Meta-analysis of data referred to in Table 3

of Scherer's 1999 Paper:

Smoking behaviour and compensation: a review of the literature

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EXECUTIVE SUMMARY

The data from the cross-sectional field studies on smoking behaviour and smoke uptake in relation to cigarette yield as given in Table 3 of the 1999 review by Scherer[1] have been entered into a database to allow detailed analysis.

Models relating log biomarker level to log nicotine yield and log cigs/day have been fitted to allow estimation of the compensation index for nicotine yield, as defined by P.N. Lee. Estimates of the compensation index vary somewhat dependent on the biomarker used (nicotine, cotinine, CO or SCN) but are consistent with substantial, but incomplete, compensation. Estimates weighted on number of subjects are very similar for nicotine in plasma, 0.65 (S.E. 0.06) and for nicotine in urine, 0.63 (0.07), but the estimate for cotinine in plasma or saliva is rather higher, 0.84 (0.04). The estimates for secondary biomarkers CO, 0.92 (0.02), and serum thiocyanate, 0.94(0.05), indicate nearly complete compensation.

The higher estimate of the compensation index for cotinine than for nicotine is related to the very high estimate of 0.98 in the large Sepkovic study. Estimates of the compensation index unweighted on study size are much more similar for nicotine (0.67 in plasma, 0.59 in urine) and cotinine (0.63 in plasma or saliva).

The effect of log cigs/day on biomarker levels is highly significant, except for serum thiocyanate. The slope of the log biomarker / log cigs/day relationship (adjusted for log nicotine yield) is estimated as 0.66 (0.06) and 0.69 (0.06) for cotinine.

Cigarettes/day explains substantially more of the variability in biomarker levels than does nicotine yield.

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1. Introduction

In Scherer's 1999 paper "Smoking behaviour and compensation: a review of the literature" [1] he attempts to examine the concept of compensation – that is the modification of smoking behaviour in an attempt to adjust for changes in cigarette constituents and design in order to maintain the levels of uptake that the smoker finds desirable. In particular in Table 3 he presents an overview of the results from a series of cross-sectional field studies comparing smoke uptake and cigarette yield. In this report we attempt to retrieve data from all the studies referred to in table 3 and to meta-analyse the data to get some estimate of levels of compensation in smokers.

2. Data

In the table below we list the studies and mark what data are available.

Table 1: Details of Studies specified by Scherer 1999, Table 3

Study	Table	N	Ncigs	N cigs on day	Nicotine Type	Cotinine Type	CO	SCN Type	Nic Yield	Tar Yield	CO Yield	HCN Yield
1. Russell et al (1980)[2]	5	330	Y	Y	Plasma		%Hb		Y	Y	Y	
2. Jaffe et al (1981)[3]	2	204	Y	Y			ppm	Saliva	Y			Y
3. Rickert and Robinson (1981)[4]	1	216	Y				%Hb	Plasma			Y	Y
4. Heller et al (1982)[5]	5.2.6	200	Est ISS		Serum	Serum	%Hb		Group			
	5.4.1-5.4.4	142 (Est)	Y		Plasma	Plasma	%Hb		Y			
5. Ebert et al (1983)[6]	1	76	Y		Plasma		ppm		Y	Y	Y	
6. Hill et al (1983)[7]	Fig 2	450	Est ISS		Plasma	Plasma	%Hb	Plasma	Y			
7. Benowitz et al (1983)[8]	2 way plot	272										
8. Petitti and Friedman (1983)[9]	Nothing	7706										
9. Folsom et al (1984)[10]	4	2561						Plasma	Y	Y	Y	
10. Gori and Lynch (1985)[11]	Fig 2	865			Plasma				Y			
11. Russell et al (1986)[12]	1	392	Y	Y	Plasma	Plasma	%Hb		Y	Y	Y	
12. Bridges et al (1986)[13]	4,5,6	108	Y		Plasma	Plasma	%Hb	Plasma	Y			
12a. Bridges et al (1990a, 1990b)[14 15]	2,4	329	Y		Plasma	Plasma	%Hb	Plasma	Y			
13. Maron and Fortmann (1987)[16]	1	713	Y				ppm	Plasma	Group			
14. Sepkovic et al (1990)[17]	Fig All	1832 (909)	Y			Plasma	%Hb		Y			
15. Höfer et al (1990)[18]	2,4	144	Y		Plasma	Plasma	ppm		Y	Y	Y	
16. Rosa et al (1992)[19]	2,3	155	Y			Plasma			Y			
17. Woodward and Tunstall-Pedoe (1992,1993) [20 21]	1993 Table 6	2754	Y			Plasma	ppm	Plasma	Y	Y	Y	
18. Coultas et al (1993)[22]	1	298	Y			Saliva	ppm					
19. Byrd et al (1995)[23]	1	33	Y		Urine				Y			
20. Hee et al (1995)[24]	1,2,3	108	Y		Urine		%Hb		Y	Y	Y	
21. Pritchard and Robinson (1996)[25]	Meta-analysis	4970										

Study	Table	N	Ncigs	N cigs on day	Nicotine Type	Cotinine Type	CO	SCN Type	Nic Yield	Tar Yield	CO Yield	HCN Yield
22. Andersson et al (1996)[26]	1,2,3 + Text	124	Y		Urine	Saliva			Y	NFDPM		
23. Byrd et al (1997)[27]	Raw data	72	Y		Urine				Y	Y		

Legend

N	Number of subjects with suitable data
Ncigs	Average number of cigarettes smoked per day
N cigs on day	Number of cigarettes smoked on day of study
Y	Yes – available from paper
Est ISS	Number estimated from grouped information using International Smoking Statistics[28]
Type	Plasma – concentration in blood plasma (or serum) in ng/ml Saliva – concentration in saliva in mg/ml Urine – mg of total metabolites nicotine + cotinine in 24 hour urine collection %Hb - % Carboxyhaemoglobin in expired air ppm – CO in expired air as ppm
Group	Data only available in grouped form, such as <0.6 or 0.6 to 0.8

For the kind of analyses we wish to perform we will require an estimate of the yield of the cigarette and of the number of cigarettes smoked as well as the variable we are trying to model. From the table above it is clear that many studies only give us very limited amounts of such information for our main variables.

For some studies no real data were available:

- Study 7 just had showed data as two 2-way plots of first cigarettes per day and then FTC nicotine yield versus blood cotinine concentration. The plots were too small for any useful data to be retrieved.

- Study 8 had no suitable data of interest available.

- Study 10, the Gori paper, also only had figures available in a 2-way plot. As these data were used in the meta-analysis of Pritchard et al (Study 21) an attempt was made to pull the data out of this graph into a form that could be analysed. However, no data on the number of cigarettes smoked were available, so it is of little use in our analyses.

- Study 21 was only a meta-analysis by Pritchard et al[25] of studies already mentioned: 7: Benowitz, 12: Bridges, 10: Gori, 6: Hill, 15: Höfer, 16: Rosa, 11: Russell and 17: Woodward.

Sometimes data on number of cigarettes were only available in groupings such as 1 – 10 cigarettes per day. This has been translated to a particular value by making use of the table in Appendix III of International Smoking Statistics (Second Edition) [28] which gives prevalence of smoking by different groupings of cigarettes per day.

When trying to enter data for study 4, the Heller paper[5], there were only groupings available for both the nicotine yield and the number of cigarettes from the main table of interest: Table 5.2.6. In the report itself there were individual data available for a subset of the people surveyed. Though the copy was rather unclear it was decided that it would be more advantageous to estimate the values from the bad photocopy than to have to estimate yields and numbers of cigarettes and then try to analyse the data. Note that we used the data from Tables 5.4.1 to 5.4.4 labelled "1" – that is Nikotin/Serum 1, Cotinin/Serum 1 and COHb 1.

For study 23, Byrd et al 1997, we were fortunate to have been sent the individual data and so these data were used in the analysis.

For blood and saliva measurements values have been taken or converted to ng/ml.

When taken from a 24 hour urine sample, nicotine was measured from all available metabolites including cotinine, so there are no separate cotinine values.

Study 20, the Hee paper[24], presented the results as the Barlow index and in units of "µmol/24/h" rather than the units used in some other papers which used "mg/24" hour. The Heller paper also used µmol/l, but the results looked very similar to the other results. The Hee paper talks about converting to a "cotinine equivalent" but this is not explained and I have been unable to find any information about this. There is a possible conversion factor of 5.68 between cotinine ng/ml and nmol/l and a factor of 6.614 between nicotine mg/l and µmol/l. Neither of these looked suitable for converting mean values for Hee of 35 to 62 to the values of around 20 seen in the other papers and would certainly not be suitable for the Heller data. For now, no conversion factor has been used, but a study related constant is added in many models which should automatically align the results to changes in units.

As the urine values include both nicotine and cotinine derivatives, the values have been included when looking at uptake of nicotine and when looking at cotinine values in the body.

3. Model

The principal model of interest is that the smoking uptake (U) depends upon the yield of the cigarette (Y) and the number of cigarettes smoked per day (N) by the equation:

$$U \propto Y^{1-\alpha} N^{\beta}$$

The compensation index (CI) is defined as α. No compensation is equivalent to a value of $\alpha = 0$, while full compensation suggests a value of $\alpha = 1$. In our linear modelling we present the estimates as $\alpha' = 1 - \alpha$; for this variable 1 is equivalent to no compensation and 0 to full compensation.

Taking logs gives us a linear model to fit to the data:

$$\log(U) = \mu + (1 - \alpha)\log(Y) + \beta \log(N) + \varepsilon$$

where, as variables such as nicotine and cotinine are usually taken as log normal, it will be reasonable to assume ε is normally distributed.

Note that by taking logs we exclude cases that are non-smokers or have values of the variables of interest of zero.

In some studies, such as Heller 1982 and the two Byrd studies, we have data from individual subjects, whereas in others we only have the mean data for various subsets of the data. To allow for this in the model we perform weighted regression, using the numbers of subjects as the weighting variable. (Note that as standard error is [standard deviation]/$\sqrt{n}$, this is approximately equivalent to weighting by 1/Variance of the studies). In our tables of results we show the number of individual estimates available from each study.

We present various tables showing the results of fitting this form of model predicting our variables of interest: nicotine levels, cotinine levels, CO levels and thiocyanate levels (SCN) using as predictive variables the nicotine yield, the form in which the levels were measured, the number of cigarettes and the sex of the subjects. We present:

Deviance:	Generalised fit of the model, equivalent to residual sum of squares
DF	Degrees of freedom for the current fit of the model
Drop Dev:	Drop in deviance when bringing in a new explanatory variable – this is followed by a P value representing the significance of bringing in this variable
Estimate:	An estimate of the parameter estimate in the model. Note that for log nicotine yield this is $\alpha' = 1 - \alpha$, where α is the compensation index defined in section 3.

S.E.	Standard error of the parameter estimate (this is unaffected by "1-" transformation). This is followed by a P value representing the significance of a test for the estimate from the value zero and some 95% Confidence limits on the estimate.
Aliased	This is given against levels which are included in the overall mean (or "Constant" term) and hence have no separate value.

The P levels are given in standard coded form:

***/+++/---	P < 0.001
**/++/--	P <0.01
*/+/-	P <0.05
(*)/(+)/(-)	P <0.1
NS	P >0.1

Where "+ "represents positive effects and "-" negative effects.

4. Results

We concentrate on relating our four main response variables, nicotine, cotinine, CO and thiocyanate (SCN) to the nicotine yield of the cigarettes and number of cigarettes smoked. We include all forms by which the response variable is measured - plasma (serum), saliva and urine – allowing for this in the model before adding in our other explanatory variables.

4.1 Nicotine

Table 2 gives details of the 12 studies that have data on nicotine uptake and nicotine yield. The estimates of α' (unadjusted for cigarette consumption) vary quite markedly from .09 to .79 over the studies. Fitting a model with different intercepts but the same value of α' over the studies leads to an overall estimate (and standard error) of 0.27 (0.02). This model causes a drop in deviance of 59.0% from 768.31 on 1069 degrees of freedom (DF) to 315.36 on 1057 DF. The study by Gori and Lynch, which has the largest weight, has a relatively low estimate of α'. Even so, the simple unweighted estimate of α' based on the 12 individual study estimates, 0.34, is not so different from the weighted estimate of 0.27.

Table 3 gives details of the 11 studies that have data on nicotine uptake, nicotine yield and number of cigarettes – thus losing the Gori and Lynch study, which has no details on numbers of cigarettes smoked. This leaves 1618 subjects for plasma nicotine and 337 with urinary nicotine. The mean level (unweighted) for nicotine is significantly higher as measured by urinary nicotine metabolites, 23.41 mg/24h versus a mean value of 17.26 mg/ml for plasma nicotine .

Table 4 presents the results of fitting the model to the data. The estimates of α' after allowing for number of cigarettes smoked vary markedly, as in the unadjusted analysis, from 0.11 to 0.78. Estimating an overall mean value for α' by fitting different intercepts but the same slope for each study gives a value of 0.33 (0.04). Note the deviance of this model is 148.20 on 284 DF. The deviance when allowing a different slope for each study is 139.85 on 274 DF, giving an F statistic of 1.64 for allowing a different slope for each study. This is non-significant, suggesting that the overall estimate of 0.33 does not materially vary over the different studies. When we consider just the drop in deviance due to log nicotine after allowing for different means for each study, and not allowing for log cigarettes per day (log cigs/day), the deviance drops 12.7% from 251.10 on 286 DF to 219.12 on 285 DF. The drop in deviance due to log nicotine, after allowing for different means for each study and for log cigs/day, is somewhat larger, at 16.9% from 178.41 on 285 DF to 148.20 on 284 DF. In this analysis no study has particularly large weight, and the unweighted estimate of α', based on the 11 individual study estimates, 0.33, is the same as the overall weighted estimate.

The estimate of β, the slope for log cigs/day, is highly significant, 0.66 (0.06). However, there is some evidence of a sharper slope for urinary nicotine, with a value of 0.99 (0.17) versus 0.62 (0.06) for plasma nicotine ($p<0.05$ for the F test for including two different estimates in the model).

Fitting a model where the same intercept is used for each study (though a different intercept for plasma nicotine than urinary nicotine) gives a higher estimate for α' of 0.49 (0.08). However, this model did not fit the data nearly so well, with a final deviance of 400.45 on 293 DF. Including sex in the model reduces the deviance significantly, but it is still nowhere near the deviance achieved using different intercepts for different studies.

Nicotine in plasma may have a different compensation index to that measured in metabolites of urine. However we cannot simply examine this by adding in a term in the model, as studies such as Heller 1982 have both types of value available, and we would like to get the best estimate using all the available data. Table 5 show the results for analysing the studies with plasma values separately from those with urinary nicotine values. Once again it is clear that fitting a separate intercept for each study improves the fit markedly. The estimate for α' using the separate intercept model is 0.35 (0.06) for log plasma nicotine and an almost identical 0.37 (0.07) for the log urinary metabolites, the full models accounting for 78.6% and 47.6% of the deviance respectively. The unweighted estimates of α' are little different, at 0.33 for plasma and 0.41 for urinary metabolites.

Examining the drop in deviance due to just log nicotine, allowing for different means per study but not log cigs/day, we see a drop of 13.8% from 186.12 on 173 DF to 160.39 on 172 DF for log plasma nicotine but only 6.6% from 215.38 on 251 DF to 201.12 on 250 DF for log urinary nicotine. As above, the drop in deviance is larger for models including log cigs/day, a 17.6% drop from 126.50 on 172 DF to 104.23 on 171 DF for log plasma nicotine and a 9.7% drop from 167.90 on 250 DF to 151.59 on 249 DF for log urinary nicotine.

4.2 Cotinine

Table 6 gives details of the 12 studies that have data on cotinine from plasma, saliva, or from urinary metabolites, nicotine yield and number of cigarettes. This gives 5947 subjects for plasma cotinine, 213 for urinary cotinine and 124 for salivary cotinine. The mean levels (unweighted) for cotinine are similar for plasma and saliva, but clearly different for urine, which is lower by an order of magnitude. Table 7 shows weighted regression analysis of log cotinine. The estimates for α' from individual studies are more variable than those for nicotine, the range being from 0.02 to 0.83. Estimating one overall value for α' gives a value of 0.18 (0.03), a lower value than for nicotine, though the estimate for the slope for log cigs/day is very similar at 0.69 (0.06). Once again models using the same intercept for all studies do not fit nearly as well, even allowing for different values for the way the cotinine was measured and for a difference between the sexes. It should be noted that the 12 individual study estimates of α' vary widely, from 0.02 to 0.82, and that the Sepkovic study, which has a very large weight, has the lowest α' estimate. A simple unweighted mean of the 12 estimates is 0.38, much higher than the weighted estimate of 0.18.

The model with a different intercept per study, log cigs/day and the same estimate of α' for each study results in a deviance of 231.27 on 296 DF. Bringing in a different estimate of α' for each study reduces the deviance to 201.53 on 285 DF, giving an F statistic of 3.82 which is significant at $p<0.001$, confirming the heterogeneity between the estimates of α' over the studies.

Examining the drop in deviance just due to log nicotine, allowing for different means per study but not log cigs/day, we see a drop of 9.4% from 373.25 on 298 DF to 338.16 on 297 DF, while allowing for log cigs/day gives a 8.7% drop from 253.25 on 297 DF to 231.27 on 296 DF.

The values for urinary metabolites are identical to those used in the analysis for nicotine, so it is clear that the estimate using plasma and salivary cotinine must be lower than before. Table 8 shows the analysis for plasma and saliva only, and the resulting weighted estimate of α' is only 0.16 (0.04). The drop in deviance with this subset of the data is 9.0% from 311.85 on 190 DF to 283.72 on 189 DF without log cigs/day, while with log cigs/day it gives only a 7.5% drop from 202.23 on 189 DF to 187.12 on 188 DF. Note also that bringing in a different estimate of α' over all the studies reduces the deviance significantly further, to 164.27 on DF, giving an F statistic of 3.13 ($p<0.01$). Thus even within the plasma and salivary data there is significant heterogeneity between the estimates of α'. As before, the unweighted estimate of α', 0.37, is much higher than the weighted estimate of 0.16, reflecting the large contribution of the Sepkovic estimate of 0.02 to the weighted figure.

4.3 CO

Though clearly we are most interested in relating the primary biomarkers of nicotine and its metabolites to nicotine yield it is also of interest to look at some of the other smoking related variables measured. First we look at CO levels, though it must be borne in mind that this variable can be greatly affected by the time since the last cigarette. Table 9 shows the 12 studies with data on CO values, nicotine yield and number of cigarettes. This gives 3254 subjects with % COHb measurements and 3887 subjects measured as ppm. These measurements, not surprisingly, have different mean values, 4.21 (0.18) for %COHb and 25.25 (1.50) for ppm. From Table 10 it can be seen that the estimates of α' are slightly less variable than above, and that we have some estimates that are less than zero, ranging from –0.1 to 0.33, with an overall estimate of 0.08 (0.02). An unweighted estimate is slightly higher, at 0.13. The drop in deviance due to log nicotine yield is only 4.0% without including log cigs/day and only slightly larger at 5.7% with log cigs/day. It is again clear that not allowing for models with different intercepts for each study gives much larger values for the deviance. There is a clear effect of log cigs/day, with an estimate for β of 0.46 (0.05). This seems consistent over the ways of measuring CO, with estimates of 0.48 (0.06) for %COHb versus 0.42 (0.08) for ppm.

4.4 Thiocyanate (SCN)

Table 11 gives details of the 5 studies with data on SCN values, nicotine yield and number of cigarettes. There are 4106 subjects with plasma readings and 150 with saliva readings. Saliva readings are significantly higher than the plasma readings, 169.13 (6.98) vs 141.59 (4.98) respectively in the unweighted analysis. Table 12 shows that, when not allowing for sex, log SCN is mildly related to log number of cigarettes, but not to log nicotine yield where the weighted estimate of α' is 0.06 (0.05), little different from the unweighted estimate of 0.07. When including sex in the model, the effect of log number of cigarettes is much larger and more significant, with an estimate β of 0.34 (0.05). In this model log nicotine yield was also significant, though quite small, with α' 0.08 (0.03). It is difficult to tell if these are real effects, or if we are overfitting models to small amounts of data.

4.5 Summary of estimates

Table 13 summarizes the estimates of the compensation index for nicotine yields for the various biomarkers. Note that a 50% reduction in nicotine yield would predict reductions in the biomarker level of 24%, 19% and 13% for compensation index estimates of, respectively, 0.6, 0.7 and 0.8. In all cases the index is very highly significantly greater than 0, implying that compensation certainly exists. However, the index is always less than 1 (significantly so except for the limited data for thiocyanate) with estimates ranging from 0.63 to 0.84 for the primary biomarkers of nicotine and cotinine. The secondary biomarkers of CO and SCN have estimates very close to 1, but then we are comparing these to nicotine yield rather than CO or SCN yield.

The estimates of the compensation index appear rather higher for cotinine than for nicotine. This is related to the analysis being weighted on the number of subjects, and the Sepkovic study being very large and having a high compensation index estimate of 0.98 for cotinine. Unweighted estimates of the compensation index are quite similar for nicotine and for cotinine (nicotine total 0.67, nicotine in plasma 0.67, nicotine in urine 0.59, cotinine total 0.62, cotinine in plasma 0.62).

These estimates are adjusted by log cigs/day. Comparing the deviance of the model involving log nicotine yield, the percentage of variance in log biomarker explained by log nicotine yield ranges from 7.5% to 17.6% for the primary biomarkers, and only from 5.3% to 5.7% for the secondary biomarkers.

The compensation index estimates for nicotine (total and plasma only) and for SCN show no significant variation by study. Significant heterogeneity is seen for urinary nicotine, cotinine and for CO. However, even then all the individual study estimates for cotinine and urinary nicotine show partial compensation (0 < index <1).

Table 14 summarizes the estimates of the slope of the relationship between log biomarker and log cigs/day (adjusted for log nicotine yield). With the exception of the limited data for SCN, all the slopes are highly significantly positive, with the nicotine and cotinine estimates around 0.7. A slope of 0.7 implies that a 100% increase in number of cigarettes smoked results in a 62% increase in biomarker level. The variance explained by log cigs/day is clearly greater than that explained by log nicotine.

5. Summary and Conclusions

The data from the cross-sectional field studies on smoking behaviour and smoke uptake in relation to cigarette yield as given in Table 3 of the 1999 review by Scherer[1] have been entered into a database to allow detailed analysis.

Models relating log biomarker level to log nicotine yield and log cigs/day have been fitted to allow estimation of the compensation index for nicotine yield, as defined by P.N. Lee. Estimates of the compensation index vary somewhat dependent on the biomarker used (nicotine, cotinine, CO or SCN) but are consistent with substantial, but incomplete, compensation. Estimates weighted on number of subjects are very similar for nicotine in plasma, 0.65 (S.E. 0.06) and for nicotine in urine, 0.63 (0.07), but the estimate for cotinine in plasma or saliva is rather higher, 0.84 (0.04). The estimates for secondary biomarkers CO, 0.92 (0.02), and serum thiocyanate, 0.94(0.05), indicate nearly complete compensation.

The higher estimate of the compensation index for cotinine than for nicotine is related to the very high estimate of 0.98 in the large Sepkovic study. Estimates of the compensation index unweighted on study size are much more similar for nicotine (0.67 in plasma, 0.59 in urine) and cotinine (0.63 in plasma or saliva).

The effect of log cigs/day on biomarker levels is highly significant, except for serum thiocyanate. The slope of the log biomarker / log cigs/day relationship (adjusted for log nicotine yield) is estimated as 0.66 (0.06) and 0.69 (0.06) for cotinine. Cigarettes/day explains substantially more of the variability in biomarker levels than does nicotine yield.

6. References

1. Scherer G. Smoking behaviour and compensation: a review of the literature. *Psychopharmacology* 1999;**145**:1-20.

2. Russell MAH, Jarvis M, Iyer R, Feyerabend C. Relation of nicotine yields of cigarettes to blood nicotine concentrations in smokers. *BMJ* 1980;**Apr 5**:972-6.

3. Jaffe JH, Kanzler M, Friedman L, Stunkard AJ, Verebey K. Carbon monoxide and thiocyanate levels in low tar/nicotine smokers. *Addict Behav* 1981;**6**:337-43.

4. Rickert WS, Robinson JC. Estimating the hazards of less hazardous cigarettes. II. Study of cigarette yields of nicotine, carbon monoxide, and hydrogen cyanide in relation to levels of cotinine, carboxyhemoglobin, and thiocyanate in smokers. *J Toxicol Environ Health* 1981;**7**:391-403.

5. Heller W-D, Meisel R, Richter F, Scherer G. *Abschlussbericht zur Pilotstudie. Feldstudie zum Rauchverhalten*. 1982.

6. Ebert RV, McNabb ME, McCusker KT, Snow SL. Amount of nicotine and carbon monoxide inhaled by smokers of low-tar, low-nicotine cigarettes. *JAMA* 1983;**250**:2840-2.

7. Hill P, Haley NJ, Wynder EL. Cigarette smoking: carboxyhemoglobin, plasma nicotine, cotinine and thiocyanate vs self-reported smoking data and cardiovascular disease. *J Chronic Dis* 1983;**36**:439-49.

8. Benowitz NL, Hall SM, Herning RI, Peyton J, III, Jones RT, Osman A-L. Smokers of low-yield cigarettes do not consume less nicotine. *N Engl J Med* 1983;**309**:139-42.

9. Petitti DB, Friedman GD. Evidence for compensation in smokers of low yield cigarettes. *Int J Epidemiol* 1983;**12**:487-9.

10. Folsom AR, Pechacek TF, De Gaudemaris R, Luepker RV, Jacobs DR, Jr., Gillum RF. Consumption of 'low-yield' cigarettes: its frequency and relationship to serum thiocyanate. *Am J Public Health* 1984;**74**:564-8.

11. Gori GB, Lynch CJ. Analytical cigarette yields as predictors of smoke bioavailability. *Regul Toxicol Pharmacol* 1985;**5**:314-26.

12. Russell MAH, Jarvis MJ, Feyerabend C, Saloojee Y. Reduction of tar, nicotine and carbon monoxide intake in low tar smokers. *J Epidemiol Community Health* 1986;**40**:80-5.

13. Bridges RB, Humble JW, Turbek JA, Rehm SR. Smoking history, cigarette yield and smoking behavior as determinants of smoke exposure. *Eur J Respir Dis* 1986;**69(Suppl 146)**:129-37.

14. Bridges RB, Combs JG, Humble JW, Turbek JA, Rehm SR, Haley NJ. Puffing topography as a determinant of smoke exposure. *Pharmacol Biochem Behav* 1990;**37**:29-39.

15. Bridges RB, Combs JG, Humble JW, Turbek JA, Rehm SR, Haley NJ. Population characteristics and cigarette yield as determinants of smoke exposure. *Pharmacol Biochem Behav* 1990;**37**:17-28.

16. Maron DJ, Fortmann SP. Nicotine yield and measures of cigarette smoke exposure in a large population: are lower-yield cigarettes safer? *Am J Public Health* 1987;**77**:546-9.

17. Sepkovic DW, Colosimo SG, Axelrad CM, Haley NJ. Long-term use of "low nicotine yield" cigarettes. In: *Effects of nicotine on biological systems symposium. Hamburg, Germany June 28-30*. 1990;90 + 10 pages.

18. Höfer I, Nil R, Bättig K. Nicotine yield as determinant of smoke exposure indicators and puffing behavior. *Pharmacol Biochem Behav* 1991;**40**:139-49.

19. Rosa M, Pacifici R, Altieri I, Pichini S, Ottaviani G, Zuccaro P. How the steady-state cotinine concentration in cigarette smokers is directly related to nicotine intake. *Clin Pharmacol Ther* 1992;**52**:324-9.

20. Woodward M, Tunstall-Pedoe H. Do smokers of lower tar cigarettes consume lower amounts of smoke components? Results from the Scottish Heart Health Study. *Br J Addict* 1992;**87**:921-8.

21. Woodward M, Tunstall-Pedoe H. Self-titration of nicotine: evidence from the Scottish Heart Health Study. *Addiction* 1993;**88**:821-30.

22. Coultas DB, Stidley CA, Samet JM. Cigarette yields of tar and nicotine and markers of exposure to tobacco smoke. *Am Rev Respir Dis* 1993;**148**:435-40.

23. Byrd GD, Robinson JH, Caldwell WS, deBethizy JD. Comparison of measured and FTC-predicted nicotine uptake in smokers. *Psychopharmacology* 1995;**122**:95-103.

24. Hee J, Callais F, Momas I, Laurent AM, Min S, Molinier P, *et al*. Smokers' behaviour and exposure according to cigarette yield and smoking experience. *Pharmacol Biochem Behav* 1995;**52**:195-203.

25. Pritchard WS, Robinson JH. Examining the relation between usual-brand nicotine yield, blood cotinine concentration and the nicotine-"compensation" hypothesis. *Psychopharmacology* 1996;**124**:282-4.

26. Andersson G, Vala EK, Curvall M. The influence of cigarette consumption and smoking machine yields of tar and nicotine on the nicotine uptake and oral mucosal lesions in smokers. *J Oral Pathol Med* 1997;**26**:117-23.

27. Byrd GD, Davis RA, Caldwell WS, Robinson JH, deBethizy JD. A further study of FTC yield and nicotine absorption in smokers. *Psychopharmacology* 1998;**139**:291-9.

28. Forey B, Hamling J, Lee P, Wald N, editors. *International Smoking Statistics. A collection of historical data from 30 economically developed countries,* 2nd edition. London and Oxford: Wolfson Institute of Preventive Medicine and Oxford University Press; 2002. Errata available at www.pnlee.co.uk/ISS2.htm.

Table 2

Meta-analysis of studies in Scherer 1999A Table 3
Frequency Table
Studies of Interest: nicotine >0 and nicotine yield >0

Study		Number of Data points per study 1 Plasma	Number of Data points per study 2 Urine	Total Number of Subjects 1 Plasma	Total Number of Subjects 2 Urine
	N	953	117	2391	337
Russell et al (1980)		5	0	222	
Heller et al (1982)		145	0	145	
Ebert et al (1983)		3	0	76	
Hill et al (1983)		12	0	370	
Gori and Lynch (1985)		773	0	773	
Russel et al (1986)		6	0	392	
Bridges et al (1986,90)		5	0	269	
Hofer et al (1991)		4	0	144	
Byrd et al (1995)		0	33		33
Hee et al (1995)		0	6		108
Andersson et at (1996)		0	6		124
Byrd et al (1997)		0	72		72

<u>Weighted on number of subjects</u>

Log Nicotine

	Deviance	(DF)
Model 1	768.31	(1069)

Log Nicotine predicted by
Log Nicotine Yield per Study

		Deviance	(DF)			
		302.90	(1046)			
		Estimate	S.E.	P	95%CIl	95%CIu
Russell et al (1980)	5	0.23	0.14	N.S.	-0.05	0.51
Heller et al (1982)	145	0.59	0.12	+++	0.36	0.82
Ebert et al (1983)	3	0.22	0.11	+	0.02	0.43
Hill et al (1983)	12	0.48	0.09	+++	0.31	0.66
Gori and Lynch (1985)	773	0.21	0.03	+++	0.15	0.27
Russel et al (1986)	6	0.36	0.11	+++	0.15	0.58
Bridges et al (1986,90)	5	0.34	0.16	+	0.03	0.64
Hofer et al (1991)	4	0.34	0.08	+++	0.19	0.49
Byrd et al (1995)	33	0.79	0.13	+++	0.54	1.04
Hee et al (1995)	6	0.31	0.11	++	0.09	0.53
Andersson et at (1996)	6	0.10	0.27	N.S.	-0.44	0.64
Byrd et al (1997)	72	0.09	0.07	N.S.	-0.05	0.23

Model with same slope for Log Nicotine Yield per study

	Deviance	(DF)			
	315.36	(1057)			
	Estimate	S.E.	P	95%CIl	95%CIu
Log Nicotine Yield	0.27	0.02	+++	0.22	0.31

Table 3

Meta-analysis of studies in Scherer 1999A Table 3
Frequency Table
Studies of Interest: number of cigarettes >0, nicotine >0 and nicotine yield >0

		Number of Data points per study		Total Number of Subjects	
		1	2	1	2
		Plasma	Urine	Plasma	Urine
Study					
	N	953	117	1618	337
Russell et al (1980)		5	0	222	
Heller et al (1982)		145	0	145	
Ebert et al (1983)		3	0	76	
Hill et al (1983)		12	0	370	
Russel et al (1986)		6	0	392	
Bridges et al (1986,90)		5	0	269	
Hofer et al (1991)		4	0	144	
Byrd et al (1995)		0	33		33
Hee et al (1995)		0	6		108
Andersson et at (1996)		0	6		124
Byrd et al (1997)		0	72		72

Nicotine

N	180	117
Mean	17.26	23.41
St.Err	0.88	1.08
St.Dev	11.78	11.73
Var P		N.S.
F		19.38
P		+++

Table 4

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, nicotine >0 and nicotine yield >0

<u>Weighted on number of subjects</u>

Log Nicotine

	Deviance	(DF)
Model 1	609.71	(296)
(Different mean for way nicotine measured)		
Model : means for each study	251.10	(286)
: + log cigs/day only	178.41	(285)
: + log Nic Yield only	219.12	(285)

Log Nicotine predicted by
Log Nicotine Yield per Study
Adjusted by log number of cigarettes per day

	Deviance	(DF)
	139.85	(274)

		Estimate	S.E.	P	95%CIl	95%CIu
Russell et al (1980)	5	0.19	0.19	N.S.	-0.19	0.57
Heller et al (1982)	145	0.55	0.16	+++	0.24	0.86
Ebert et al (1983)	3	0.29	0.14	+	0.01	0.56
Hill et al (1983)	12	0.48	0.12	+++	0.25	0.72
Russel et al (1986)	6	0.31	0.15	+	0.02	0.59
Bridges et al (1986,90)	5	0.22	0.21	N.S.	-0.20	0.63
Hofer et al (1991)	4	0.30	0.10	++	0.10	0.50
Byrd et al (1995)	33	0.78	0.17	+++	0.44	1.11
Hee et al (1995)	6	0.31	0.15	+	0.02	0.60
Andersson et at (1996)	6	0.11	0.36	N.S.	-0.60	0.83
Byrd et al (1997)	72	0.13	0.09	N.S.	-0.05	0.32

Model with same slope for Log Nicotine Yield per study

	Deviance	(DF)
	148.20	(284)

	Estimate	S.E.	P	95%CIl	95%Ciu
Log Nicotine Yield	0.33	0.04	+++	0.24	0.41
Log cigs/day	0.66	0.06	+++	0.55	0.77

Model with same slope for Log Nicotine Yield per study, different slope for log cigs/day by Nicotine Type

	Deviance	(DF)	Drop Dev	P
	146.14	(283)	2.06	*

		Estimate	S.E.	P	95%CIl	95%Ciu
Log Nicotine Yield		0.33	0.04	+++	0.25	0.41
Log cigs/day (Plasma)	180	0.62	0.06	+++	0.50	0.73
Log cigs/day (Urine)	117	0.99	0.17	+++	0.64	1.33

Model with same intercept and slope for Log Nicotine Yield per study

	Deviance	(DF)	Drop Dev	P
	400.45	(293)	92.04	***

		Estimate	S.E.	P	95%CIl	95%Ciu
Constant		1.35	0.23	+++		
Values in Body: Nicotine type						
Plasma	180	Aliased				
Urine	117	0.49	0.08	+++	0.34	0.64
Log Nicotine Yield		0.52	0.06	+++	0.41	0.63
Log cigs/day		0.57	0.07	+++	0.43	0.70

Table 4

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, nicotine >0 and nicotine yield >0

<u>Weighted on number of subjects</u>

Log Nicotine

Model with same intercept and slope for Log Nicotine Yield per study, including Sex

		Deviance	(DF)	Drop Dev	P		
		354.89	(291)	45.56	***		
		Estimate	S.E.	P		95%CIl	95%Ciu
Constant		1.60	0.23	+++			
Values in Body: Nicotine type							
Plasma	180	Aliased					
Urine	117	0.40	0.08	+++		0.25	0.56
Log Nicotine Yield		0.45	0.06	+++		0.34	0.56
Log cigs/day		0.48	0.07	+++		0.35	0.62
Sex							
Males	265	Aliased					
Females	8	0.29	0.06	+++		0.16	0.42
Both	24	-0.15	0.06	-		-0.28	-0.02

Table 5

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, nicotine >0 and nicotine yield >0

<u>Weighted on number of subjects</u>

Log Nicotine

<u>Plasma values only</u>

	Deviance	(DF)
Model 1	486.27	(179)
Model : means for each study	186.12	(173)
: + log cigs/day only	126.50	(172)
: + log Nic Yield only	160.39	(172)

Log Nicotine predicted by
Log Nicotine Yield per Study
Adjusted by log number of cigarettes per day

		Deviance	(DF)			
		101.95	(165)			
		Estimate	S.E.	P	95%CIl	95%CIu
Russell et al (1980)	5	0.19	0.21	N.S.	-0.23	0.61
Heller et al (1982)	145	0.55	0.17	++	0.21	0.89
Ebert et al (1983)	3	0.28	0.16	(+)	-0.02	0.59
Hill et al (1983)	12	0.48	0.13	+++	0.22	0.74
Russel et al (1986)	6	0.31	0.16	(+)	-0.01	0.63
Bridges et al (1986,90)	5	0.22	0.23	N.S.	-0.23	0.68
Hofer et al (1991)	4	0.30	0.11	++	0.08	0.52

Model with same slope for Log Nicotine Yield per study

	Deviance	(DF)			
	104.23	(171)			
	Estimate	S.E.	P	95%CIl	95%Ciu
Log Nicotine Yield	0.35	0.06	+++	0.24	0.46
Log cigs/day	0.62	0.06	+++	0.49	0.74

Model with same intercept and slope for Log Nicotine Yield per study

	Deviance	(DF)			
	227.56	(177)			
	Estimate	S.E.	P	95%CIl	95%Ciu
Constant	0.56	0.25	+		
Log Nicotine Yield	0.58	0.07	+++	0.44	0.71
Log cigs/day	0.81	0.08	+++	0.66	0.96

Model with same intercept and slope for Log Nicotine Yield per study, including Sex

		Deviance	(DF)	Drop Dev	P		
		215.15	(175)	12.40	**		
		Estimate	S.E.	P		95%CIl	95%CIu
Constant		0.87	0.27	++			
Log Nicotine Yield		0.51	0.07	+++		0.37	0.66
Log cigs/day		0.72	0.08	+++		0.56	0.88
Sex							
Males	156	Aliased					
Females	5	0.12	0.07	N.S.		-0.03	0.26
Both	19	-0.14	0.07	-		-0.27	-0.00

Table 5

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, nicotine >0 and nicotine yield >0

Weighted on number of subjects

Urine values (including metabolites) only

Log Nicotine

	Deviance	(DF)
Model 1	296.97	(255)
Model : means for each study	215.38	(251)
: + log cigs/day only	167.90	(250)
: + log Nic Yield only	201.12	(250)

Log Nicotine predicted by
Log Nicotine Yield per Study
Adjusted by log number of cigarettes per day

		Deviance	(DF)			
		143.55	(245)			
		Estimate	S.E.	P	95%CIl	95%CIu
Heller et al (1982)	139	0.70	0.17	+++	0.37	1.04
Byrd et al (1995)	33	0.77	0.18	+++	0.42	1.12
Hee et al (1995)	6	0.31	0.16	(+)	-0.00	0.62
Andersson et at (1996)	6	0.12	0.39	N.S.	-0.65	0.88
Byrd et al (1997)	72	0.16	0.10	N.S.	-0.04	0.36

Model with same slope for Log Nicotine Yield per study

	Deviance	(DF)			
	151.59	(249)			
	Estimate	S.E.	P	95%CIl	95%CIu
Log Nicotine Yield	0.37	0.07	+++	0.23	0.50
Log cigs/day	1.03	0.11	+++	0.81	1.26

Model with same intercept and slope for Log Nicotine Yield per study

	Deviance	(DF)			
	287.02	(253)			
	Estimate	S.E.	P	95%CIl	95%CIu
Log Nicotine Yield	0.24	0.08	++	0.07	0.40
Log cigs/day	-0.01	0.11	N.S.	-0.22	0.21

Model with same intercept and slope for Log Nicotine Yield per study, including Sex

		Deviance	(DF)	Drop Dev	P		
		243.38	(251)	43.64	***		
		Estimate	S.E.	P		95%CIl	95%CIu
Constant		2.09	0.35	+++			
Log Nicotine Yield		0.36	0.08	+++		0.21	0.52
Log cigs/day		0.35	0.12	++		0.12	0.58
Sex							
Males	248	Aliased					
Females	3	1.01	0.15	+++		0.71	1.30
Both	5	0.22	0.45	N.S.		-0.66	1.10

Table 6

Meta-analysis of studies in Scherer 1999A Table 3
Frequency Table
Studies of Interest: number of cigarettes >0, cotinine >0 and nicotine yield >0

		Number of Data points per study			Total Number of Subjects		
		1	2	3	1	2	3
		Plasma	Urine	Saliva	Plasma	Urine	Saliva
Study							
	N	193	119	6	5947	213	124
Heller et al (1982)		146	0	0	146		
Hill et al (1983)		12	0	0	370		
Russel et al (1986)		6	0	0	392		
Bridges et al (1986,90)		5	0	0	269		
Sepkovic et al (1990)		8	0	0	1747		
Hofer et al (1991)		4	0	0	144		
Rosa et al (1992)		4	0	0	125		
Woodward & Tunstall-Pedoe 1992		8	0	0	2754		
Byrd et al (1995)		0	33	0		33	
Hee et al (1995)		0	6	0		108	
Andersson et at (1996)		0	0	6			124
Byrd et al (1997)		0	72	0		72	

Cotinine

N	193	111	6
Mean	194.62	23.34	250.82
St.Err	9.24	1.14	23.31
St.Dev	128.42	11.96	57.09
Var P		***	(*)
F		198.43	1.76
P		---	N.S.

Table 7

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, cotinine >0 and nicotine yield >0

Weighted on number of subjects

Log Cotinine

	Deviance	(DF)
Model 1 (Overall mean)	1666.39	(309)
Model : means for each study	373.25	(298)
: + log cigs/day only	253.25	(297)
: + log Nic Yield only	338.16	(297)

	n	Estimate	S.E.	P	95%CIl	95%CIu
Log Cotinine predicted by Log Nicotine Yield per Study Adjusted by log number of cigarettes per day		Deviance	(DF)			
		201.53	(285)			
		Estimate	S.E.	P	95%CIl	95%CIu
Heller et al (1982)	146	0.76	0.18	+++	0.40	1.12
Hill et al (1983)	12	0.42	0.14	++	0.15	0.70
Russel et al (1986)	6	0.08	0.17	N.S.	-0.25	0.42
Bridges et al (1986,90)	5	0.24	0.25	N.S.	-0.25	0.73
Sepkovic et al (1990)	8	0.02	0.05	N.S.	-0.07	0.12
Hofer et al (1991)	4	0.24	0.12	+	0.01	0.47
Rosa et al (1992)	4	0.82	0.25	++	0.33	1.32
Woodward & Tunstall-Pedoe	8	0.27	0.09	++	0.10	0.44
Byrd et al (1995)	33	0.78	0.20	+++	0.39	1.16
Hee et al (1995)	6	0.31	0.17	(+)	-0.03	0.65
Andersson et at (1996)	6	0.50	0.42	N.S.	-0.34	1.34
Byrd et al (1997)	72	0.13	0.11	N.S.	-0.09	0.35

Model with same slope for Log Nicotine Yield per study

	Deviance	(DF)	P	95%CIl	95%CIu
	231.27	(296)			
Log Nicotine Yield	0.18	0.03	+++	0.11	0.25
Log cigs/day	0.69	0.06	+++	0.58	0.81

Model with same slope for Log Nicotine Yield per study, different slope for log cigs/day by Cotinine Type

	n	Deviance	(DF)	Drop Dev	P	95%CIl	95%CIu
		230.21	(294)	1.06	N.S.		
Log Nicotine Yield		0.19	0.03	+++		0.12	0.25
Log cigs/day (Plasma)	193	0.68	0.06	+++		0.56	0.80
Log cigs/day (Urine)	111	0.98	0.25	+++		0.49	1.46
Log cigs/day (Saliva)	6	0.67	0.43	N.S.		-0.17	1.51

Model with same intercept and slope for Log Nicotine Yield per study

	n	Deviance	(DF)			
		495.07	(305)			
		Estimate	S.E.	P	95%CIl	95%Ciu
Constant		3.93	0.19	+++		
Cotinine Type						
Plasma	193	Aliased				
Urine	111	-1.98	0.09	---	-2.17	-1.80
Saliva	6	0.01	0.12	N.S.	-0.22	0.24
Log Nicotine Yield		0.29	0.04	+++	0.20	0.37
Log cigs/day		0.54	0.06	+++	0.42	0.66

Table 7

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, cotinine >0 and nicotine yield >0

<u>Weighted on number of subjects</u>

Log Cotinine

Model with same intercept and slope for Log Nicotine Yield per study, including Sex

		Deviance	(DF)	Drop Dev	P		
		488.18	(303)	6.89	N.S.		
		Estimate	S.E.	P		95%CIl	95%Ciu
Constant		3.74	0.21	+++			
		Estimate	S.E.	P		95%CIl	95%CIu
Cotinine Type							
Plasma	193	Aliased					
Urine	111	-1.96	0.10	---		-2.16	-1.77
Saliva	6	0.07	0.12	N.S.		-0.17	0.30
Log Nicotine Yield		0.29	0.05	+++		0.19	0.38
Log cigs/day		0.59	0.07	+++		0.46	0.72
Sex							
Males	267	Aliased					
Females	10	0.09	0.04	+		0.00	0.18
Both	33	0.05	0.04	N.S.		-0.03	0.14

Table 8

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, cotinine >0 and nicotine yield >0

Weighted on number of subjects

Plasma and Saliva Only

Log Cotinine

		Deviance	(DF)
Model 1		576.42	(198)
Model : means for each study		311.85	(190)
: + log cigs/day only		202.23	(189)
: + log Nic Yield only		283.72	(189)

Log Cotinine predicted by
Log Nicotine Yield per Study
Adjusted by log number of cigarettes per day

		Deviance	(DF)			95%CIl	95%CIu
		164.27	(180)				
		Estimate	S.E.	P		95%CIl	95%CIu
Heller et al (1982)	146	0.76	0.21	+++		0.35	1.17
Hill et al (1983)	12	0.42	0.16	++		0.11	0.74
Russel et al (1986)	6	0.08	0.19	N.S.		-0.30	0.47
Bridges et al (1986,90)	5	0.24	0.28	N.S.		-0.31	0.80
Sepkovic et al (1990)	8	0.02	0.05	N.S.		-0.08	0.13
Hofer et al (1991)	4	0.24	0.13	(+)		-0.02	0.51
Rosa et al (1992)	4	0.83	0.28	++		0.27	1.39
Woodward & Tunstall-Pedoe	8	0.27	0.10	++		0.08	0.47
Andersson et at (1996)	6	0.50	0.49	N.S.		-0.46	1.46

Model with same slope for Log Nicotine Yield per study

		Deviance	(DF)				
		187.12	(188)				
Log Nicotine Yield		0.16	0.04	+++		0.08	0.25
Log cigs/day		0.68	0.07	+++		0.55	0.82

Model with same intercept and slope for Log Nicotine Yield per study

		Deviance	(DF)				
		337.98	(196)				
		Estimate	S.E.	P		95%CIl	95%CIu
Constant		3.39	0.21	+++			
Log Nicotine Yield		0.24	0.05	+++		0.14	0.33
Log cigs/day		0.73	0.07	+++		0.59	0.86
		Deviance	(DF)	Drop Dev	P		
		332.48	(194)	5.50	N.S.		
		Estimate	S.E.	P		95%CIl	95%CIu
Constant		3.23	0.23	+++			
Log Nicotine Yield		0.23	0.05	+++		0.13	0.33
Log cigs/day		0.77	0.07	+++		0.62	0.91
Sex							
Males	164	Aliased					
Females	7	0.08	0.05	(+)		-0.01	0.17
Both	28	0.04	0.04	N.S.		-0.04	0.13

Table 9

Meta-analysis of studies in Scherer 1999A Table 3
Frequency Table
Studies of Interest: number of cigarettes >0, CO >0 and nicotine yield >0

		Number of Data points per study		Total Number of Subjects	
		1	2	1	2
		%Hb	ppm	%Hb	ppm
Study					
	N	188	27	3254	3887
Russell et al (1980)		5	0	222	
Jaffe1981		0	8		200
Heller et al (1982)		146	0	146	
Ebert et al (1983)		0	3		76
Hill et al (1983)		12	0	370	
Russel et al (1986)		6	0	392	
Bridges et al (1986,90)		5	0	269	
Maron and Fortmann (1987)		0	4		713
Sepkovic et al (1990)		8	0	1747	
Hofer et al (1991)		0	4		144
Woodward & Tunstall-Pedoe 1992		0	8		2754
Hee et al (1995)		6	0	108	

CO

N	188	27
Mean	4.21	25.25
St.Err	0.18	1.72
St.Dev	2.50	8.93
Var P		***
F		686.27
P		+++

Table 10

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, CO >0 and nicotine yield >0

<u>Weighted on number of subjects</u>

Log CO

	Deviance	(DF)
Model 1	4101.38	(214)
Model : means for each study	167.86	(203)
: + log cigs/day only	113.70	(202)
: + log Nic Yield only	161.08	(202)

Log CO predicted by
Log Nicotine Yield per Study
Adjusted by log number of cigarettes per day

Deviance	(DF)
95.09	(190)

		Estimate	S.E.	P	95%CIl	95%CIu
Russell et al (1980)	5	-0.10	0.19	N.S.	-0.48	0.27
Jaffe1981	8	0.06	0.07	N.S.	-0.08	0.20
Heller et al (1982)	146	0.33	0.15	+	0.03	0.64
Ebert et al (1983)	3	0.10	0.14	N.S.	-0.17	0.38
Hill et al (1983)	12	0.13	0.12	N.S.	-0.10	0.36
Russel et al (1986)	6	0.16	0.14	N.S.	-0.13	0.44
Bridges et al (1986,90)	5	0.05	0.21	N.S.	-0.36	0.46
Maron and Fortmann (1987)	4	0.07	0.05	N.S.	-0.02	0.16
Sepkovic et al (1990)	8	-0.02	0.04	N.S.	-0.10	0.06
Hofer et al (1991)	4	0.11	0.10	N.S.	-0.09	0.31
Woodward & Tunstall-Pedoe	8	0.32	0.07	+++	0.18	0.46
Hee et al (1995)	6	0.32	0.15	+	0.03	0.61

Model with same slope for Log Nicotine Yield per study

Deviance	(DF)
107.23	(201)

	Estimate	S.E.	P	95%CIl	95%CIu
Log Nicotine Yield	0.08	0.02	+++	0.04	0.13
Log cigs/day	0.46	0.05	+++	0.37	0.55

Model with same slope for Log Nicotine Yield per study, different slope for log cigs/day by CO Type

Deviance	(DF)	Drop Dev	P
107.07	(200)	0.16	N.S.

		Estimate	S.E.	P	95%CIl	95%CIu
Log Nicotine Yield		0.08	0.02	+++	0.04	0.13
Log cigs/day (%Hb)	188	0.48	0.06	+++	0.36	0.59
Log cigs/day (ppm)	27	0.42	0.08	+++	0.27	0.58

Model with same intercept and slope for Log Nicotine Yield per study

Deviance	(DF)	
319.69	(211)	140.20

		Estimate	S.E.	P	95%CIl	95%CIu
CO Type						
%Hb	188	Aliased				
ppm	27	1.48	0.03	+++	1.42	1.54
Log Nicotine Yield		0.12	0.04	+++	0.05	0.19
Log cigs/day		0.56	0.06	+++	0.45	0.68

Model with same intercept and slope for Log Nicotine Yield per study, including Sex

Deviance	(DF)	Drop Dev	P
314.17	(209)	5.52	N.S.

		Estimate	S.E.	P	95%CIl	95%CIu
Constant		-0.11	0.20	N.S.		
CO Type						
%Hb	188	Aliased				
ppm	27	1.47	0.03	+++	1.41	1.54
Log Nicotine Yield		0.12	0.04	++	0.05	0.19
Log cigs/day		0.59	0.06	+++	0.47	0.71
Sex						
Males	168	Aliased				
Females	16	0.07	0.04	(+)	-0.01	0.15
Both	31	0.01	0.04	N.S.	-0.07	0.09

Table 11

Meta-analysis of studies in Scherer 1999A Table 3
Frequency Table
Studies of Interest: number of cigarettes >0, SCN >0 and nicotine yield >0

		Number of Data points per study		Total Number of Subjects	
		1	2	1	2
		%Hb	ppm	%Hb	ppm
Study					
	N	29	8	4106	150
Jaffe et al (1981)		0	8		150
Hill et al (1983)		12	0	370	
Bridges et al (1986,90)		5	0	269	
Maron and Fortmann (1987)		4	0	713	
Woodward & Tunstall-Pedoe (1992)		8	0	2754	

Values in Body: Thyocyanate (ug)

N	29	8
Mean	141.59	169.13
St.Err	4.98	6.98
St.Dev	26.84	19.75
Var P		N.S.
F		7.27
P		+

Table 12

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, SCN >0 and nicotine yield >0

<u>Weighted on number of subjects</u>

Log SCN

	Deviance	(DF)
Model 1	79.79	(36)
Model : means for each study	35.71	(32)
: + log cigs/day only	31.17	(31)
: + log Nic Yield only	33.96	(31)

Log SCN predicted by
Log Nicotine Yield per Study
Adjusted by log number of cigarettes per day

		Deviance	(DF)			
		27.76	(26)			
		Estimate	S.E.	P	95%CIl	95%CIu
Jaffe (1981)	8	-0.05	0.12	N.S.	-0.29	0.20
Hill et al (1983)	12	0.17	0.17	N.S.	-0.19	0.52
Bridges et al (1986,90)	5	0.04	0.30	N.S.	-0.59	0.66
Maron and Fortmann (1987)	4	0.05	0.07	N.S.	-0.09	0.19
Woodward & Tunstall-Pedoe (1992)	8	0.13	0.11	N.S.	-0.09	0.35

Model with same slope for Log Nicotine Yield per study

	Deviance	(DF)			
	29.52	(30)			
	Estimate	S.E.	P	95%CIl	95%CIu
Log Nicotine Yield	0.06	0.05	N.S.	-0.03	0.15
Log cigs/day	0.16	0.08	+	0.01	0.32

Model with same slope for Log Nicotine Yield per study including Sex

		Deviance	(DF)			
		10.84	(29)			
		Estimate	S.E.	P		
Constant		3.89	0.19	+++		
Sex						
Males	13	Aliased				
Females	8	0.18	0.03	+++	0.13	0.24
Both	16	0.05	0.07	N.S.	-0.09	0.19
Log Nicotine Yield		0.08	0.03	+	0.02	0.14
Log cigs/day		0.34	0.05	+++	0.23	0.45

Table 12

Meta-analysis of studies in Scherer 1999A Table 3
Linear Regression
Studies of Interest: number of cigarettes >0, SCN >0 and nicotine yield >0

<u>Weighted on number of subjects</u>

Log SCN

Model with same intercept and slope for Log Nicotine Yield per study

		Deviance	(DF)		
		56.82	(33)		

		Estimate	S.E.	P	95%CIl	95%Ciu
Constant		4.08	0.29	+++		
SCN Type						
Plasma	29	Aliased				
Saliva	8	0.10	0.12	N.S.	-0.14	0.34
Log Nicotine Yield		-0.04	0.06	N.S.	-0.15	0.08
Log cigs/day		0.28	0.10	++	0.08	0.48

Model with same intercept and slope for Log Nicotine Yield per study, including Sex

		Deviance	(DF)	Drop Dev	P
		28.03	(31)	28.79	***

		Estimate	S.E.	P	95%CIl	95%Ciu
Constant		3.55	0.25	+++		
SCN Type						
Plasma	29	Aliased				
Saliva	8	0.10	0.09	N.S.	-0.08	0.28
Log Nicotine Yield		0.03	0.04	N.S.	-0.06	0.12
Log cigs/day		0.42	0.08	+++	0.25	0.58
Sex						
Males	13	Aliased				
Females	8	0.15	0.04	+++	0.07	0.23
Both	16	0.22	0.04	+++	0.14	0.31

Table 13

Summary of estimates of compensation index (α) for nicotine yield (adjusted for cigarettes/day)

Biomarker	No of studies	No of data points	Compensation Index (S.E.)	% of variance explained[1]	Heterogeneity[2]
Primary Biomarkers					
Nicotine	11	297	0.67 (0.04)	16.7%	N.S.
- in plasma	7	180	0.65 (0.06)	17.6%	N.S.
- in urine	5	256	0.63 (0.07)	9.7%	p<0.01
Cotinine	12	310	0.82 (0.03)	8.7%	p<0.001
- in plasma or saliva	9	199	0.84 (0.04)	7.5%	p<0.01
Secondary Biomarkers					
CO	12	215	0.92 (0.02)		p<0.01
SCN	5	37	0.94 (0.05)	5.3%	N.S.

1 Explained by log nicotine yield after adjustment for study means and log cigarettes/day
2 N.S. = p≥0.1

Table 14

Summary of estimates of slope for log cigarettes/day (adjusted for log nicotine yield)

Biomarker	Slope (S.E.)	% of variance explained[1]
Nicotine	0.66 (0.06)	32.4%
- in plasma	0.62 (0.06)	35.0%
- in urine	1.03 (0.11)	24.6%
Cotinine	0.69 (0.06)	31.6%
- in plasma or saliva	0.68 (0.07)	34.0%
CO	0.46 (0.05)	33.4%
SCN	0.16 (0.08)	13.1%

1 Explained by log cigarettes/day after adjustment for study means and log nicotine yield