890	333.810	325.610	308.340	337.000
15	281.140	266.780	272.310	268.100	290.660	296.560
16	386.830	409.210	406.160	351.070	377.590	340.480
17	377.320	413.750	378.010	363.740	340.830	324.180
18	152.990	163.700	162.010	175.600	170.500	207.290
19	237.580	225.370	214.640	212.510	231.150	224.750
20	198.400	214.910	177.760	160.170	195.670	188.830
21	344.800	326.560	260.730	356.360	317.940	305.830
22	333.230	350.040	378.150	371.290	349.120	358.720
23	398.480	441.470	382.750	402.590	371.000	398.570
24	394.970	430.040	440.920	428.540	435.550	453.680
26	432.930	442.820	412.600	444.730	425.640	405.970
27	349.790	326.130	353.660	328.670	346.480	343.920
28	281.300	289.550	259.000	267.920	272.830	281.410
29	361.240	340.730	343.730	352.010	355.150	352.900
30	25.910	26.640	26.390	27.240	25.060	26.750
31	370.450	372.390	351.780	392.320	371.100	381.120
32	279.630	287.920	298.740	294.620	317.610	317.960

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
33	489.810	439.120	468.150	474.210	481.050	462.330
35	565.690	520.630	538.070	574.990	599.130	593.870
36	345.350	355.040	343.200	331.500	357.070	379.210
MEAN	334.656	335.691	331.931	332.709	332.378	336.382
SD	135.534	127.132	129.609	131.960	133.415	130.201
GEOM MEAN	296.438	299.415	294.390	294.684	294.944	298.169
GEOM SD	1.818	1.799	1.819	1.819	1.814	1.829
CV%	40.499	37.872	39.047	39.662	40.139	38.706
SEM	23.244	21.803	22.228	22.631	22.880	22.329
MIN	25.910	26.640	26.390	27.240	25.060	26.750
MAX	709.110	651.870	613.460	657.360	694.610	599.770
MEDIAN	345.075	342.345	343.465	341.285	343.655	338.740
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
1	404.390	430.850	383.900	413.330	378.000	405.420
2	435.600	377.220	356.550	399.010	420.620	402.950
3	65.330	60.940	55.490	55.130	56.920	58.050
4	456.220	457.430	489.420	471.520	527.590	553.940
5	282.060	294.250	260.940	282.250	280.220	344.390
6	434.220	435.290	454.800	380.850	396.460	362.420
7	542.650	567.270	512.980	506.730	523.240	534.560
8	192.020	202.420	206.730	209.970	206.520	241.060
9	298.770	309.090	312.390	321.710	315.700	364.690
10	214.030	249.860	244.470	235.720	217.180	225.550
11	389.090	409.130	375.530	380.050	385.400	388.200
12	173.200	166.470	184.300	185.790	189.470	179.590
13	326.120	317.950	331.550	333.930	326.790	321.160
14	359.200	332.510	345.050	348.830	322.850	353.400
15	273.510	266.650	277.410	261.180	271.660	276.540
16	331.400	370.140	372.600	369.090	358.310	410.170
17	299.180	341.520	377.360	366.270	418.170	416.930
18	191.080	190.830	158.740	178.460	188.990	200.670
19	206.780	219.790	220.090	229.010	204.880	269.040
20	175.770	183.630	181.960	192.620	195.830	267.710
21	320.180	285.400	271.470	328.040	277.970	375.030
22	368.470	380.790	399.630	353.830	355.150	389.590
23	416.370	406.390	388.790	407.690	393.280	424.380
24	441.870	429.050	456.590	443.930	443.350	588.480
26	409.590	409.670	430.170	421.120	394.900	487.030
27	364.700	378.070	389.690	351.710	376.860	302.400
28	300.280	314.530	308.690	316.500	290.710	346.710
29	366.750	380.130	406.890	372.510	346.380	410.660
30	26.920	29.360	32.040	29.150	27.010	32.200
31	379.450	351.880	394.900	370.810	369.030	418.240
32	308.130	294.270	322.160	290.860	266.530	305.150

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
33	490.850	482.380	495.070	477.110	484.580	562.000
35	534.360	576.500	583.740	551.880	589.250	581.440
36	335.940	347.110	341.450	393.980	351.240	364.630
MEAN	326.896	330.846	333.045	330.311	327.972	357.776
SD	120.518	122.189	123.941	116.653	123.353	131.270
GEOM MEAN	291.543	295.439	296.693	295.668	291.697	319.428
GEOM SD	1.804	1.795	1.801	1.798	1.819	1.802
CV%	36.867	36.932	37.215	35.316	37.611	36.691
SEM	20.669	20.955	21.256	20.006	21.155	22.513
MIN	26.920	29.360	32.040	29.150	27.010	32.200
MAX	542.650	576.500	583.740	551.880	589.250	588.480
MEDIAN	333.670	344.315	350.800	352.770	348.810	364.660
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	2.0 h
33	503.600
35	547.480
36	340.950

MEAN	342.646
SD	126.036
GEOM MEAN	305.263
GEOM SD	1.816
CV%	36.783
SEM	21.615
MIN	28.280
MAX	585.850
MEDIAN	358.665
n	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
1	172.910	148.130	178.980	148.360	169.760	169.560
2	197.670	190.620	185.120	182.770	202.490	180.030
3	46.190	50.410	45.790	44.350	54.820	39.970
4	208.560	213.690	214.000	191.750	232.910	237.030
5	121.690	116.490	112.240	120.040	124.580	129.430
6	199.390	195.970	211.590	195.910	172.150	183.050
7	369.490	332.530	328.540	321.660	307.360	319.830
8	78.880	85.390	85.010	N.S.R.	87.860	86.440
9	119.610	121.410	128.970	120.820	128.390	118.330
10	101.890	104.880	110.800	115.050	98.980	106.760
11	113.970	111.790	119.990	119.270	113.440	123.470
12	150.780	145.020	153.600	134.680	145.950	144.450
13	148.580	148.620	145.460	157.040	146.180	142.620
14	131.440	128.800	143.070	129.610	143.630	161.000
15	107.620	104.270	104.620	110.160	102.630	112.900
16	125.490	120.490	126.230	120.310	134.650	121.450
17	140.830	133.310	128.660	128.170	136.060	118.700
18	102.380	124.950	102.040	107.570	112.430	169.950
19	83.010	82.780	78.950	86.260	96.880	102.660
20	121.160	130.080	96.320	113.520	123.360	118.140
21	129.750	121.740	130.690	152.870	148.640	114.110
22	126.430	134.140	138.040	138.290	129.870	138.950
23	118.930	152.270	128.960	131.840	137.370	152.070
24	121.960	131.740	120.790	120.660	129.140	123.670
26	131.760	130.640	126.680	120.720	128.780	126.610
27	117.400	116.590	118.480	111.630	104.180	119.920
28	107.990	111.190	114.990	114.300	106.360	118.680
29	139.530	134.330	148.610	150.530	146.060	139.040
30	119.560	125.110	130.520	120.220	145.670	135.460
31	125.790	124.510	135.200	119.850	127.040	133.790
32	130.090	131.390	133.450	137.850	137.840	164.470

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
33	167.790	164.050	174.950	178.730	171.450	178.120
35	144.270	145.980	146.070	130.070	146.500	158.530
36	62.720	66.090	58.140	64.570	62.240	63.700
MEAN	134.868	134.688	135.457	134.528	136.931	139.791
SD	54.078	47.819	49.834	46.035	45.881	48.016
GEOM MEAN	126.641	127.845	127.556	127.824	130.291	132.179
GEOM SD	1.427	1.385	1.428	1.389	1.379	1.421
CV%	40.097	35.503	36.790	34.220	33.507	34.348
SEM	9.274	8.201	8.546	8.014	7.868	8.235
MIN	46.190	50.410	45.790	44.350	54.820	39.970
MAX	369.490	332.530	328.540	321.660	307.360	319.830
MEDIAN	125.640	129.440	128.965	120.820	132.260	131.610
n	34	34	34	33	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
33	182.060	185.360	178.600	179.310	172.240	184.320
35	162.000	150.480	149.640	149.090	141.400	139.940
36	58.060	59.700	60.540	63.820	65.980	65.980
MEAN	134.828	136.338	134.564	135.130	134.129	139.337
SD	38.838	41.752	40.389	37.728	36.819	37.192
GEOM MEAN	128.792	129.863	128.103	128.987	128.600	133.395
GEOM SD	1.387	1.395	1.407	1.402	1.369	1.387
CV%	28.806	30.624	30.014	27.920	27.450	26.692
SEM	6.661	7.160	6.927	6.470	6.314	6.378
MIN	40.750	41.410	35.540	33.660	39.720	37.000
MAX	259.260	281.620	279.270	249.850	246.610	232.680
MEDIAN	132.735	135.480	130.685	131.310	131.905	140.720
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	2.0 h
1	173.560
2	158.650
3	39.550
4	323.050
5	136.020
6	133.130
7	241.900
8	96.590
9	133.360
10	96.380
11	119.810
12	156.610
13	134.620
14	134.660
15	101.700
16	155.570
17	150.930
18	120.580
19	99.220
20	144.930
21	181.150
22	121.040
23	132.680
24	176.970
26	139.650
27	108.090
28	104.230
29	200.750
30	151.210
31	138.640
32	139.680

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	0.0 h	0.17 h	0.33 h	0.5 h	0.67 h	0.83 h
33	265.670	249.480	262.290	260.870	271.590	269.940
35	149.730	148.410	133.970	132.550	144.120	155.670
36	124.990	98.120	114.840	103.820	113.120	108.280
MEAN	150.881	147.184	146.533	147.530	148.276	147.781
SD	49.873	48.534	45.235	46.320	45.294	48.378
GEOM MEAN	142.751	138.705	139.003	139.613	141.094	139.562
GEOM SD	1.419	1.448	1.417	1.434	1.399	1.441
CV%	33.054	32.975	30.870	31.397	30.547	32.736
SEM	8.553	8.323	7.758	7.944	7.768	8.297
MIN	45.830	37.520	41.130	36.250	43.140	35.610
MAX	284.050	263.910	262.290	260.870	271.590	282.980
MEDIAN	147.320	143.215	146.515	146.895	142.535	147.925
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
1	128.620	130.330	134.290	123.780	139.100	143.910
2	205.050	214.660	196.760	197.650	192.580	206.150
3	30.820	31.760	30.350	31.640	35.110	34.240
4	256.670	245.070	249.480	257.120	250.830	282.590
5	173.320	176.330	158.240	168.840	173.890	175.670
6	168.200	150.170	162.160	151.690	158.540	155.980
7	177.080	177.720	166.620	170.990	153.430	171.600
8	72.310	69.230	73.950	75.300	78.850	92.560
9	160.490	172.810	160.750	162.590	168.110	189.900
10	114.590	118.320	125.450	129.300	124.740	129.300
11	161.120	165.520	166.320	157.880	169.790	167.290
12	156.650	171.020	163.380	168.030	161.900	182.760
13	141.640	141.380	169.160	148.990	157.960	143.700
14	147.800	132.110	141.370	138.410	135.050	144.740
15	141.630	141.020	151.870	131.520	149.070	160.520
16	135.320	131.690	159.610	168.390	145.310	160.640
17	135.250	165.400	160.550	170.750	164.920	186.810
18	107.180	117.530	109.940	111.020	108.790	126.810
19	148.310	117.690	147.680	157.210	138.000	152.160
20	86.680	89.020	86.490	103.580	93.020	118.800
21	133.850	121.920	124.140	141.540	103.640	161.650
22	149.430	146.200	157.370	143.830	138.770	159.670
23	120.290	124.610	110.330	121.340	111.790	116.730
24	165.310	172.330	177.840	158.430	170.340	217.420
26	108.890	113.310	109.240	108.040	114.050	135.820
27	124.200	137.100	129.090	144.740	126.900	122.580
28	131.310	131.430	131.900	141.080	128.020	116.490
29	206.020	198.000	222.800	285.370	243.820	239.330
30	128.810	143.430	134.400	140.640	131.440	137.120
31	157.860	161.010	176.850	169.020	156.380	199.800
32	96.730	97.140	95.910	92.040	95.430	105.630

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	1.0 h	1.17 h	1.33 h	1.5 h	1.67 h	1.83 h
33	267.400	260.850	240.180	247.960	254.550	258.770
35	140.460	144.760	151.080	169.220	149.500	163.910
36	102.320	107.460	107.250	114.080	116.140	118.620
MEAN	143.577	144.657	146.553	150.059	145.287	158.226
SD	46.051	45.013	44.252	48.313	45.421	48.131
GEOM MEAN	135.383	136.655	138.461	141.487	137.610	149.921
GEOM SD	1.459	1.452	1.459	1.460	1.431	1.438
CV%	32.074	31.117	30.195	32.196	31.263	30.419
SEM	7.898	7.720	7.589	8.286	7.790	8.254
MIN	30.820	31.760	30.350	31.640	35.110	34.240
MAX	267.400	260.850	249.480	285.370	254.550	282.590
MEDIAN	141.045	141.200	151.475	146.865	142.205	157.825
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	2.0 h
1	127.280
2	195.940
3	35.930
4	300.950
5	195.850
6	138.900
7	155.720
8	79.140
9	170.910
10	130.710
11	164.470
12	176.110
13	153.390
14	139.900
15	158.350
16	175.780
17	191.910
18	121.050
19	158.860
20	137.100
21	165.380
22	149.170
23	108.960
24	222.690
26	129.090
27	109.390
28	117.840
29	289.260
30	154.100
31	179.320
32	93.280

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

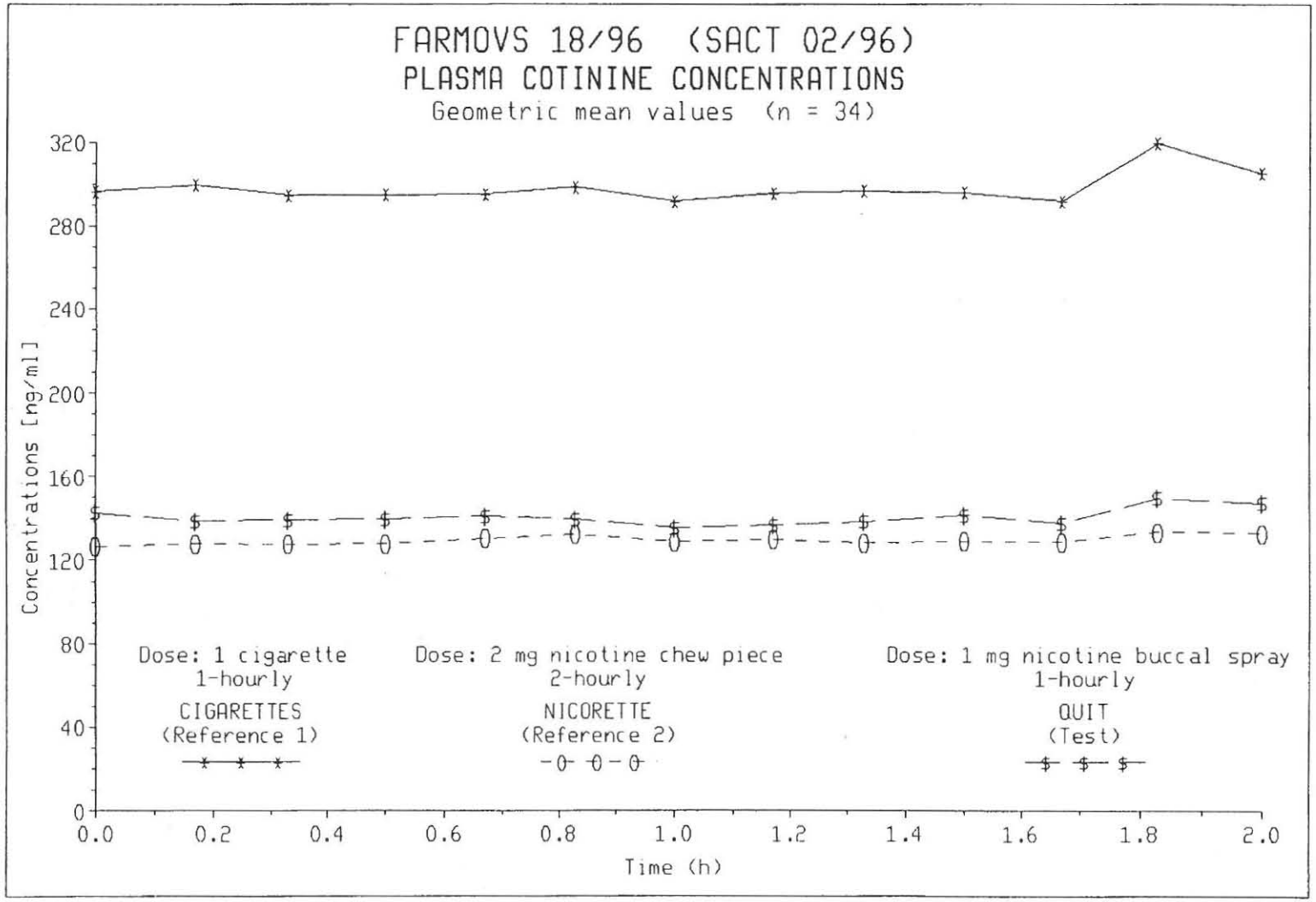
FARMOVS 18/96 (SACT 02/96)
PLASMA COTININE CONCENTRATIONS (ng/ml)
LLOQ = 6.39 ng/ml
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

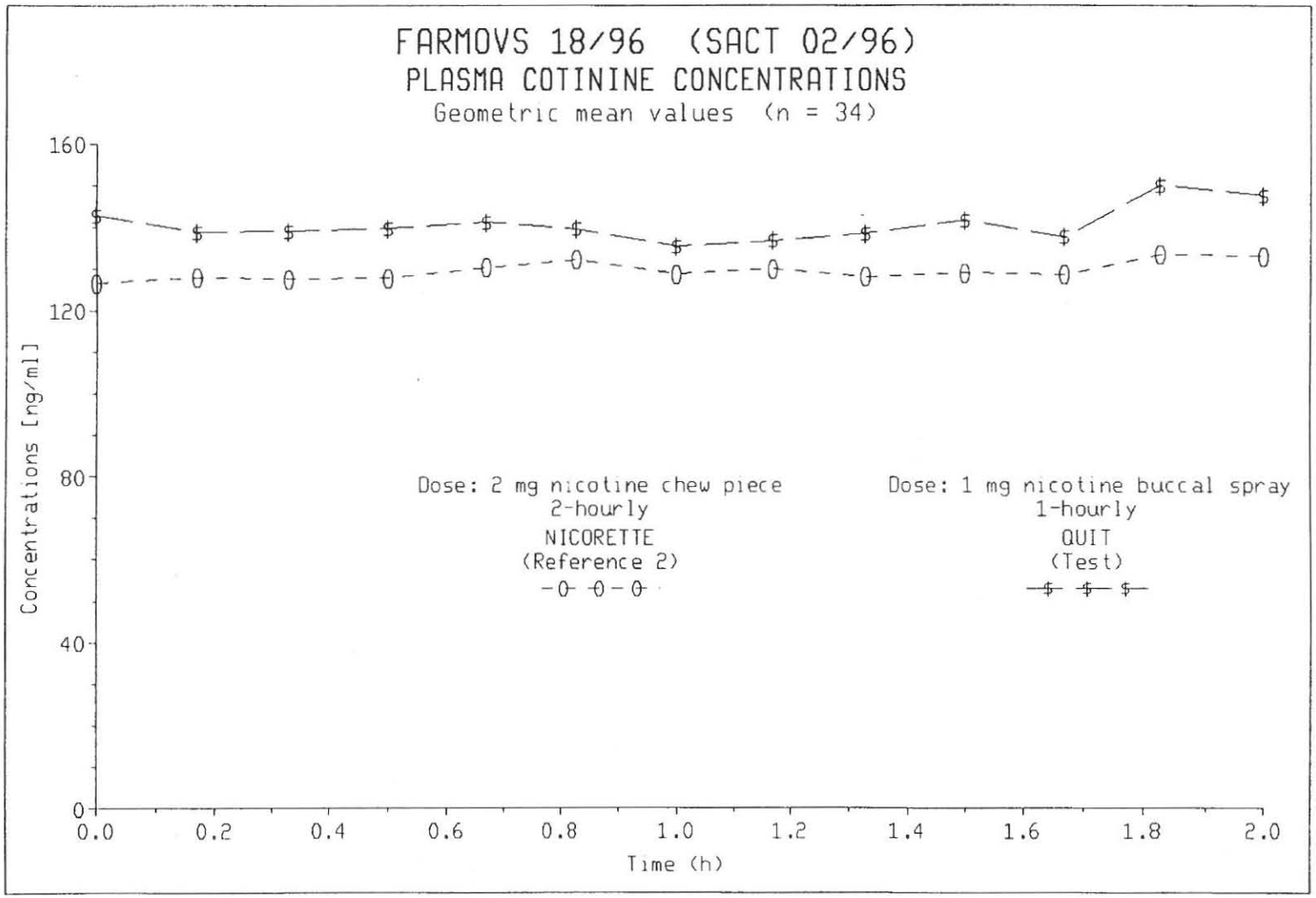
SUBJECT NO.	2.0 h
33	266.640
35	145.380
36	105.800

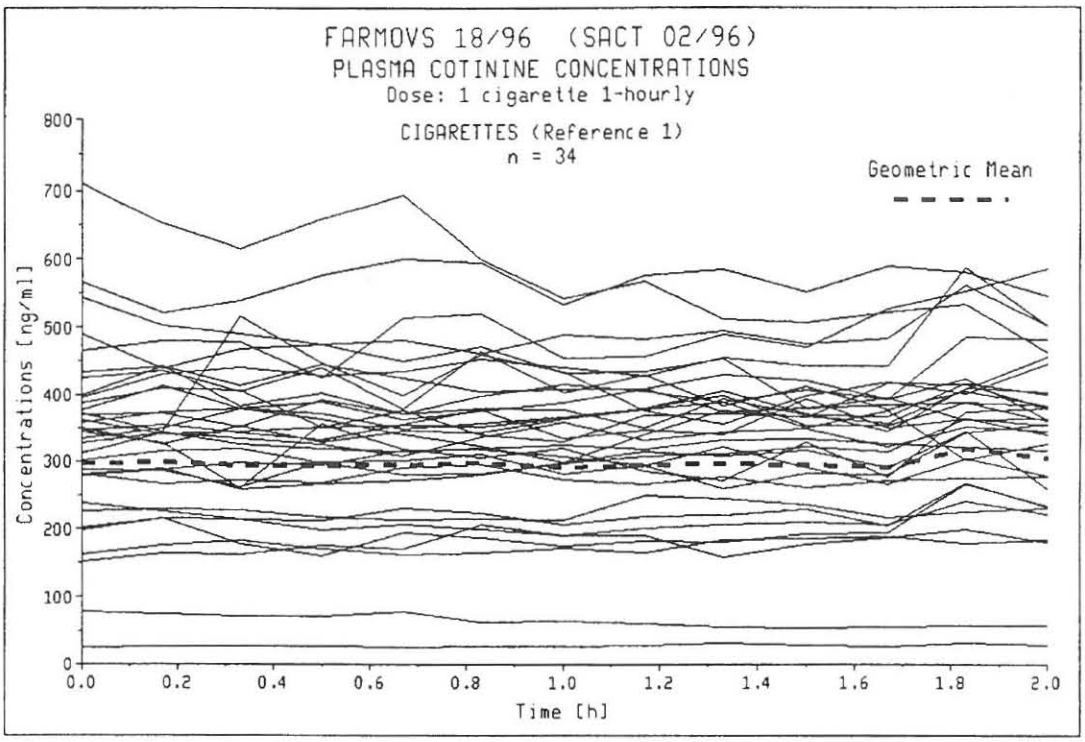
MEAN	157.193
SD	54.696
GEOM MEAN	147.423
GEOM SD	1.471
CV%	34.796
SEM	9.380
MIN	35.930
MAX	300.950
MEDIAN	153.745
n	34

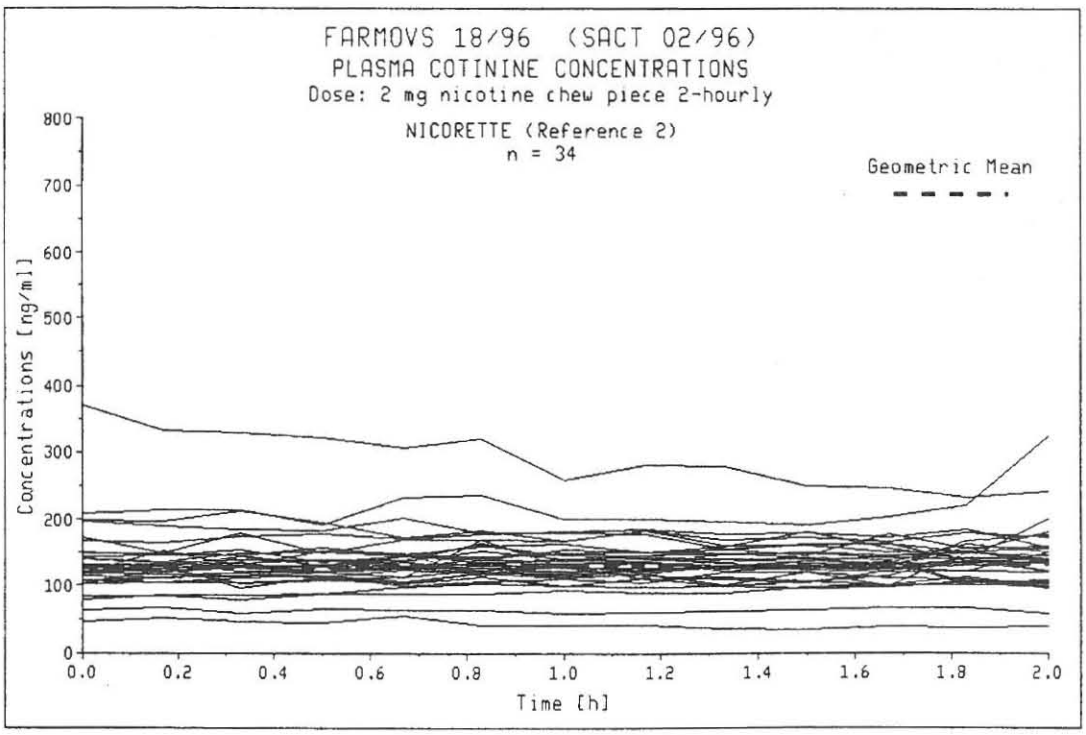
APPENDIX 13

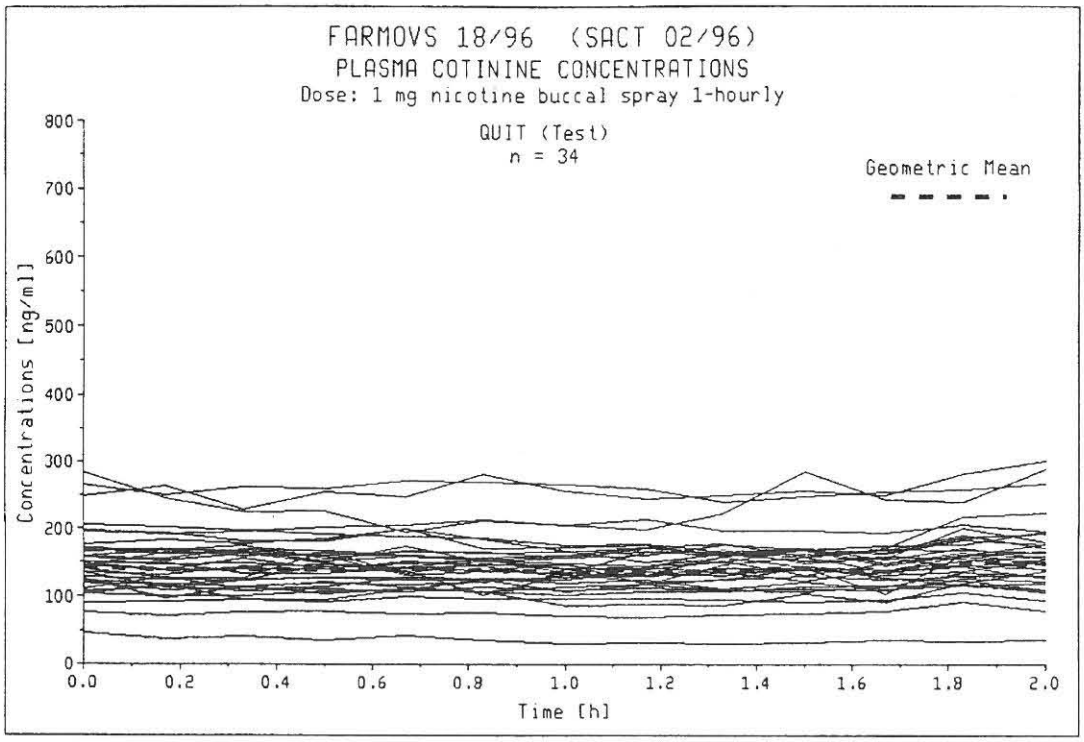
Plasma Cotinine Concentrations *vs* Time Profiles

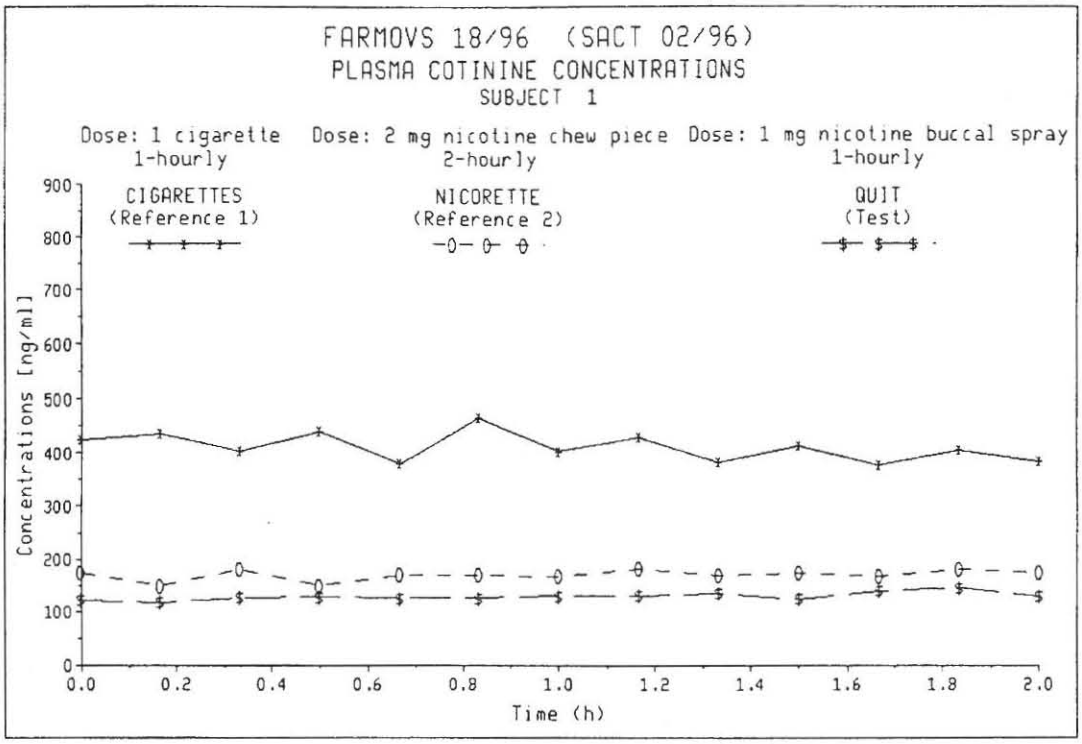


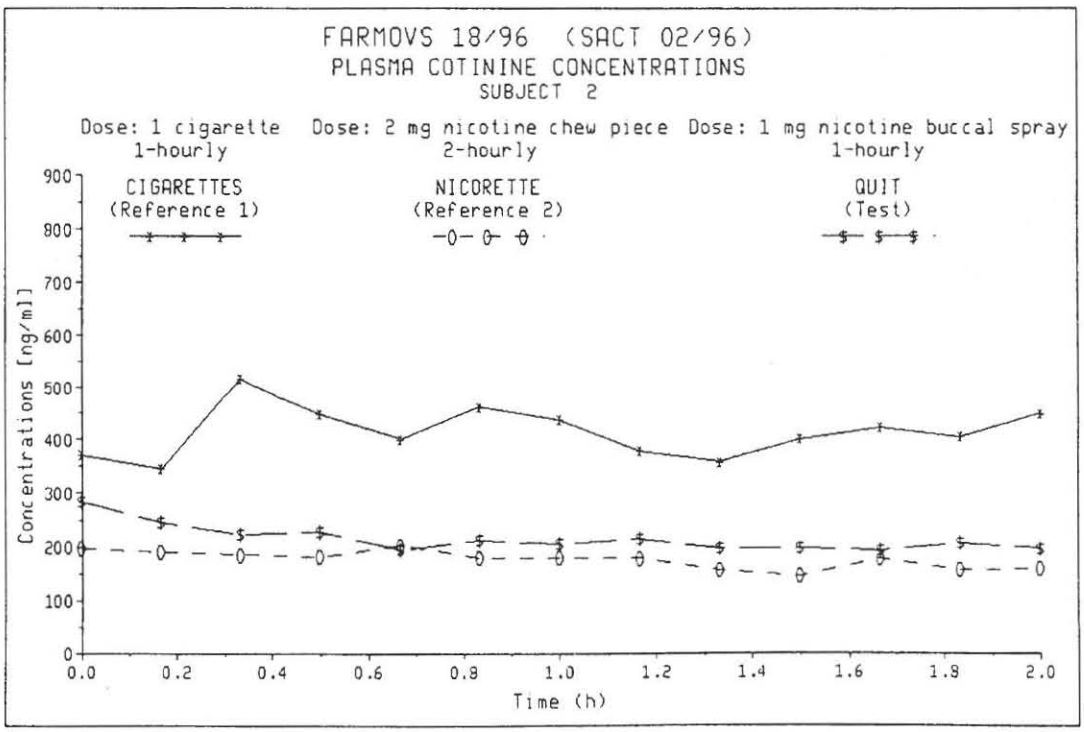


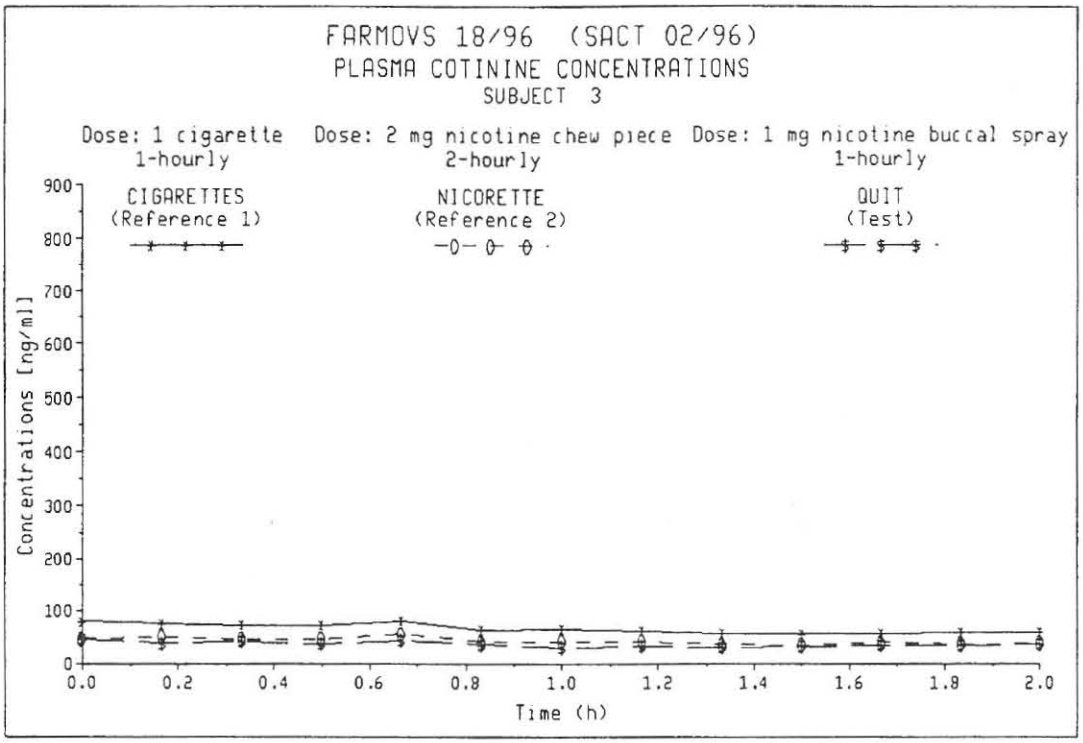


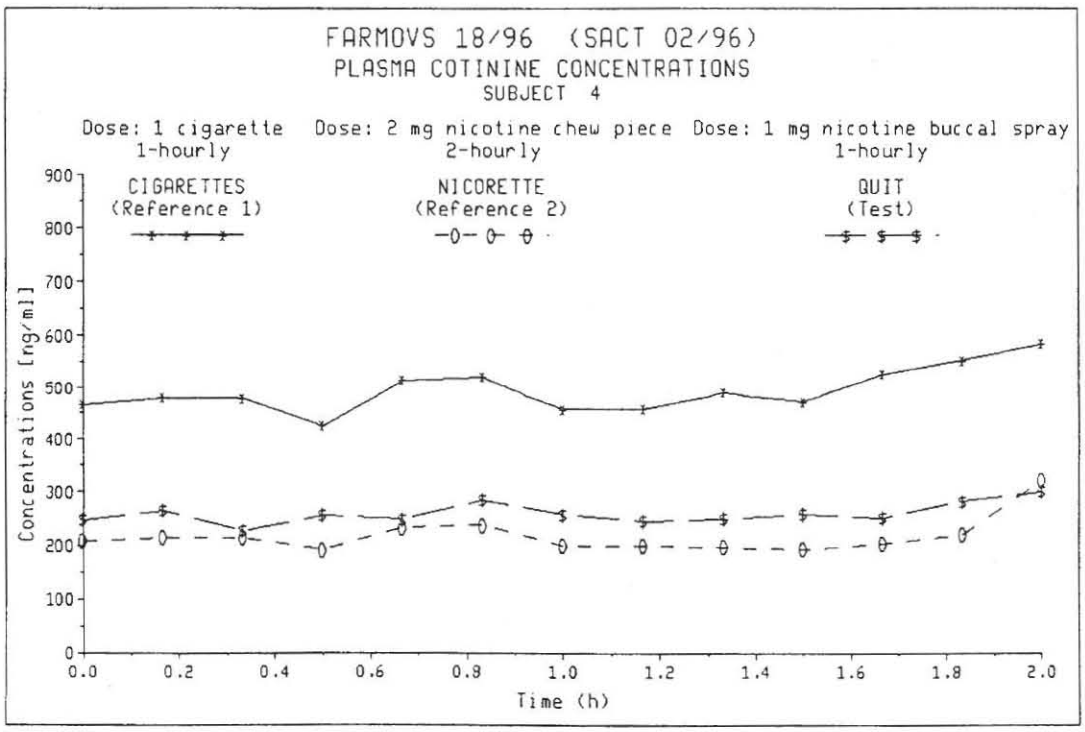


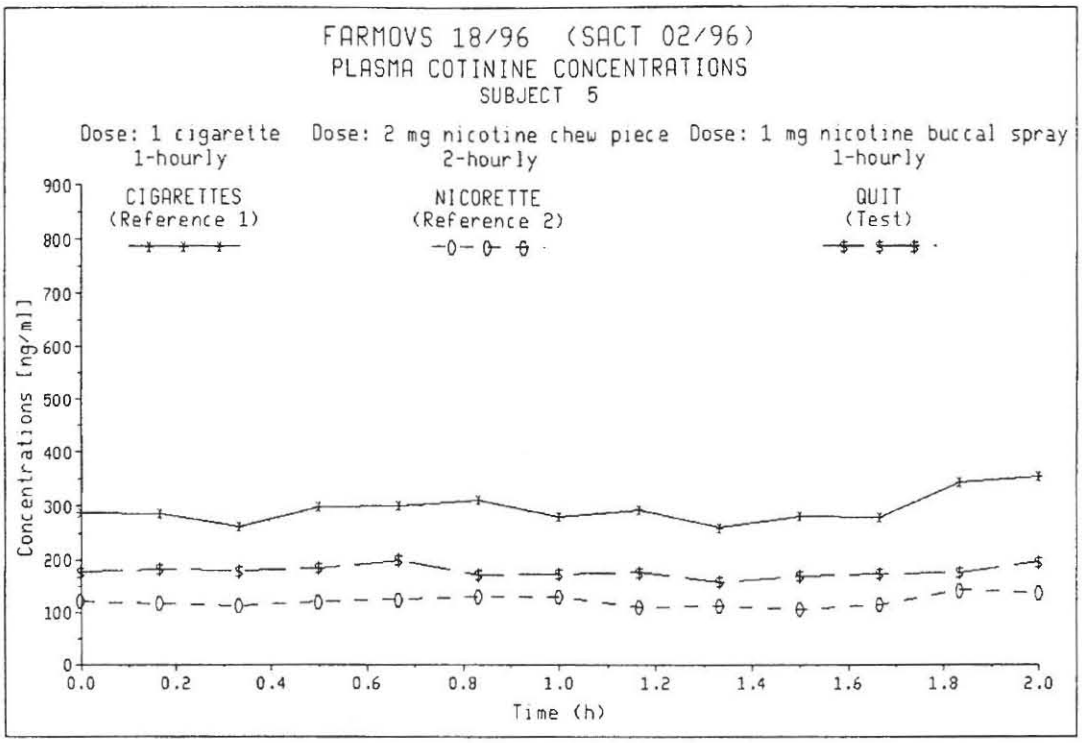


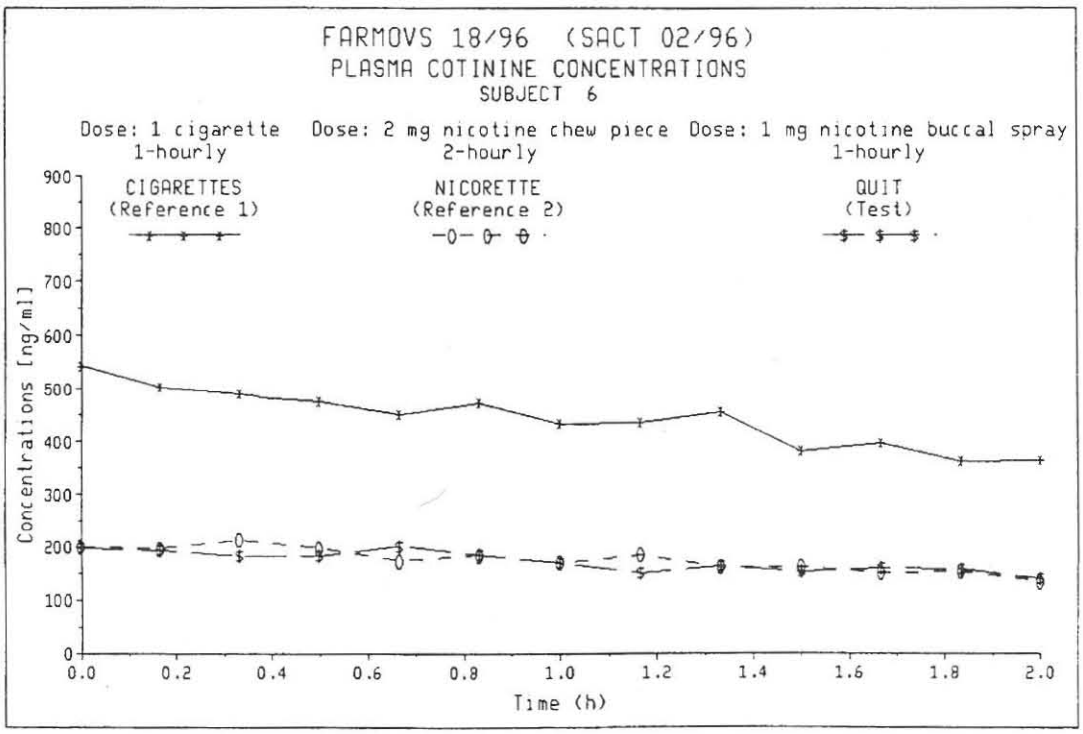


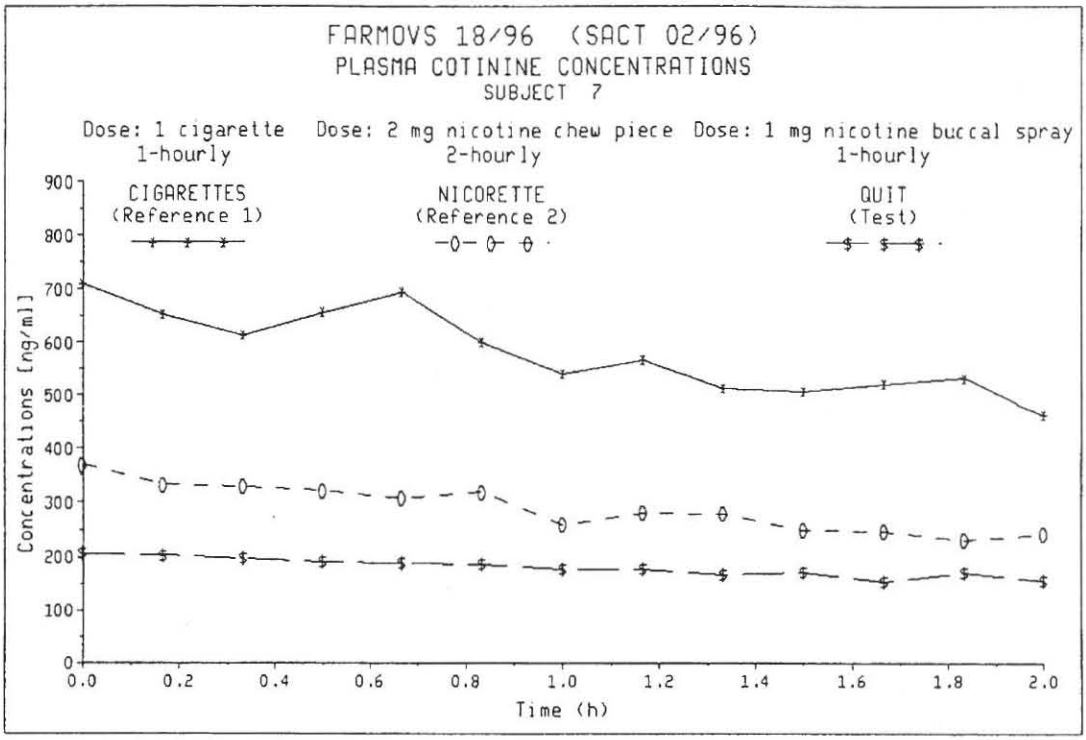


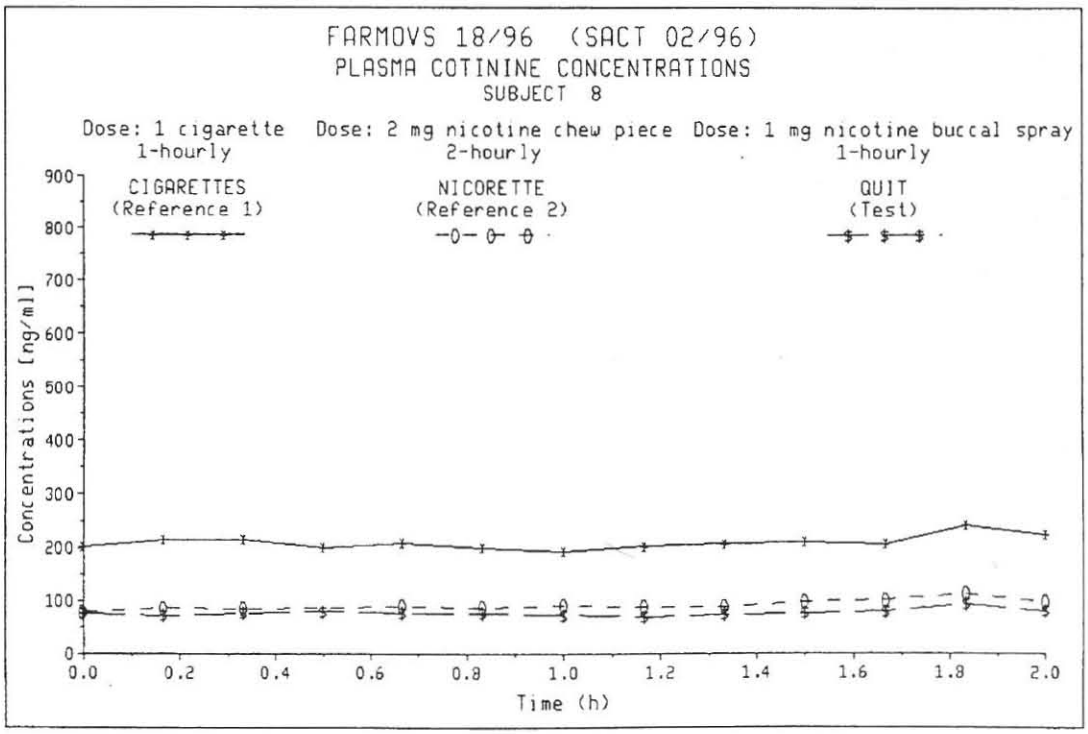


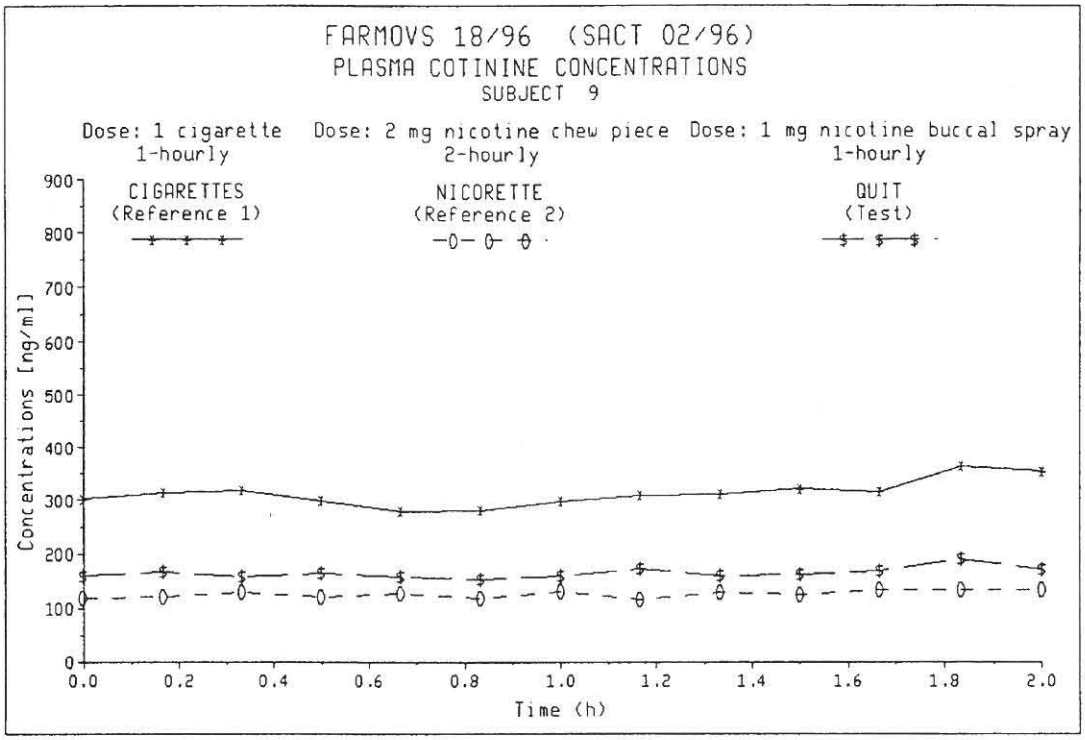


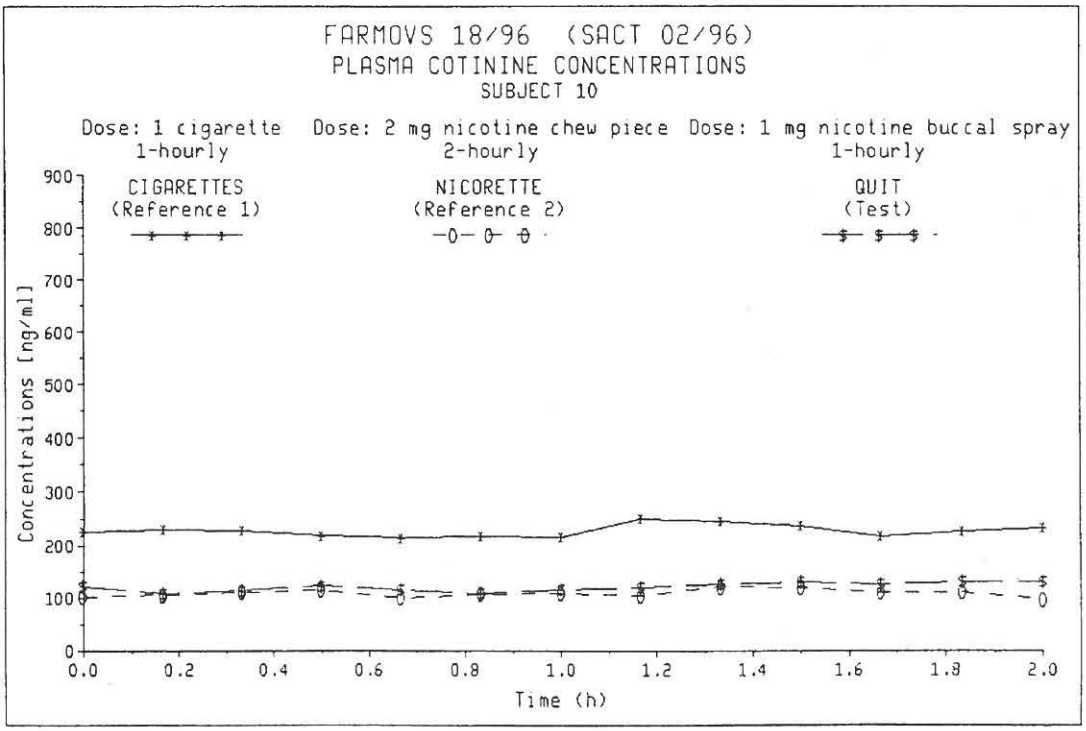


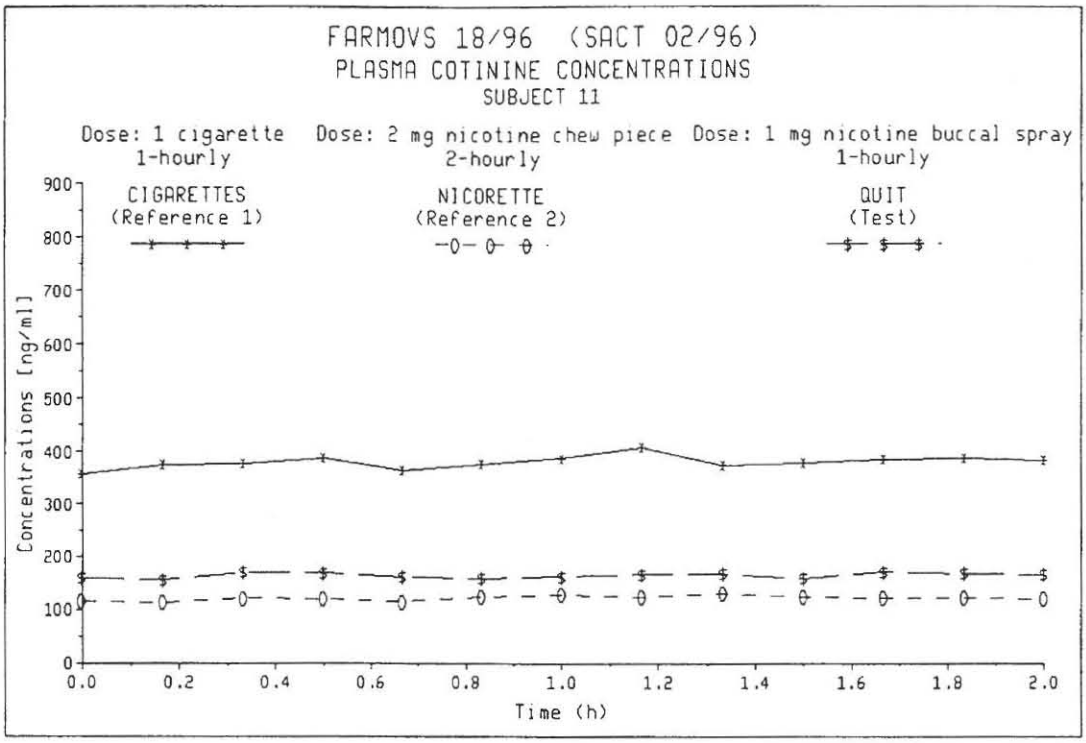


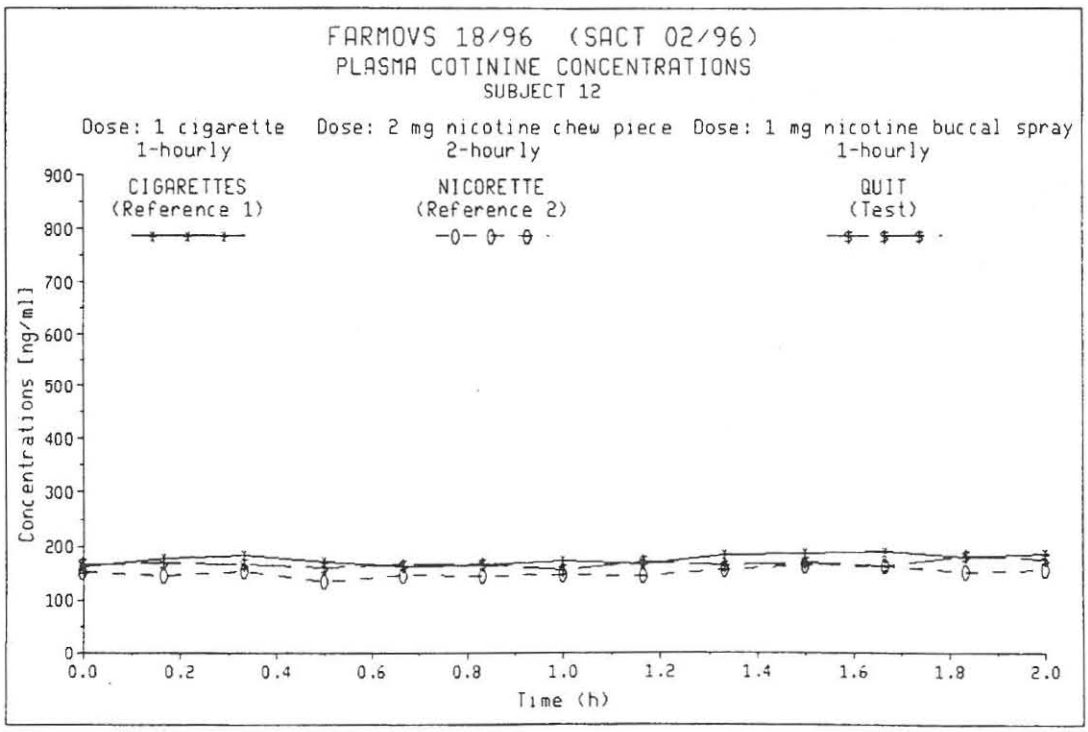


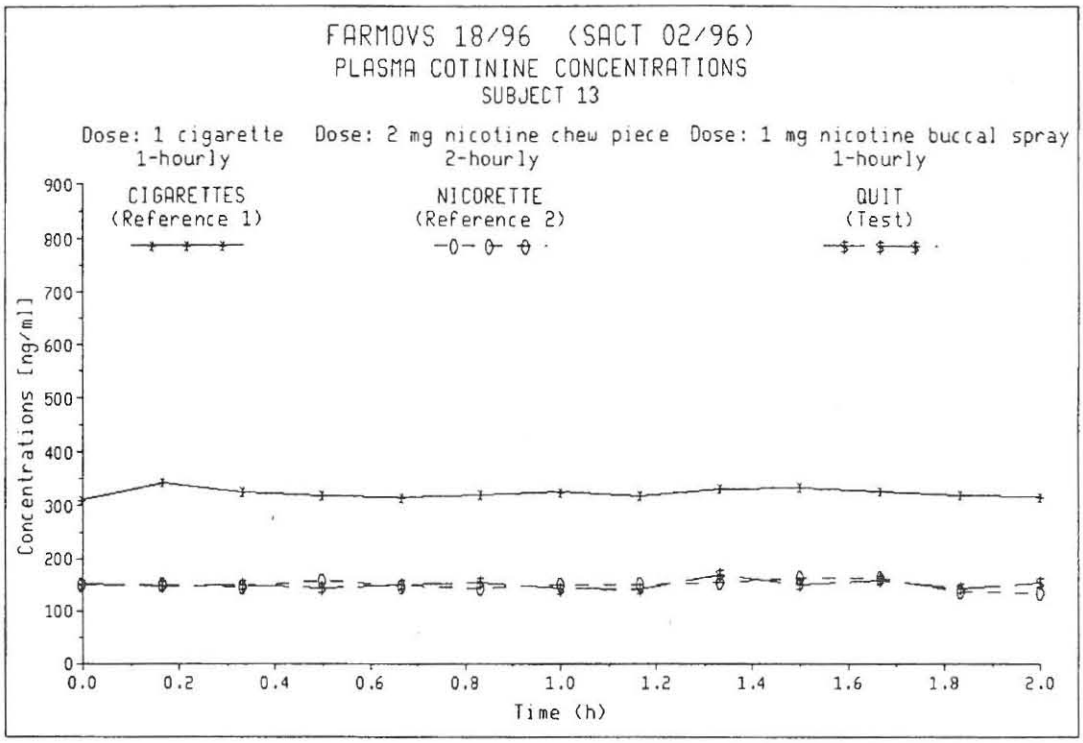


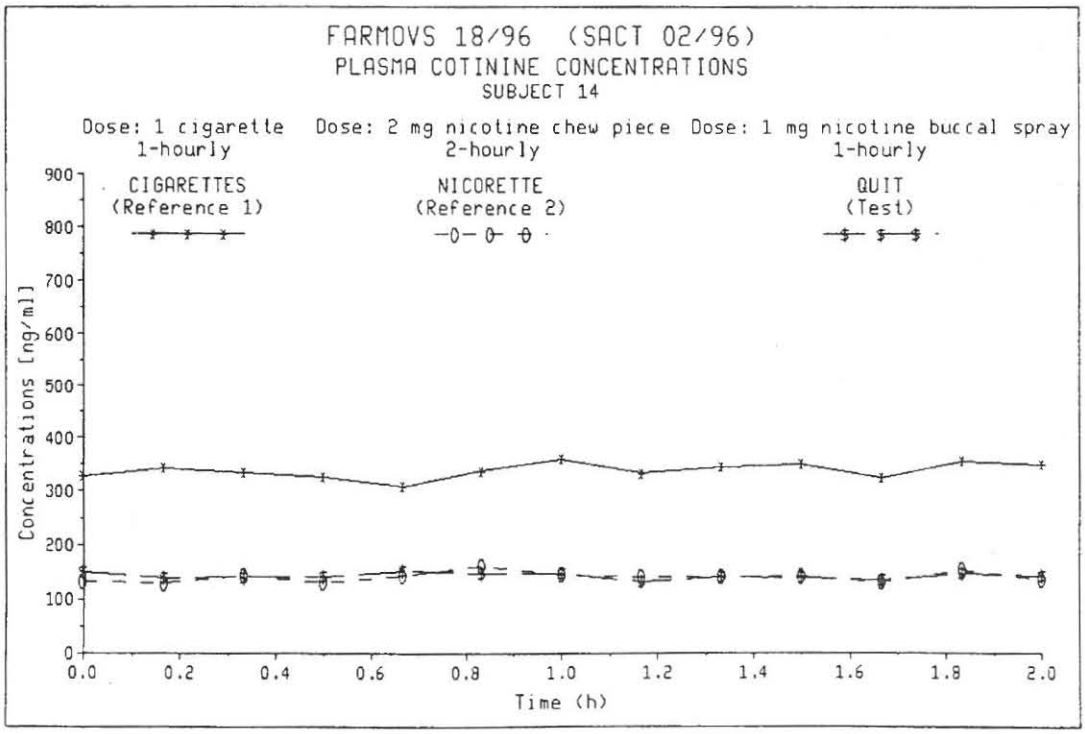


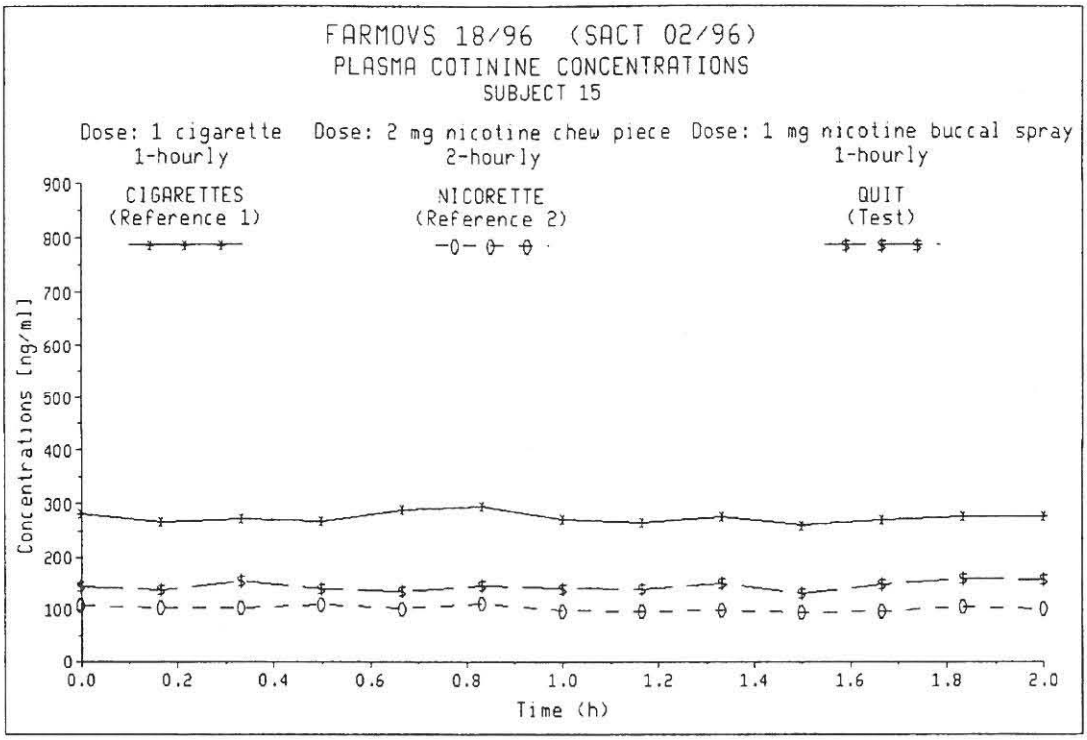


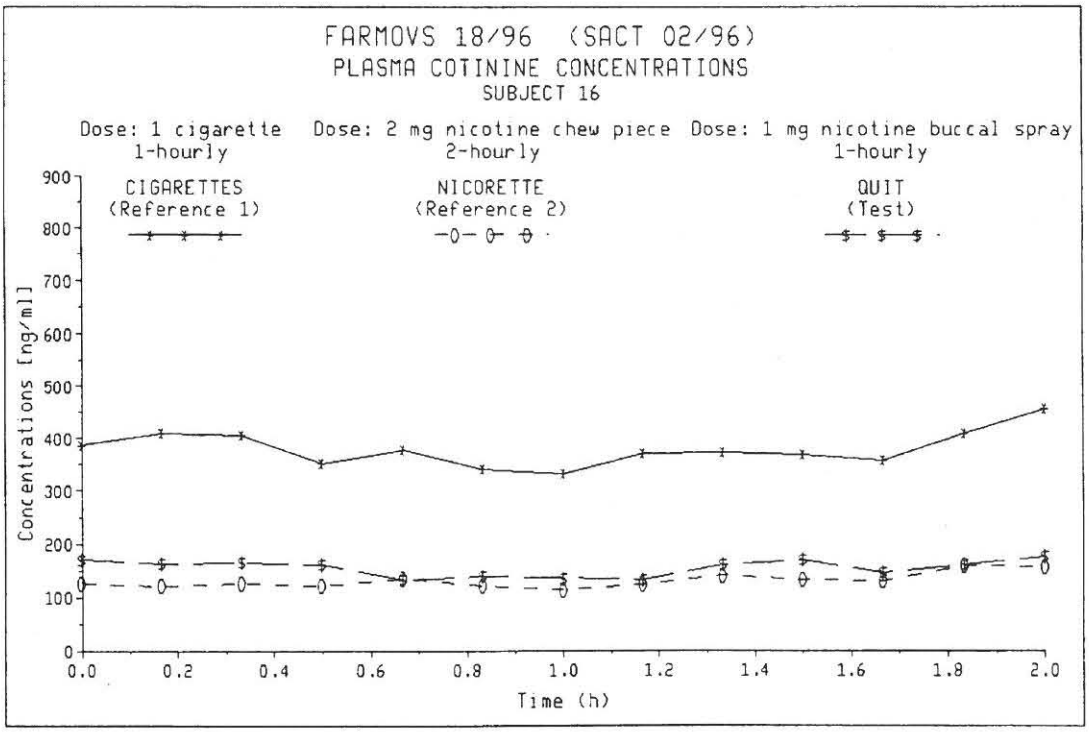


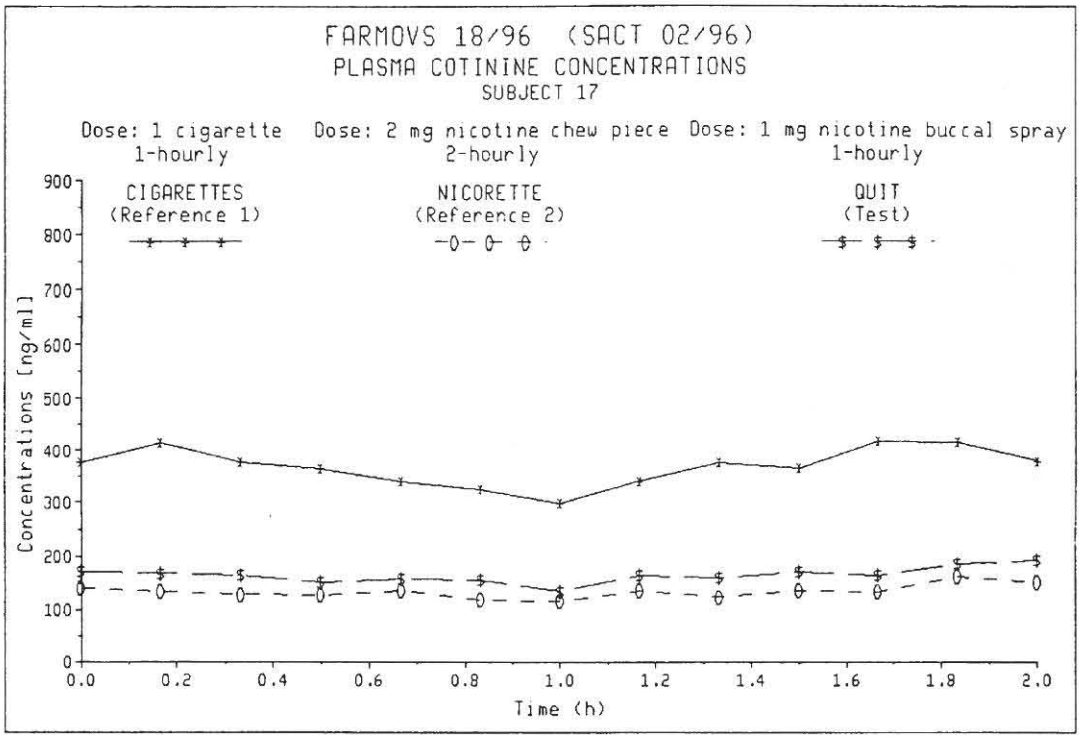


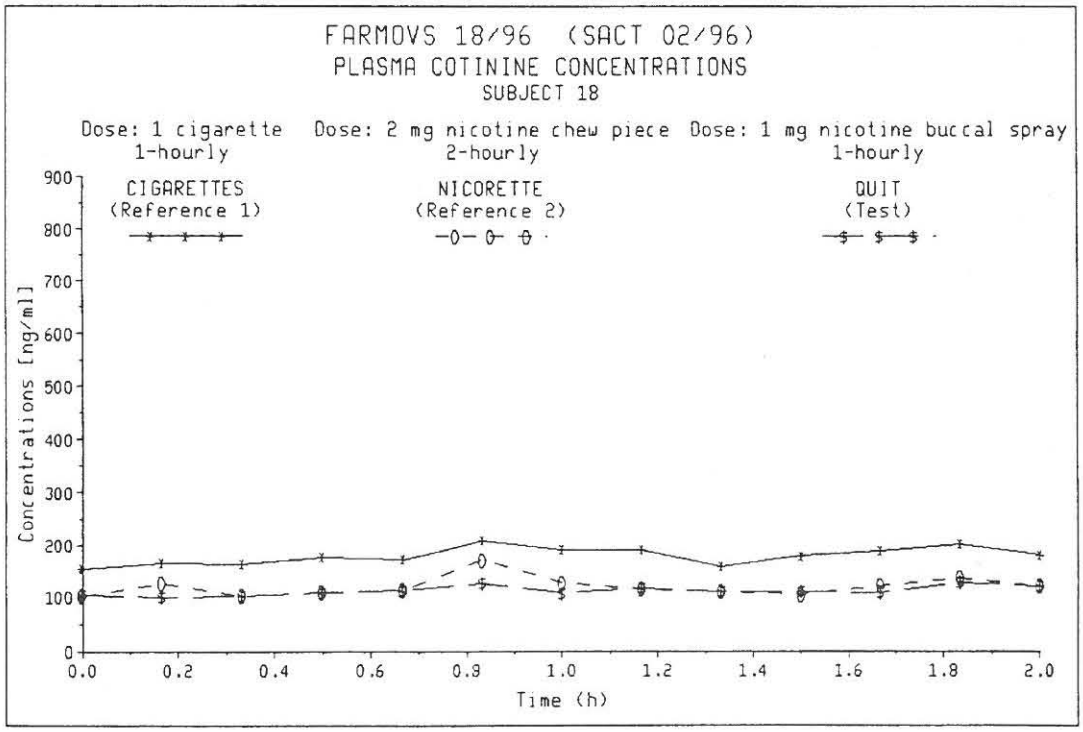


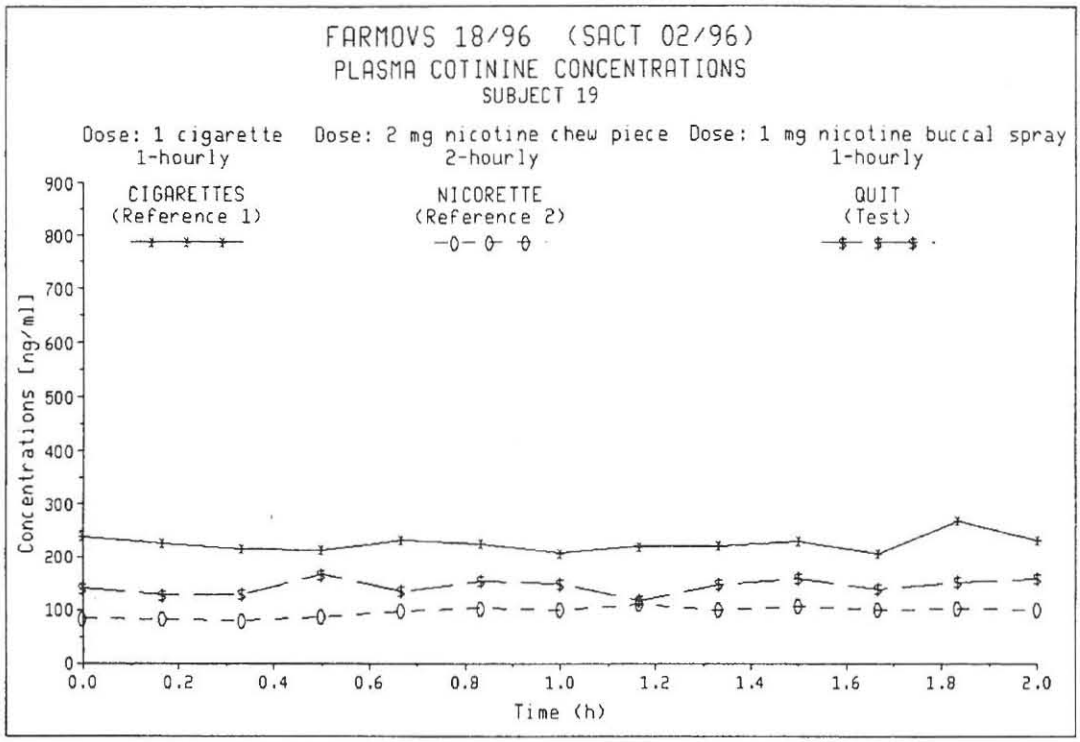


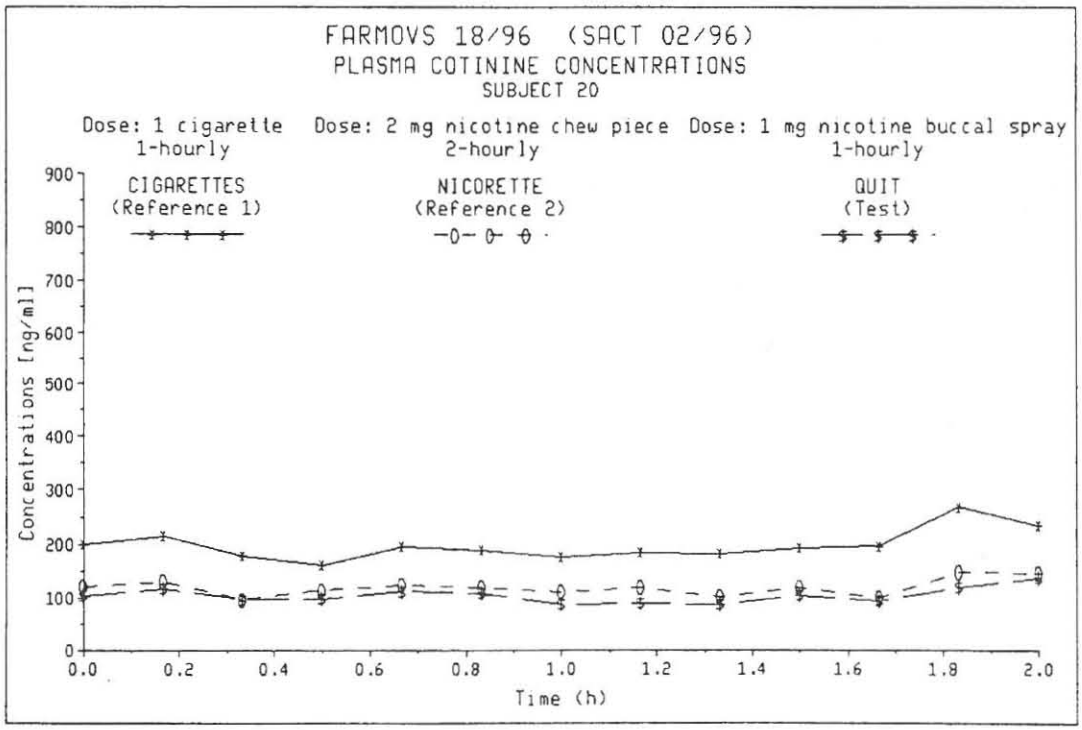


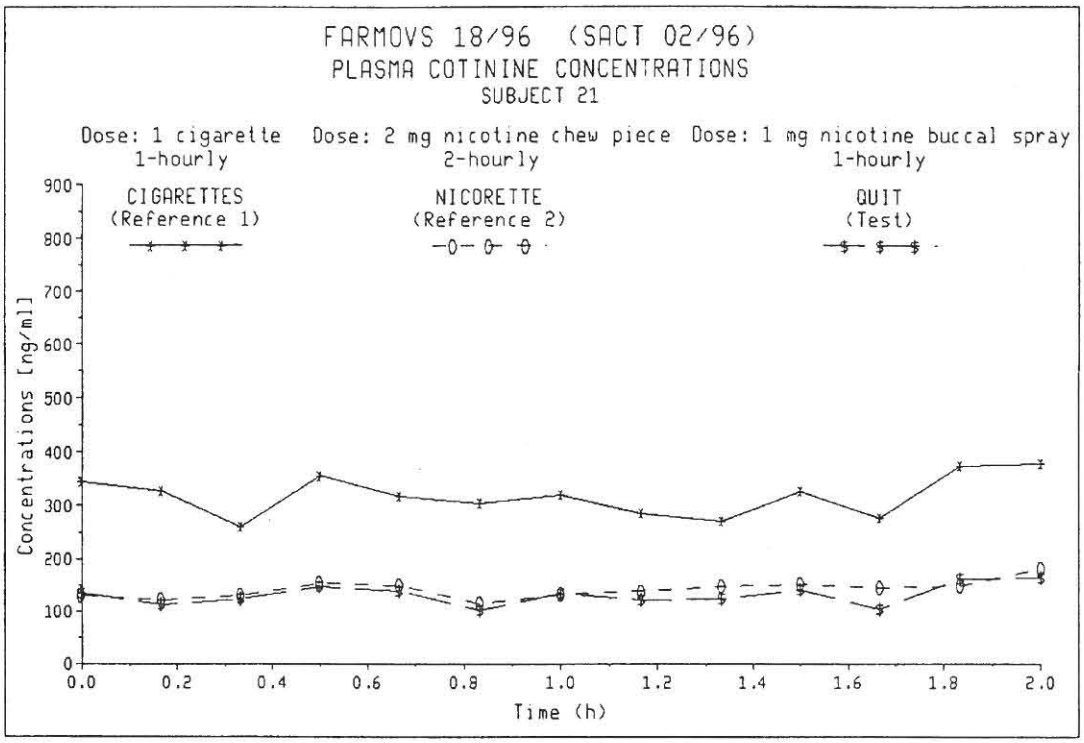


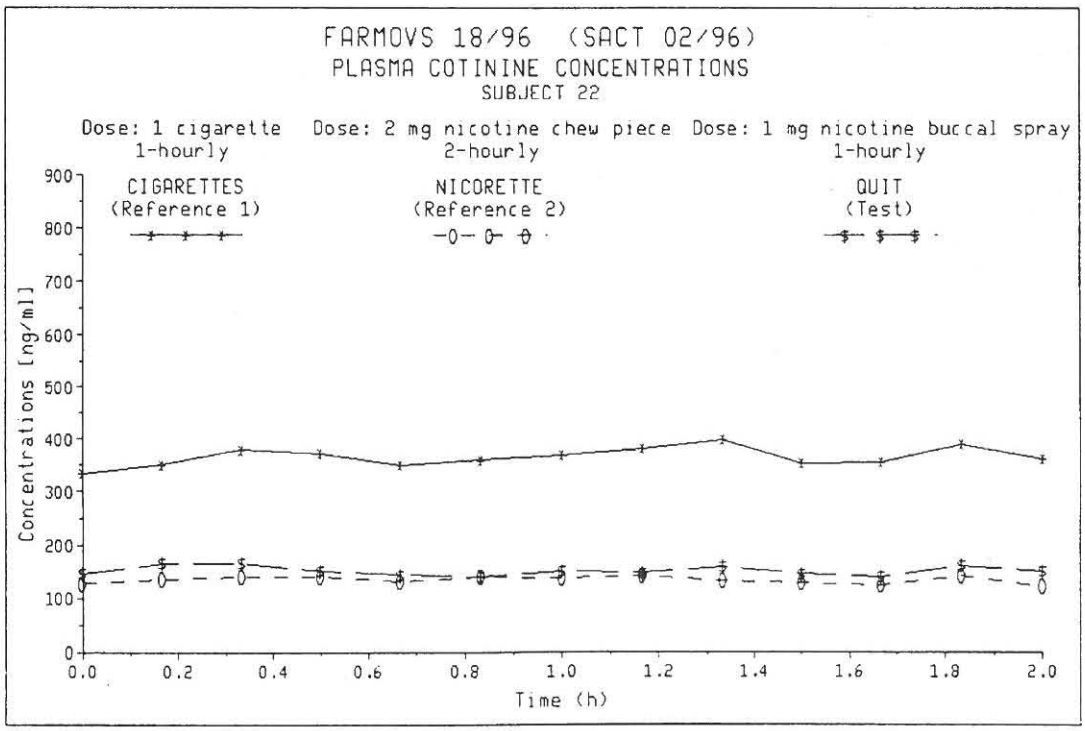


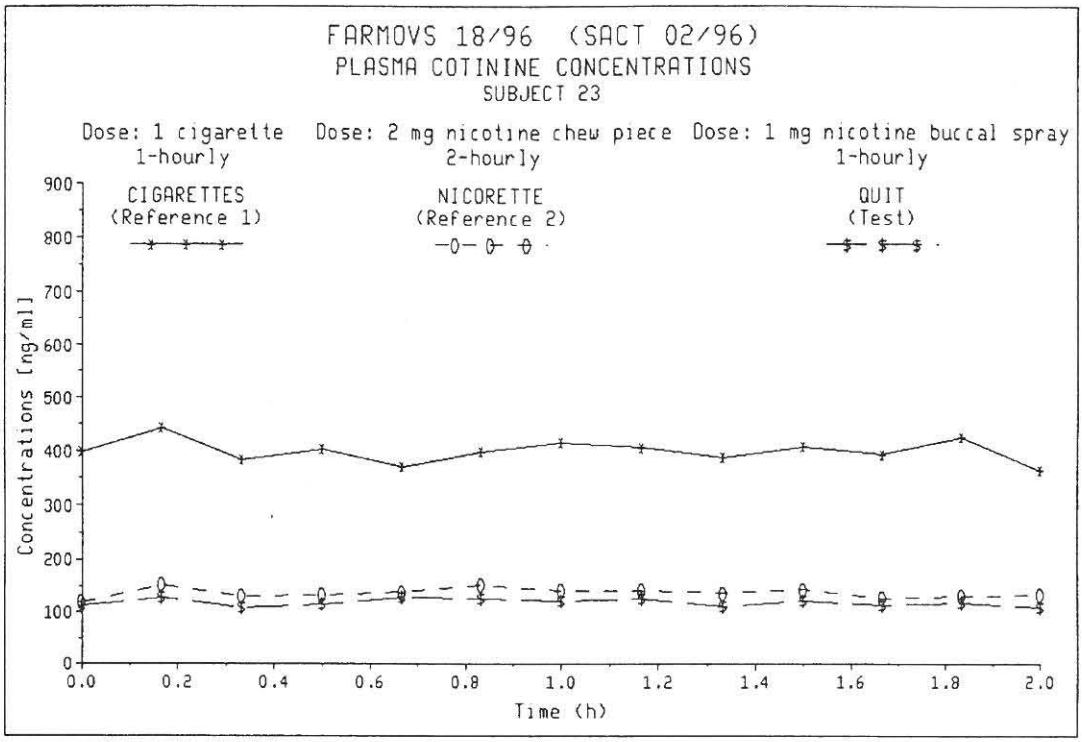


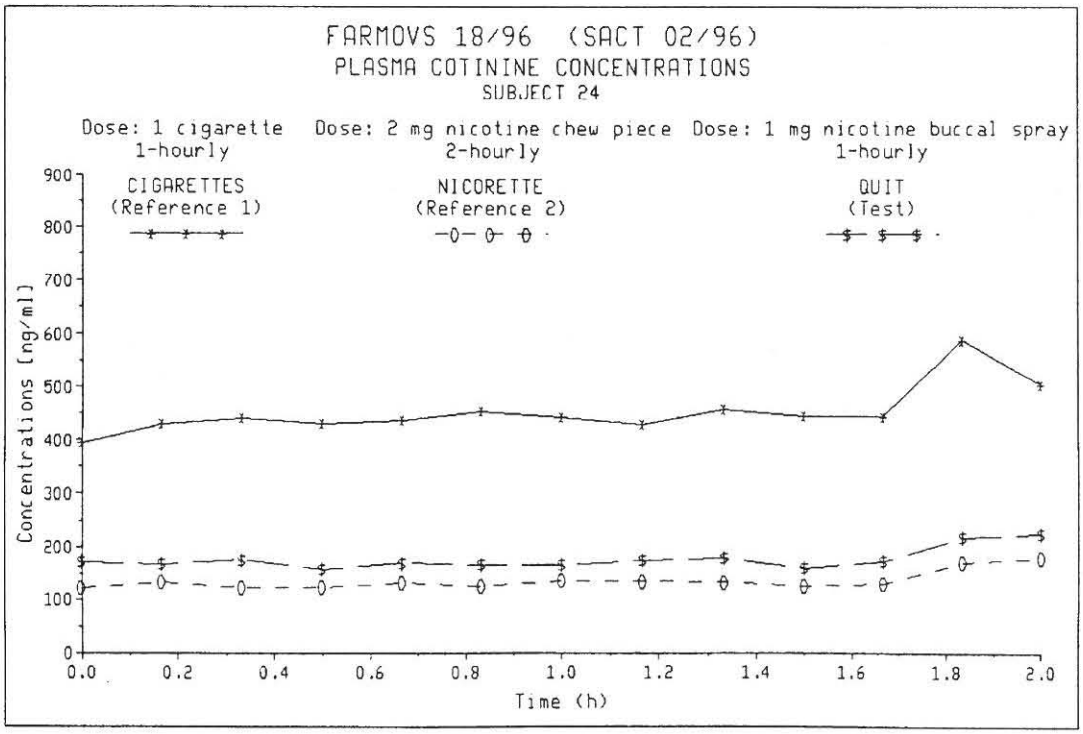


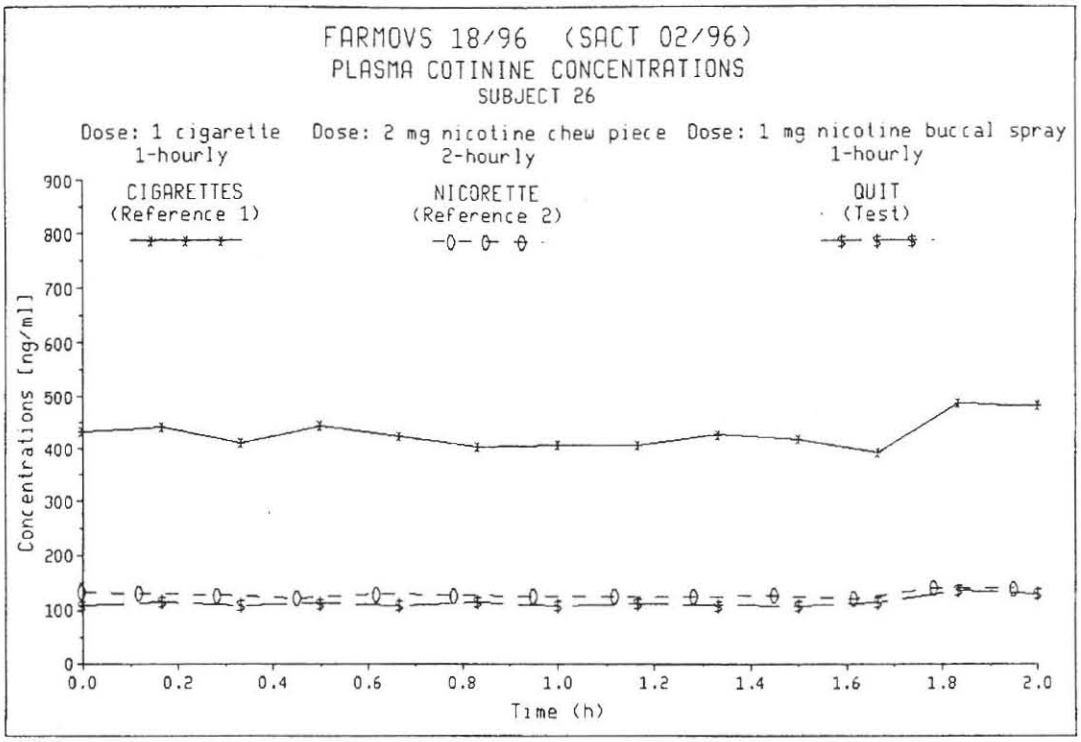


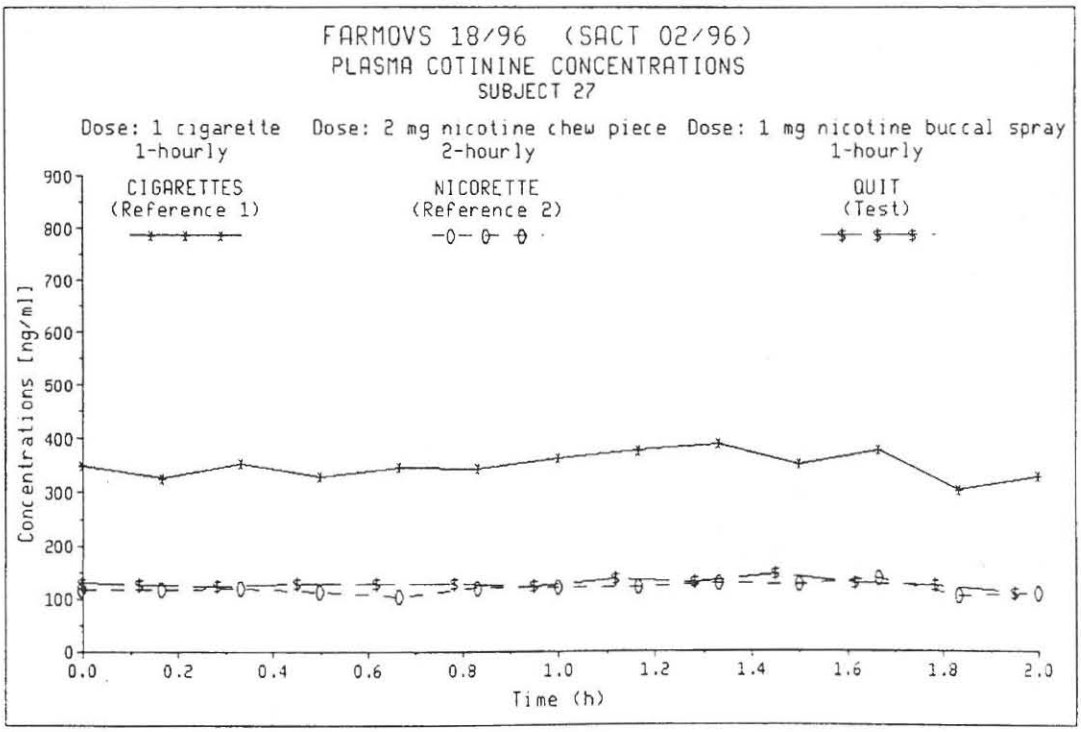


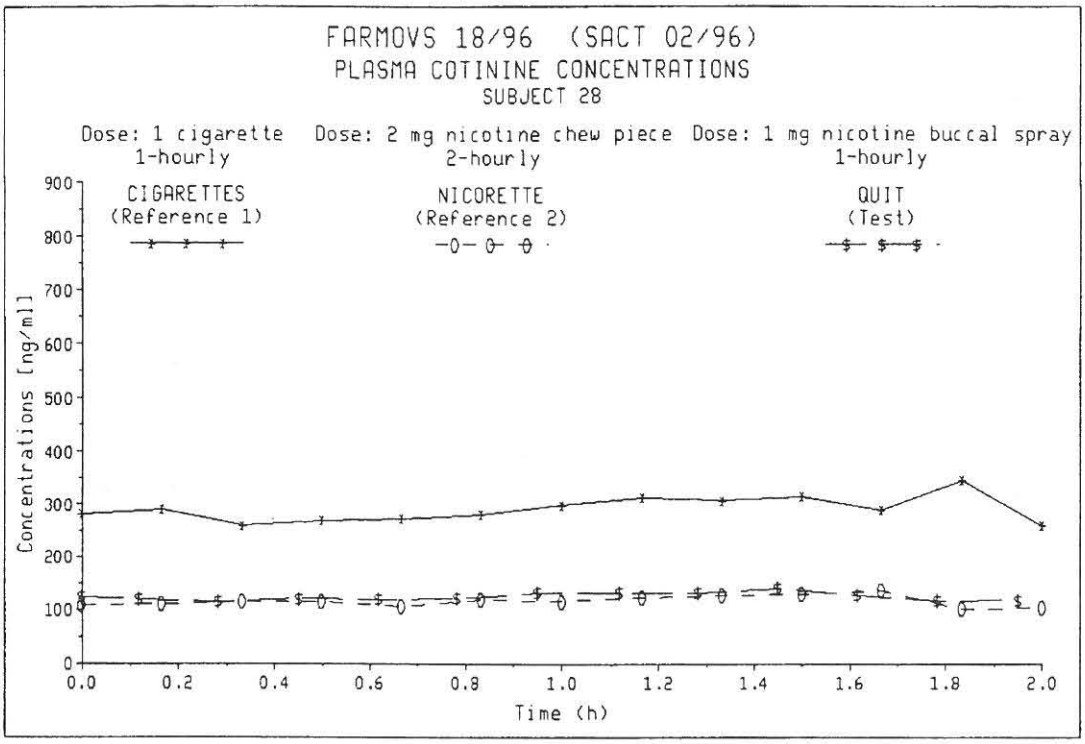


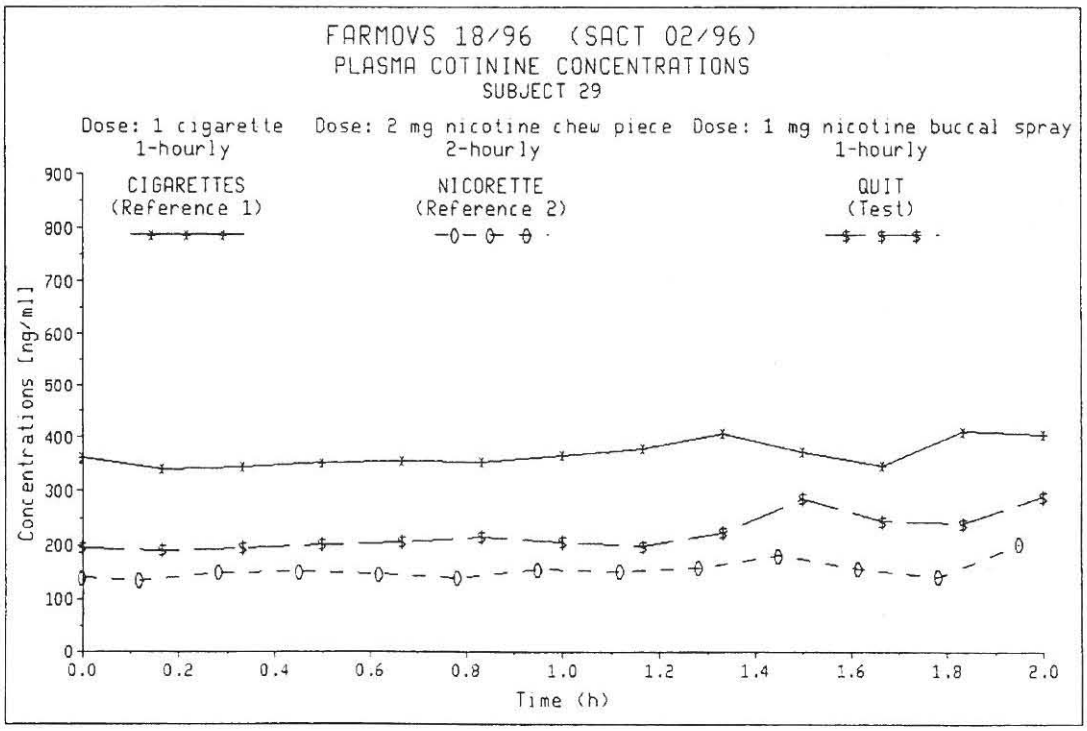


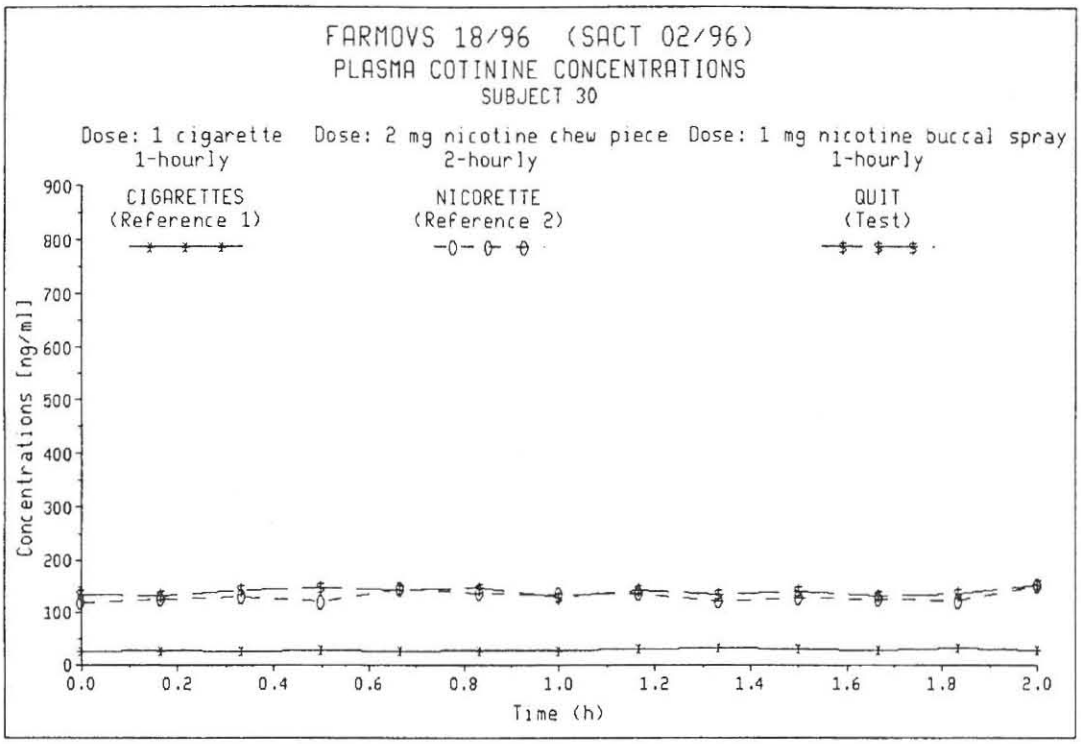


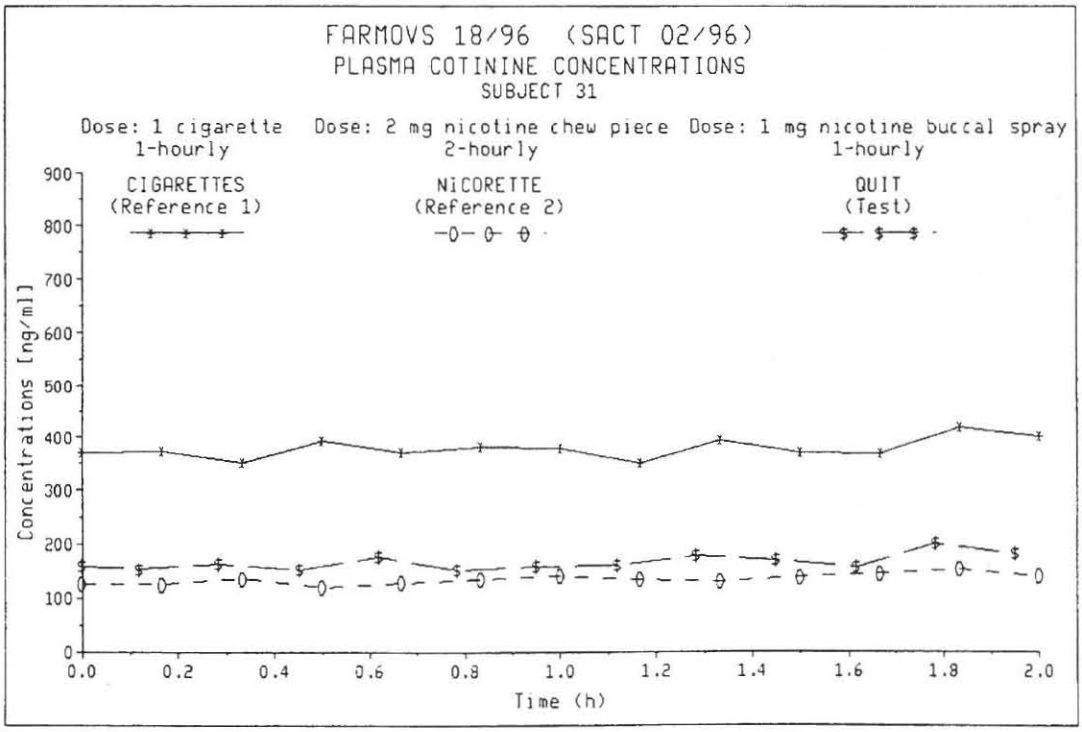


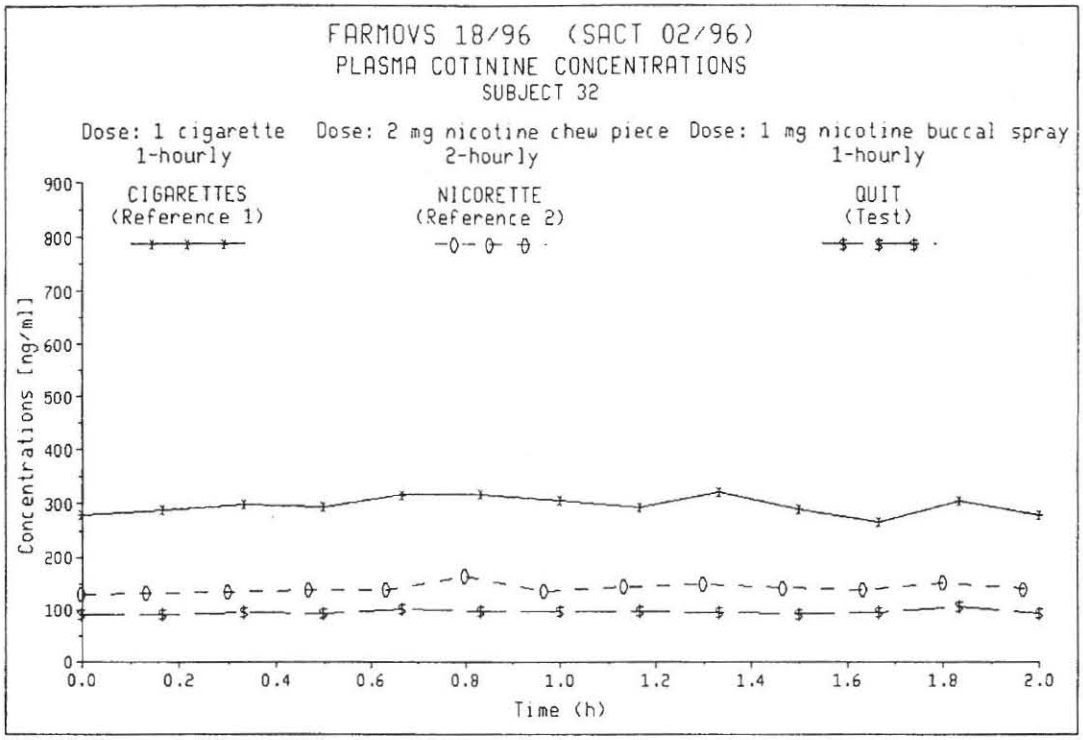


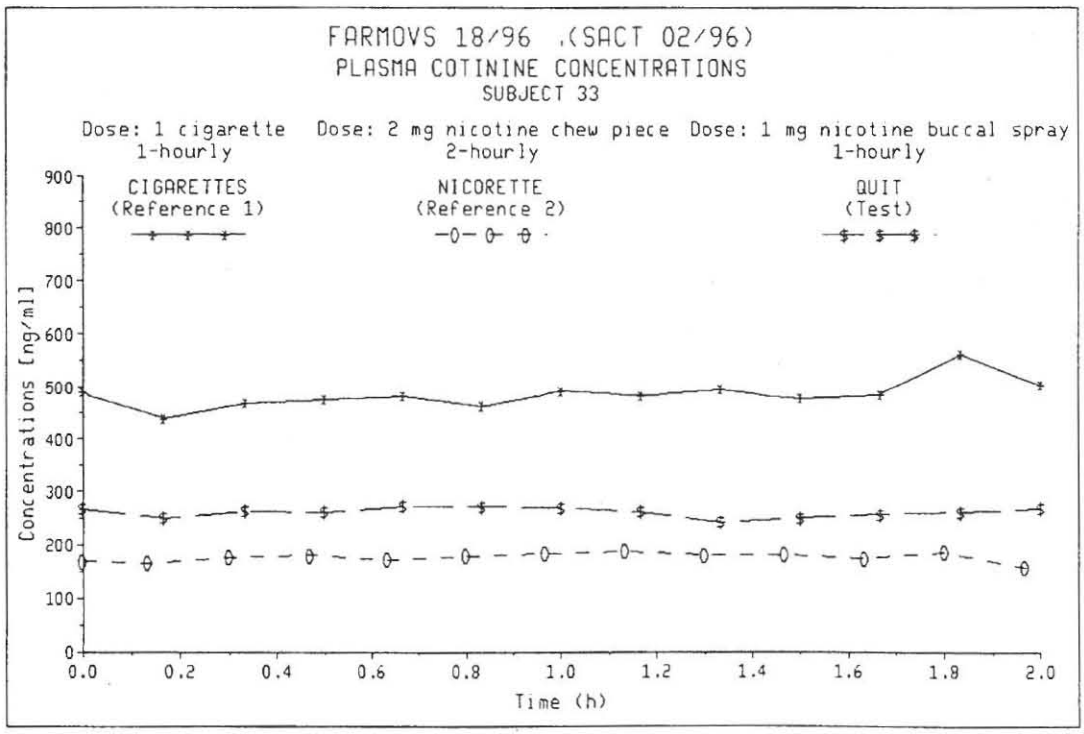


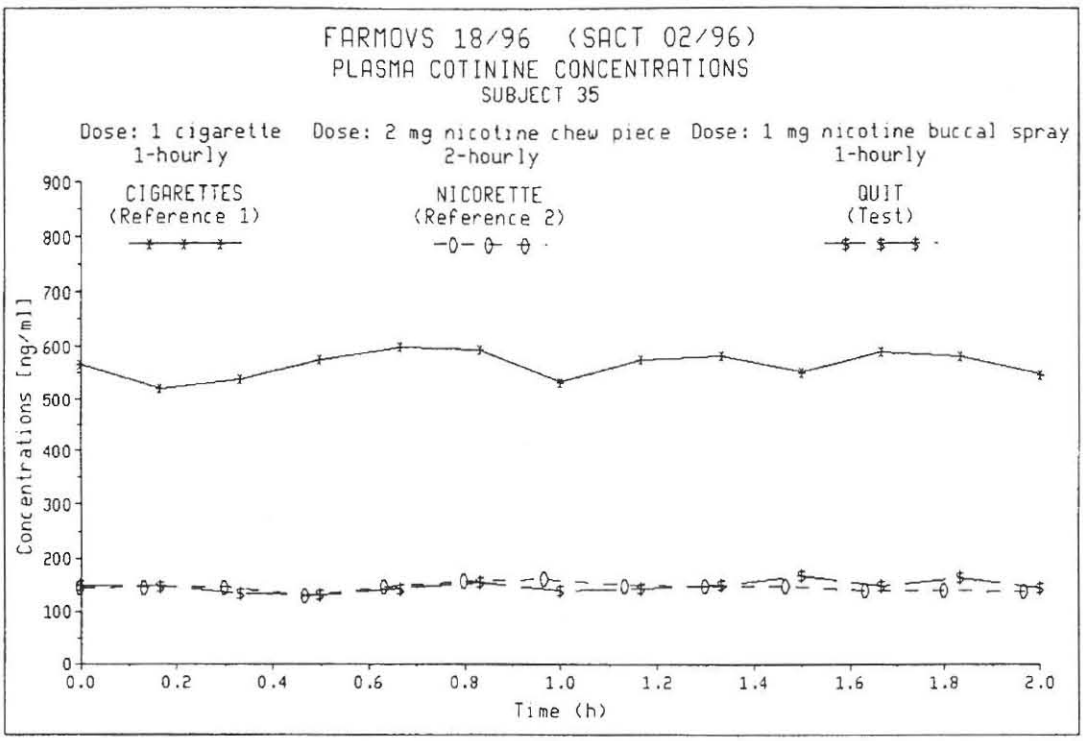


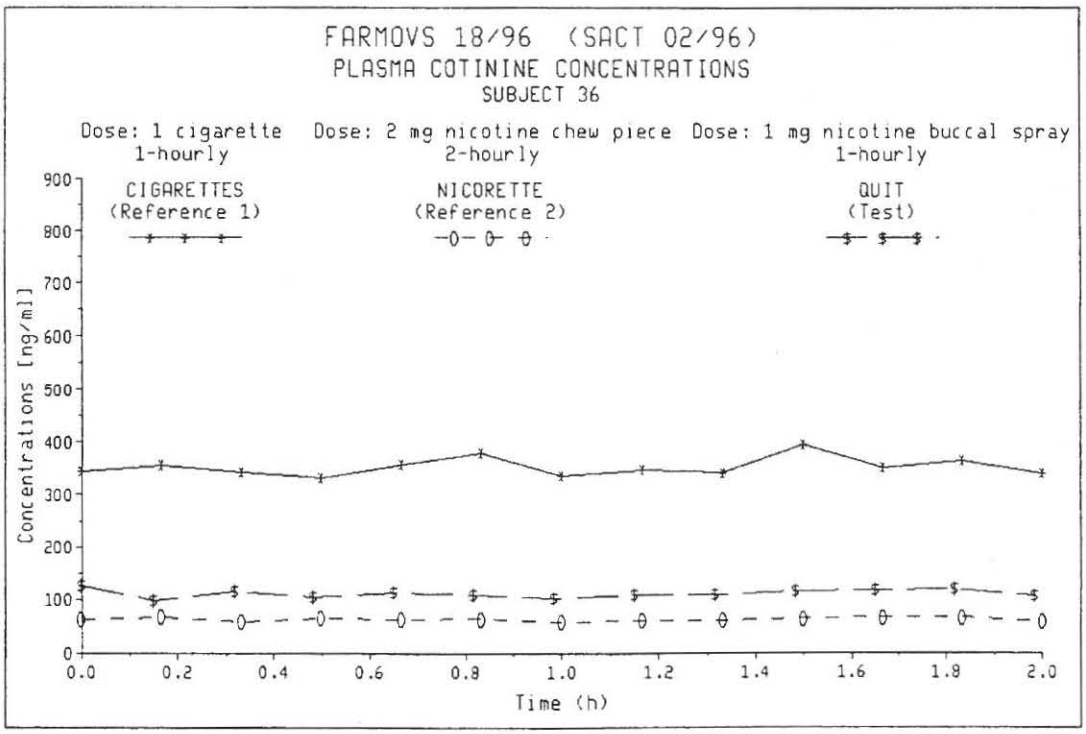












APPENDIX 14

Cotinine Pharmacokinetic Variables

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
1	466.220	430.850	466.220	378.700	378.000	378.000
2	515.590	447.620	515.590	344.990	356.550	344.990
3	79.310	65.330	79.310	62.410	55.130	55.130
4	521.100	585.850	585.850	425.720	456.220	425.720
5	312.580	355.960	355.960	262.670	260.940	260.940
6	543.190	454.800	543.190	434.220	362.420	362.420
7	709.110	567.270	709.110	542.650	464.400	464.400
8	214.850	241.060	241.060	192.020	192.020	192.020
9	318.370	364.690	364.690	280.170	298.770	280.170
10	229.990	249.860	249.860	213.430	214.030	213.430
11	389.090	409.130	409.130	358.420	375.530	358.420
12	183.770	189.470	189.470	162.800	166.470	162.800
13	341.800	333.930	341.800	310.940	317.530	310.940
14	359.200	359.200	359.200	308.340	322.850	308.340
15	296.560	277.410	296.560	266.780	261.180	261.180
16	409.210	457.810	457.810	331.400	331.400	331.400
17	413.750	418.170	418.170	299.180	299.180	299.180
18	207.290	200.670	207.290	152.990	158.740	152.990
19	237.580	269.040	269.040	206.780	204.880	204.880
20	214.910	267.710	267.710	160.170	175.770	160.170
21	356.360	379.630	379.630	260.730	271.470	260.730
22	378.150	399.630	399.630	333.230	353.830	333.230
23	441.470	424.380	441.470	371.000	364.020	364.020
24	453.680	588.480	588.480	394.970	429.050	394.970
26	444.730	487.030	487.030	405.970	394.900	394.900
27	364.700	389.690	389.690	326.130	302.400	302.400
28	300.280	346.710	346.710	259.000	260.380	259.000
29	366.750	410.660	410.660	340.730	346.380	340.730
30	27.240	32.200	32.200	25.060	26.920	25.060
31	392.320	418.240	418.240	351.780	351.880	351.780
32	317.960	322.160	322.160	279.630	266.530	266.530

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
33	490.850	562.000	562.000	439.120	477.110	439.120
35	599.130	589.250	599.130	520.630	534.360	520.630
36	379.210	393.980	393.980	331.500	335.940	331.500
MEAN	361.068	373.231	385.236	303.949	304.917	297.415
SD	140.701	135.045	146.295	114.392	112.652	108.336
GEOM MEAN	320.651	333.596	343.488	270.817	272.130	265.536
GEOM SD	1.818	1.800	1.797	1.804	1.798	1.803
CV%	38.968	36.183	37.975	37.635	36.945	36.426
SEM	24.130	23.160	25.089	19.618	19.320	18.579
MIN	27.240	32.200	32.200	25.060	26.920	25.060
MAX	709.110	589.250	709.110	542.650	534.360	520.630
MEDIAN	365.725	391.835	391.835	318.535	320.190	309.640
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
1	.833	.167	824.031	21.412	2.000
2	.333	1.000	828.232	41.196	.932
3	.667	.000	129.843	37.245	1.211
4	.833	1.000	983.357	32.568	.456
5	.833	1.000	588.073	32.316	1.253
6	.000	.333	884.857	40.859	1.440
7	.000	.167	1165.191	42.003	1.322
8	.167	.833	417.812	23.475	2.000
9	.333	.833	624.039	27.088	2.000
10	.167	.167	453.434	16.069	2.000
11	1.000	.167	763.299	13.287	2.000
12	.333	.667	352.057	15.151	2.000
13	.167	.500	648.825	9.513	2.000
14	1.000	.000	674.367	15.084	2.000
15	.833	.333	550.044	12.864	2.000
16	.167	1.000	753.074	33.572	.820
17	.167	.667	736.440	32.315	.903
18	.833	.833	359.122	30.240	1.961
19	.000	.833	448.836	28.589	2.000
20	.167	.833	391.855	54.888	.206
21	.500	1.000	631.340	37.666	1.345
22	.333	.333	733.667	18.101	2.000
23	.167	.833	802.423	19.304	2.000
24	.833	.833	906.906	42.675	.286
26	.500	.833	857.102	21.498	2.000
27	1.000	.333	700.095	24.937	2.000
28	1.000	.833	586.486	29.910	.327
29	1.000	.833	735.149	19.025	2.000
30	.500	.833	55.975	25.511	2.000
31	.500	.833	756.514	17.570	2.000
32	.833	.333	597.174	18.631	2.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
33	1.000	.833	968.926	25.364	2.000
35	.667	.667	1133.383	13.852	2.000
36	.833	.500	707.248	17.668	2.000
MEAN	.544	.622	669.093	26.219	1.602
SD	.349	.319	248.017	10.719	.605
GEOM MEAN			597.055	24.140	1.402
GEOM SD			1.801	1.520	1.875
CV%	64.105	51.176	37.068	40.884	37.755
SEM	.060	.055	42.535	1.838	.104
MIN	.000	.000	55.975	9.513	.206
MAX	1.000	1.000	1165.191	54.888	2.000
MEDIAN	.500	.833	703.672	25.151	2.000
n	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Excluding Subject 30
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
1	466.220	430.850	466.220	378.700	378.000	378.000
2	515.590	447.620	515.590	344.990	356.550	344.990
3	79.310	65.330	79.310	62.410	55.130	55.130
4	521.100	585.850	585.850	425.720	456.220	425.720
5	312.580	355.960	355.960	262.670	260.940	260.940
6	543.190	454.800	543.190	434.220	362.420	362.420
7	709.110	567.270	709.110	542.650	464.400	464.400
8	214.850	241.060	241.060	192.020	192.020	192.020
9	318.370	364.690	364.690	280.170	298.770	280.170
10	229.990	249.860	249.860	213.430	214.030	213.430
11	389.090	409.130	409.130	358.420	375.530	358.420
12	183.770	189.470	189.470	162.800	166.470	162.800
13	341.800	333.930	341.800	310.940	317.530	310.940
14	359.200	359.200	359.200	308.340	322.850	308.340
15	296.560	277.410	296.560	266.780	261.180	261.180
16	409.210	457.810	457.810	331.400	331.400	331.400
17	413.750	418.170	418.170	299.180	299.180	299.180
18	207.290	200.670	207.290	152.990	158.740	152.990
19	237.580	269.040	269.040	206.780	204.880	204.880
20	214.910	267.710	267.710	160.170	175.770	160.170
21	356.360	379.630	379.630	260.730	271.470	260.730
22	378.150	399.630	399.630	333.230	353.830	333.230
23	441.470	424.380	441.470	371.000	364.020	364.020
24	453.680	588.480	588.480	394.970	429.050	394.970
26	444.730	487.030	487.030	405.970	394.900	394.900
27	364.700	389.690	389.690	326.130	302.400	302.400
28	300.280	346.710	346.710	259.000	260.380	259.000
29	366.750	410.660	410.660	340.730	346.380	340.730
31	392.320	418.240	418.240	351.780	351.880	351.780
32	317.960	322.160	322.160	279.630	266.530	266.530

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Excluding Subject 30
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
33	490.850	562.000	562.000	439.120	477.110	439.120
35	599.130	589.250	599.130	520.630	534.360	520.630
36	379.210	393.980	393.980	331.500	335.940	331.500
MEAN	371.184	383.566	395.934	312.400	313.341	305.668
SD	129.720	122.729	134.381	104.834	102.950	98.565
GEOM MEAN	345.527	358.088	369.033	291.072	291.892	285.225
GEOM SD	1.515	1.529	1.517	1.522	1.534	1.527
CV%	34.948	31.997	33.940	33.558	32.856	32.246
SEM	22.581	21.364	23.393	18.249	17.921	17.158
MIN	79.310	65.330	79.310	62.410	55.130	55.130
MAX	709.110	589.250	709.110	542.650	534.360	520.630
MEDIAN	366.750	393.980	393.980	326.130	322.850	310.940
n	33	33	33	33	33	33

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Excluding Subject 30
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
1	.833	.167	824.031	21.412	2.000
2	.333	1.000	828.232	41.196	.932
3	.667	.000	129.843	37.245	1.211
4	.833	1.000	983.357	32.568	.456
5	.833	1.000	588.073	32.316	1.253
6	.000	.333	884.857	40.859	1.440
7	.000	.167	1165.191	42.003	1.322
8	.167	.833	417.812	23.475	2.000
9	.333	.833	624.039	27.088	2.000
10	.167	.167	453.434	16.069	2.000
11	1.000	.167	763.299	13.287	2.000
12	.333	.667	352.057	15.151	2.000
13	.167	.500	648.825	9.513	2.000
14	1.000	.000	674.367	15.084	2.000
15	.833	.333	550.044	12.864	2.000
16	.167	1.000	753.074	33.572	.820
17	.167	.667	736.440	32.315	.903
18	.833	.833	359.122	30.240	1.961
19	.000	.833	448.836	28.589	2.000
20	.167	.833	391.855	54.888	.206
21	.500	1.000	631.340	37.666	1.345
22	.333	.333	733.667	18.101	2.000
23	.167	.833	802.423	19.304	2.000
24	.833	.833	906.906	42.675	.286
26	.500	.833	857.102	21.498	2.000
27	1.000	.333	700.095	24.937	2.000
28	1.000	.833	586.486	29.910	.327
29	1.000	.833	735.149	19.025	2.000
31	.500	.833	756.514	17.570	2.000
32	.833	.333	597.174	18.631	2.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Excluding Subject 30
Dose: 1 cigarette 1-hourly
CIGARETTES (Reference 1)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
33	1.000	.833	968.926	25.364	2.000
35	.667	.667	1133.383	13.852	2.000
36	.833	.500	707.248	17.668	2.000
MEAN	.545	.616	687.673	26.240	1.590
SD	.354	.321	226.564	10.885	.610
GEOM MEAN			641.456	24.099	1.387
GEOM SD			1.522	1.530	1.887
CV%	64.924	52.149	32.947	41.481	38.369
SEM	.062	.056	39.440	1.895	.106
MIN	.000	.000	129.843	9.513	.206
MAX	1.000	1.000	1165.191	54.888	2.000
MEDIAN	.500	.833	707.248	24.937	2.000
n	33	33	33	33	33

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (h)	AUDss (ng.h/ml)	%PTF (%)	T75%Cmax (h)
1	182.350	148.130	1.167	337.634	20.270	2.000
2	202.490	145.130	.667	352.009	32.590	1.398
3	54.820	33.660	.667	84.378	50.155	.903
4	323.050	191.750	2.000	428.214	61.324	.132
5	141.800	105.460	1.833	240.832	30.179	1.477
6	211.590	133.130	.333	349.929	44.843	1.530
7	369.490	232.680	.000	577.475	47.382	1.163
8	112.000	78.880	1.833	183.200	36.157	.187
9	134.430	117.470	1.833	252.743	13.421	2.000
10	120.010	96.380	1.333	217.907	21.688	2.000
11	130.620	111.790	1.333	241.761	15.577	2.000
12	163.270	134.680	1.500	300.265	19.043	2.000
13	162.770	134.620	1.667	299.401	18.804	2.000
14	161.000	128.800	.833	281.410	22.885	2.000
15	112.900	95.880	.833	205.587	16.557	2.000
16	157.320	113.630	1.833	260.092	33.596	.907
17	163.100	117.560	1.833	267.260	34.079	.798
18	169.950	102.040	.833	240.140	56.559	.470
19	110.310	78.950	1.167	192.425	32.595	.169
20	148.020	96.320	1.833	235.132	43.975	1.148
21	181.150	114.110	2.000	281.140	47.692	.356
22	140.310	121.040	1.833	267.492	14.408	2.000
23	152.270	118.930	.167	273.500	24.380	2.000
24	176.970	120.660	2.000	265.288	42.452	.192
26	141.130	120.720	1.783	256.839	15.893	2.000
27	136.640	103.560	1.667	236.618	27.961	2.000
28	135.820	101.200	1.667	234.295	29.552	1.830
29	200.750	134.330	2.000	306.704	43.312	.766
30	151.210	119.560	2.000	259.771	24.368	2.000
31	151.230	119.850	1.833	268.277	23.394	2.000
32	164.470	130.090	.800	284.318	24.184	2.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 2 mg nicotine chew piece 2-hourly
NICORETTE (Reference 2)

SUBJECT NO.	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (h)	AUDss (ng.h/ml)	%PTF (%)	T75%Cmax (h)
33	185.360	156.580	1.133	352.049	16.350	2.000
35	162.000	130.070	.967	293.287	21.774	2.000
36	66.090	58.060	.167	124.888	12.860	2.000
MEAN	161.079	118.991	1.334	272.125	30.008	1.454
SD	58.036	34.528	.614	83.624	13.252	.696
GEOM MEAN	152.170	113.670		259.595	27.313	1.155
GEOM SD	1.413	1.387		1.384	1.556	2.320
CV%	36.029	29.017	46.026	30.730	44.162	47.858
SEM	9.953	5.922	.105	14.341	2.273	.119
MIN	54.820	33.660	.000	84.378	12.860	.132
MAX	369.490	232.680	2.000	577.475	61.324	2.000
MEDIAN	154.795	119.245	1.584	266.274	26.170	2.000
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
1	128.620	143.910	143.910	116.060	123.780	116.060
2	284.050	214.660	284.050	194.650	192.580	192.580
3	45.830	35.930	45.830	30.820	30.350	30.350
4	282.980	300.950	300.950	227.580	245.070	227.580
5	200.100	195.850	200.100	171.350	158.240	158.240
6	200.430	168.200	200.430	168.200	138.900	138.900
7	205.470	177.720	205.470	177.080	153.430	153.430
8	78.780	92.560	92.560	72.030	69.230	69.230
9	167.250	189.900	189.900	154.090	160.490	154.090
10	122.100	130.710	130.710	107.290	114.590	107.290
11	168.650	169.790	169.790	154.880	157.880	154.880
12	169.510	182.760	182.760	156.650	156.650	156.650
13	153.420	169.160	169.160	141.640	141.380	141.380
14	152.400	147.800	152.400	138.850	132.110	132.110
15	156.190	160.520	160.520	136.440	131.520	131.520
16	169.980	175.780	175.780	131.640	131.690	131.640
17	170.520	191.910	191.910	135.250	135.250	135.250
18	124.700	126.810	126.810	100.270	107.180	100.270
19	165.650	158.860	165.650	126.610	117.690	117.690
20	116.730	137.100	137.100	86.680	86.490	86.490
21	146.930	165.380	165.380	102.420	103.640	102.420
22	164.620	159.670	164.620	137.810	138.770	137.810
23	128.290	124.610	128.290	108.870	108.960	108.870
24	174.410	222.690	222.690	156.320	158.430	156.320
26	114.910	135.820	135.820	107.090	108.040	107.090
27	128.870	144.740	144.740	123.820	109.390	109.390
28	131.310	141.080	141.080	114.910	116.490	114.910
29	214.460	289.260	289.260	191.200	198.000	191.200
30	146.860	154.100	154.100	128.810	128.810	128.810
31	174.840	199.800	199.800	151.090	156.380	151.090
32	101.290	105.630	105.630	91.230	92.040	91.230

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Cmax (0-1h) (ng/ml)	Cmax (1-2h) (ng/ml)	Cmax (0-2h) (ng/ml)	Cmin (0-1h) (ng/ml)	Cmin (1-2h) (ng/ml)	Cmin (0-2h) (ng/ml)
33	271.590	267.400	271.590	249.480	240.180	240.180
35	155.670	169.220	169.220	132.550	140.460	132.550
36	124.990	118.620	124.990	98.120	102.320	98.120
MEAN	160.071	166.732	171.853	135.935	134.894	132.518
SD	51.435	52.129	55.123	42.820	42.536	41.187
GEOM MEAN	151.693	157.722	162.742	128.431	127.525	125.424
GEOM SD	1.417	1.444	1.423	1.447	1.444	1.439
CV%	32.132	31.265	32.076	31.501	31.533	31.081
SEM	8.821	8.940	9.453	7.344	7.295	7.064
MIN	45.830	35.930	45.830	30.820	30.350	30.350
MAX	284.050	300.950	300.950	249.480	245.070	240.180
MEDIAN	155.930	162.950	165.515	133.900	131.900	131.875
n	34	34	34	34	34	34

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
1	1.000	.833	256.773	21.692	2.000
2	.000	.167	425.873	42.956	.614
3	.000	1.000	71.407	43.357	1.052
4	.833	1.000	515.716	28.454	2.000
5	.667	1.000	354.818	23.595	2.000
6	.667	.000	342.572	35.922	1.885
7	.000	.167	360.217	28.894	1.661
8	.500	.833	153.125	30.472	1.157
9	.167	.833	330.516	21.669	2.000
10	.500	1.000	238.773	19.617	2.000
11	.333	.667	326.414	9.136	2.000
12	.167	.833	333.837	15.642	2.000
13	.833	.333	299.508	18.550	2.000
14	.667	.000	283.799	14.299	2.000
15	.333	.833	291.377	19.905	2.000
16	.000	1.000	304.823	28.961	1.154
17	.000	1.000	327.455	34.606	.931
18	.833	.833	223.042	23.798	2.000
19	.500	1.000	286.079	33.529	1.131
20	.167	1.000	204.563	49.481	.602
21	.500	1.000	260.039	48.424	.916
22	.167	.833	300.023	17.872	2.000
23	.167	.167	236.921	16.394	2.000
24	.333	1.000	347.986	38.145	.823
26	.167	.833	227.249	25.285	2.000
27	.000	.450	255.470	27.674	2.000
28	1.000	.450	248.574	21.056	2.000
29	.833	1.000	440.957	44.476	.706
30	.500	1.000	278.620	18.154	2.000
31	.617	.783	332.009	29.343	2.000
32	.667	.833	192.357	14.972	2.000

PROGRAM: S T A T S (V 1.3)

Division of Biometry
FARMOVS Research Centre for Clinical Pharmacology and Drug Development
University of the OFS, Bloemfontein

FARMOVS 18/96 (SACT 02/96)
COTININE PHARMACOKINETIC VARIABLES
Dose: 1 mg nicotine buccal spray 1-hourly
QUIT (Test)

SUBJECT NO.	Tmax (0-1h) (h)	Tmax (1-2h) (h)	AUDss (0-2h) (ng.h/ml)	%PTF (0-2h) (%)	T75%Cmax (0-2h) (h)
33	.667	.000	518.342	12.119	2.000
35	.833	.500	296.866	24.705	2.000
36	.000	.817	219.921	24.436	2.000
MEAN	.430	.706	296.648	26.694	1.666
SD	.328	.343	91.092	10.553	.512
GEOM MEAN			281.197	24.702	1.562
GEOM SD			1.429	1.502	1.487
CV%	76.176	48.591	30.707	39.533	30.756
SEM	.056	.059	15.622	1.810	.088
MIN	.000	.000	71.407	9.136	.602
MAX	1.000	1.000	518.342	49.481	2.000
MEDIAN	.500	.833	294.122	24.570	2.000
n	34	34	34	34	34

APPENDIX 15

Body Mass Index

APPENDIX 15

Body Mass Index

BODY WEIGHT* IN KILOGRAMS ACCORDING TO HEIGHT** AND BODY MASS INDEX						
	Age Group *(yr)*					
Height *(cm)*	**18 - 24yr**	**25 - 34yr**	**35 - 44yr**	**45 - 54yr**	**55 - 64yr**	**65+ yr**
140.0	33.5 - 51.7	35.3 - 53.9	37.1 - 56.1	38.8 - 58.2	40.6 - 60.4	42.3 - 62.5
141.0	34.0 - 52.5	35.8 - 54.7	37.6 - 56.9	39.4 - 59.1	41.2 - 61.3	42.9 - 63.5
142.0	34.5 - 53.2	36.3 - 55.4	38.1 - 57.6	40.0 - 59.8	41.8 - 62.2	43.6 - 64.3
143.0	34.9 - 54.0	36.8 - 56.2	38.6 - 58.5	40.5 - 60.7	42.4 - 63.0	44.2 - 65.2
144.0	35.5 - 54.8	37.4 - 57.0	39.2 - 59.3	41.0 - 61.6	42.9 - 63.9	44.8 - 66.1
145.0	36.0 - 55.6	37.9 - 57.9	39.8 - 60.2	41.7 - 62.5	43.6 - 64.8	45.5 - 67.1
146.0	36.5 - 56.3	38.3 - 58.6	40.3 - 60.9	42.2 - 63.4	44.1 - 65.7	46.1 - 68.0
147.0	37.0 - 57.1	38.9 - 59.5	40.9 - 61.8	42.8 - 64.2	44.7 - 66.6	46.7 - 69.0
148.0	37.4 - 57.9	39.4 - 60.3	41.4 - 62.7	43.4 - 65.0	45.4 - 67.4	47.3 - 69.8
149.0	38.0 - 58.6	40.0 - 61.2	42.0 - 63.6	44.0 - 66.0	46.0 - 68.4	48.0 - 70.8
150.0	38.5 - 59.4	40.5 - 61.9	42.6 - 64.3	44.6 - 66.9	46.6 - 69.3	48.6 - 71.8
151.0	39.0 - 60.2	41.0 - 62.8	43.1 - 65.2	45.2 - 67.8	47.3 - 70.3	49.2 - 72.8
152.0	39.5 - 60.9	41.6 - 63.6	43.7 - 66.1	45.7 - 68.6	47.8 - 71.2	49.9 - 73.7
153.0	40.1 - 61.8	42.1 - 64.5	44.3 - 67.0	46.4 - 69.5	48.4 - 72.2	50.6 - 74.7
154.0	40.6 - 62.6	42.7 - 65.2	44.8 - 67.9	47.0 - 70.4	49.1 - 73.0	51.2 - 75.7
155.0	41.1 - 63.5	43.3 - 66.1	45.5 - 68.8	47.6 - 71.3	49.8 - 74.0	51.9 - 76.7
156.0	41.6 - 64.2	43.8 - 66.9	46.0 - 69.6	48.2 - 72.3	50.4 - 74.9	52.6 - 77.7
157.0	42.1 - 65.1	44.4 - 67.8	46.6 - 70.5	48.8 - 73.3	51.0 - 75.9	53.3 - 78.7
158.0	42.7 - 65.9	44.9 - 68.6	47.2 - 71.4	49.4 - 74.1	51.7 - 76.9	53.9 - 79.6
159.0	43.2 - 66.8	45.5 - 69.5	47.8 - 72.4	50.0 - 75.1	52.4 - 77.9	54.6 - 80.6
160.0	43.7 - 67.5	46.1 - 70.4	48.4 - 73.3	50.7 - 76.0	53.0 - 78.9	55.3 - 81.6
161.0	44.4 - 68.4	46.7 - 71.3	49.1 - 74.1	51.3 - 77.0	53.7 - 79.9	56.0 - 82.7
162.0	44.9 - 69.3	47.3 - 72.2	49.6 - 75.0	51.9 - 78.0	54.4 - 80.8	56.7 - 83.7
163.0	45.5 - 70.2	47.9 - 73.0	50.2 - 76.0	52.7 - 79.0	55.1 - 81.8	57.4 - 84.8
164.0	46.0 - 71.1	48.4 - 73.9	50.9 - 76.9	53.3 - 79.9	55.7 - 82.8	58.1 - 85.8
165.0	46.6 - 71.8	49.1 - 74.9	51.5 - 77.9	53.9 - 80.8	56.4 - 83.9	58.8 - 86.9
166.0	47.2 - 72.7	49.6 - 75.8	52.1 - 78.8	54.5 - 81.8	57.1 - 84.9	59.5 - 87.9
167.0	47.7 - 73.6	50.2 - 76.8	52.7 - 79.8	55.3 - 82.8	57.8 - 85.9	60.2 - 88.9
168.0	48.2 - 74.5	50.8 - 77.7	53.4 - 80.7	55.9 - 83.8	58.4 - 86.9	60.9 - 90.0
169.0	48.9 - 75.5	51.4 - 78.5	54.0 - 81.7	56.6 - 84.8	59.1 - 88.0	61.7 - 91.1
170.0	49.4 - 76.3	52.0 - 79.5	54.6 - 82.6	57.2 - 85.8	59.9 - 89.0	62.5 - 92.2
171.0	50.0 - 77.2	52.7 - 80.5	55.3 - 83.6	57.9 - 86.9	60.6 - 90.0	63.2 - 93.3
172.0	50.6 - 78.1	53.3 - 81.4	55.9 - 84.6	58.6 - 87.9	61.2 - 91.1	63.9 - 94.4
173.0	51.2 - 79.0	53.9 - 82.3	56.6 - 85.6	59.2 - 88.9	61.9 - 92.2	64.6 - 95.5
174.0	51.8 - 80.0	54.5 - 83.3	57.2 - 86.6	59.9 - 89.9	62.6 - 93.3	65.4 - 96.6
175.0	52.4 - 80.8	55.2 - 84.3	57.9 - 87.6	60.6 - 91.0	63.4 - 94.4	66.2 - 97.7
176.0	53.0 - 81.7	55.8 - 85.1	58.5 - 88.6	61.3 - 92.0	64.1 - 95.4	66.9 - 98.8
177.0	53.6 - 82.7	56.4 - 86.1	59.2 - 89.7	62.0 - 93.1	64.9 - 96.5	67.7 - 99.9
178.0	54.2 - 83.6	57.1 - 87.1	59.9 - 90.6	62.7 - 94.1	65.6 - 97.6	68.4 - 101.1
179.0	54.8 - 84.6	57.7 - 88.1	60.6 - 91.6	63.5 - 95.2	66.3 - 98.7	69.2 - 102.3

APPENDIX 15 *(continued)*

Body Mass Index *(continued)*

BODY WEIGHT* IN KILOGRAMS ACCORDING TO HEIGHT** AND BODY MASS INDEX						
	Age Group *(yr)*					
Height *(cm)*	**18 - 24yr**	**25 - 34yr**	**35 - 44yr**	**45 - 54yr**	**55 - 64yr**	**65+ yr**
180.0	55.4 - 85.6	58.3 - 89.1	61.2 - 92.6	64.2 - 96.3	67.1 - 99.8	70.0 - 103.4
181.0	56.1 - 86.6	59.0 - 90.1	61.9 - 93.7	64.9 - 97.3	67.8 - 100.9	70.8 - 104.6
182.0	56.6 - 87.5	59.6 - 91.1	62.6 - 94.7	65.6 - 98.3	68.6 - 102.0	71.6 - 105.7
183.0	57.2 - 88.4	60.3 - 92.1	63.3 - 95.8	66.3 - 99.4	69.4 - 103.2	72.4 - 106.9
184.0	57.9 - 89.4	60.9 - 93.1	64.0 - 96.8	67.1 - 100.5	70.1 - 104.3	73.2 - 108.0
185.0	58.5 - 90.4	61.7 - 94.2	64.7 - 97.9	67.8 - 101.6	70.9 - 105.4	74.0 - 109.2
186.0	59.1 - 91.3	62.3 - 95.2	65.4 - 98.9	68.5 - 102.7	71.6 - 106.6	74.7 - 110.3
187.0	59.9 - 92.3	63.0 - 96.3	66.2 - 100.0	69.2 - 103.8	72.4 - 107.8	75.5 - 111.5
188.0	60.5 - 93.3	63.6 - 97.2	66.8 - 101.1	70.0 - 104.9	73.2 - 108.9	76.3 - 112.8
189.0	61.1 - 94.3	64.3 - 98.2	67.5 - 102.2	70.7 - 106.2	74.0 - 110.1	77.1 - 114.0
190.0	61.7 - 95.3	65.0 - 99.3	68.2 - 103.3	71.5 - 107.3	74.7 - 111.2	77.9 - 115.2
191.0	62.4 - 96.4	65.7 - 100.4	68.9 - 104.3	72.3 - 108.4	75.5 - 112.4	78.8 - 116.4
192.0	63.0 - 97.3	66.3 - 101.4	69.7 - 105.4	73.0 - 109.5	76.3 - 113.5	79.7 - 117.6
193.0	63.7 - 98.3	67.1 - 102.5	70.4 - 106.5	73.7 - 110.7	77.2 - 114.7	80.5 - 118.8
194.0	64.3 - 99.3	67.8 - 103.5	71.1 - 107.7	74.5 - 111.8	78.1 - 115.9	81.3 - 120.0
195.0	65.1 - 100.4	68.5 - 104.6	71.8 - 108.8	75.3 - 113.0	78.8 - 117.2	82.2 - 121.3
196.0	65.7 - 101.4	69.1 - 105.6	72.6 - 109.9	76.1 - 114.1	79.6 - 118.4	83.0 - 122.5
197.0	66.4 - 102.5	69.8 - 106.7	73.3 - 111.0	76.8 - 115.3	80.4 - 119.6	83.9 - 123.9
198.0	67.1 - 103.5	70.6 - 107.8	74.1 - 112.1	77.6 - 116.5	81.2 - 120.8	84.7 - 125.1
199.0	67.8 - 104.6	71.3 - 108.9	74.9 - 113.3	78.4 - 117.7	82.0 - 122.0	85.6 - 126.4
200.0	68.4 - 105.6	72.0 - 110.0	75.6 - 114.4	79.2 - 118.8	82.8 - 123.2	86.4 - 127.6

* Weight: wearing indoor clothing
** Height: without shoes

The Division of Biometry of FARMOVS has made a statistical adaptation of the published reference table for BMI.

- to make provision for the inclusion of subjects 18 years of age
- extending the upper and lower bounds of ranges by 10%
- to make provision for the odd numbers that have been omitted from the published reference table.

APPENDIX 16

Adverse Events

APPENDIX 16: LISTING OF ADVERSE EVENTS AS PER QUESTIONNAIRE (Page 1of 4)

Frequency rating: 1 = never (or N/A), 2 = sometimes, 3 = often, 4 = following every application (or every night for abn. dreams)
Intensity rating: 1 = a lot, 2 = a little, 3 = not at all (or N/A)

Subj	Product	Heartburn		Bloated Feeling		Hiccups		Sneezing		Abn. dreams		Other		
No.		Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Symptom	Freq.	Intensity
01	Quit	2	2	2	2	N/A	N/A	N/A	N/A	2	3	Burn mouth	3	2
01	Nicorette	2	3	3	1	N/A	N/A	N/A	N/A	3	3	Raw/ burn tongue, throat	3	2
02	Quit	N/A	N/A	N/A	N/A	2	2	2	2	3	3	Burn mouth	4	1
02	Nicorette	N/A	N/A	N/A	N/A	2	2	N/A	N/A	4	3	N/A	N/A	N/A
03	Quit	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
03	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
04	Quit	2	2	2	2	2	3	N/A	N/A	N/A	N/A	Burn mouth	4	2
04	Nicorette	2	2	3	2	2	3	N/A	N/A	N/A	N/A	Burn throat	2	2
05	Quit	4	2	4	2	3	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A
05	Nicorette	4	2	4	2	3	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A
06	Quit	2	3	2	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
06	Nicorette	2	3	2	2	N/A	N/A	N/A	N/A	N/A	N/A	Cough	2	3
07	Quit	4	1	4	1	3	2	N/A	N/A	N/A	N/A	Burn tongue	4	1
07	Nicorette	3	1	3	1	2	2	N/A	N/A	N/A	N/A	Burn tongue	3	2
08	Quit	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
08	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3	3	Burping	4	2
09	Quit	2	2	N/A	N/A	N/A	N/A	2	3	N/A	N/A	N/A	N/A	N/A
09	Nicorette	3	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Burping	3	2

APPENDIX 16: LISTING OF ADVERSE EVENTS AS PER QUESTIONNAIRE (Page 2 of 4)

Frequency rating: 1 = never (or N/A), 2 = sometimes, 3 = often, 4 = following every application (or every night for abn. dreams)
Intensity rating: 1 = a lot, 2 = a little, 3 = not at all (or N/A)

Subj	Product	Heartburn		Bloated Feeling		Hiccups		Sneezing		Abn. dreams		Other		
No.		Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Symptom	Freq.	Intensity
10	Quit	N/A	N/A	N/A	N/A	3	1	3	2	N/A	N/A	N/A	N/A	N/A
10	Nicorette	N/A	N/A	N/A	N/A	3	1	3	2	N/A	N/A	N/A	N/A	N/A
11	Quit	2	2	2	2	4	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A
11	Nicorette	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
12	Quit	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2	3	N/A	N/A	N/A
12	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2	3	N/A	N/A	N/A
13	Quit	3	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
13	Nicorette	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
14	Quit	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
14	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
15	Quit	2	3	3	3	4	3	2	3	N/A	N/A	N/A	N/A	N/A
15	Nicorette	3	3	2	3	2	3	3	3	N/A	N/A	N/A	N/A	N/A
16	Quit	N/A	N/A	3	2	N/A	N/A	2	3	N/A	N/A	N/A	N/A	N/A
16	Nicorette	2	3	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
17	Quit	N/A	N/A	2	2	N/A	N/A	N/A	N/A	2	2	N/A	N/A	N/A
17	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2	2	N/A	N/A	N/A
17	*MILD SYMPTOMS OF FLU, FROM DAY 6 TILL 4 DAYS AFTER COMPLETION OF STUDY. REQUIRED NO THERAPY*													
18	Quit	4	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
18	Nicorette	2	2	2	2	2	2	N/A	N/A	N/A	N/A	Burping	4	2

APPENDIX 16: LISTING OF ADVERSE EVENTS AS PER QUESTIONNAIRE (Page 3 of 4)

Frequency rating: 1 = never (or N/A), 2 = sometimes, 3 = often, 4 = following every application (or every night for abn. dreams)
Intensity rating: 1 = a lot, 2 = a little, 3 = not at all (or N/A)

Subj No.	Product	Heartburn		Bloated Feeling		Hiccups		Sneezing		Abn. dreams		Other		
		Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Symptom	Freq.	Intensity
19	Quit	2	2	N/A	N/A	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A
19	Nicorette	2	2	N/A	N/A	2	2	N/A	N/A	N/A	N/A	Burn throat	3	2
20	Quit	2	2	2	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20	Nicorette	2	2	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
21	Quit	N/A	N/A	2	2	N/A	N/A	N/A	N/A	3	3	N/A	N/A	N/A
21	Nicorette	N/A	N/A	2	2	N/A	N/A	N/A	N/A	N/A	N/A	Throat irritation Mucus in throat	4 4	1 4
22	Quit	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
22	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
23	Quit	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
23	Nicorette	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
24	Quit	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
24	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
25	*DROP-OUT ON DAY 6 (Quit) DUE TO FLU. REQUIRED THERAPY FOR RELIEF OF MINOR SYMPTOMS. NO QUESTIONNAIRE COMPLETED*													
26	Quit	2	2	N/A	N/A	N/A	N/A	2	3	N/A	N/A	N/A	N/A	N/A
26	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
27	Quit	N/A	N/A	N/A	N/A	2	2	N/A	N/A	2	3	N/A	N/A	N/A
27	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Nausea	3	1

APPENDIX 16: LISTING OF ADVERSE EVENTS AS PER QUESTIONNAIRE (Page 4 of 4)

Frequency rating: 1 = never (or N/A), 2 = sometimes, 3 = often, 4 = following every application (or every night for abn. dreams)
Intensity rating: 1 = a lot, 2 = a little, 3 = not at all (or N/A)

Subj	Product	Heartburn		Bloated Feeling		Hiccups		Sneezing		Abn. dreams		Other		
No.		Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Freq.	Intensity	Symptom	Freq.	Intensity
28	Quit	N/A	N/A	N/A	N/A	2	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A
28	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
29	Quit	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
29	Nicorette	2	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
30	Quit	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
30	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
31	Quit	N/A	N/A	N/A	N/A	3	2	2	3	N/A	N/A	Burn throat Numbness of cheek	3 2	2 2
31	Nicorette	3	2	2	3	N/A	N/A	N/A	N/A	N/A	N/A	Burn throat	2	2
32	Quit	N/A	N/A	N/A	N/A	2	3	2	3	2	2	N/A	N/A	N/A
32	Nicorette	3	1	N/A	N/A	N/A	N/A	3	2	N/A	N/A	Mouth irrit.	3	1
33	Quit	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
33	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
34	*DROP-OUT ON DAY 1 (cigarettes) DUE TO FLU. REQUIRED THERAPY FOR RELIEF OF MINOR SYMPTOMS. NO QUESTIONNAIRE COMPLETED*													
35	Quit	2	3	N/A	N/A	N/A	N/A	2	2	N/A	N/A	N/A	N/A	N/A
35	Nicorette	3	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
36	Quit	N/A	N/A	N/A	N/A	3	2	N/A	N/A	N/A	N/A	Choking feeling	4	2
36	Nicorette	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Choking feeling	4	2