Estimating compensation from brand switching studies

A commentary on the material considered in the review paper by Scherer published in Psychopharmacology (**145**: 1-20)

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EXECUTIVE SUMMARY

When switching to a brand with a reduced machine nicotine yield, smokers may compensate by altering how the cigarettes are smoked or the number of cigarettes smoked. This document considers the evidence in the 1999 review by Scherer relating to brand-switching studies, in which variation in nicotine uptake (as usually measured by cotinine) or daily cigarette consumption is related to variation in the nicotine yield of the brand smoked. Most attention is given to those 11 studies considered by Scherer to be most suitable for determining compensation.

Methods of estimating compensation are discussed and an index derived which takes the value 1 for full compensation (no change in intake following a change in yield) and 0 for no compensation (proportional change in intake the same as the proportional change in yield). Difficulties in estimating the compensation index from the published material are discussed; these derive mainly from failure to present individual subject data, and presentation of statistics which show between-person variability in intake for different cigarettes, but not between-person variability in change in intake.

For each of the 11 studies, the available data are reviewed, and compensation indices with approximate 95% confidence intervals are presented. Where, in a study, smokers had switched between three or more types of cigarette, Scherer had estimated compensation indices relating intake to yield for various pairwise comparisons. Here, a more appropriate single estimate of the compensation index is derived based on all the available data for a specific group of subjects. Overall the 11 studies provided 14 independent estimates of the compensation index.

All 14 estimates of the compensation index are significantly greater than 0, so clearly compensation occurs. With one minor exception, all the estimates are significantly less than 1, so compensation is not complete. With two exceptions, compensation indices are all estimated to be in the range 0.71 to 0.86. Lower compensation indices were seen in two studies where, unusually, the low nicotine yield experimental cigarettes had extremely high tar/nicotine ratios. Provided attention is restricted to studies in which tar/nicotine ratios are reasonably typical of cigarettes on the market, a compensation index around 0.75 would be an appropriate estimate. An index of 0.75 would imply that a 50% reduction in machine nicotine yield would result in a 16% reduction in nicotine intake and that a 90% reduction in yield would result in a 44% reduction in intake.

The conclusion that compensation is substantial, but certainly not complete seems consistent with evidence from other brand-switching studies cited by Scherer and from limited observational studies of changes in intake within smokers.

Compensation in terms of increased cigarette consumption is also discussed, but in less detail. The evidence suggests that it is quite minor, with even a 10 fold reduction in yield being associated with an increase in consumption of only around 20%.

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1. Introduction

The literature review of smoking behaviour and compensation by Scherer (1999)[1] summarizes, in Table 4, evidence from selected brand switching studies in an attempt to quantify the extent of compensation. The studies were selected based on four criteria:

1. The difference in the nicotine yield of the old and new cigarette should be at least 0.1 mg/cigarette.
2. Nicotine uptake should be determined by cotinine in blood (serum or plasma) or by measuring the area under the curve (AUC) for nicotine blood levels over several hours.
3. The new cigarette should be smoked for at least two days.
4. The numbers of smokers investigated for each condition should be five.

Table 4 shows, for 25 brand switching situations within 11 studies, data including the number of subjects, the duration of the study (days during which the new cigarette was smoked), the machine nicotine yields of the two cigarettes being compared (Y_o, Y_1), the biomarker used (nicotine or cotinine) and the biomarker levels of the two cigarettes (B_o, B_1). Here the subscript 0 refers to the old cigarette and 1 to the new cigarette. Also included are three derived statistics:

% change in nicotine yield $\quad Y_C = 100(Y_1 - Y_0)/Y_0$, (1)

% change in biomarker $\quad B_C = 100(B_1 - B_0)/B_0$, and (2)

compensation index $\quad I_1 = 1 - B_C / Y_C$ (3)

The compensation index takes the value 1 ("complete compensation") if the biomarker level is unchanged, i.e. if $B_0 = B_1$ so that $B_C = 0$. It takes the value 0 ("no compensation") if the percent changes are identical, i.e. if $B_C = Y_C$.

2. <u>Comparing Scherer's compensation index and the index I usually use</u>

When analysing compensation previously I have used an alternative index, I_2, defined by the relationship

$$B = \mu Y^{1-I_2} \tag{4}$$

where B is the biomarker level, Y is the nicotine yield, μ is a constant and I_2 again takes the value 0 for no compensation and 1 for complete compensation. Since

$$B_0 = \mu Y_0^{1-I_2} \text{ and} \tag{5}$$

$$B_1 = \mu Y_1^{1-I_2} \tag{6}$$

it follows that

$$B_1 / B_0 = (Y_1 / Y_0)^{1-I_2} \tag{7}$$

so that

$$\log(B_1 / B_0) = (1 - I_2)\log(Y_1 / Y_0) \text{ and} \tag{8}$$

$$I_2 = 1 - \frac{\log(B_1 / B_0)}{\log(Y_1 / Y_0)} \tag{9}$$

Since $B_1 / B_0 = 1 + \left(\dfrac{B_1 - B_0}{B_0}\right)$, (10)

since $Y_1 / Y_0 = 1 + \left(\dfrac{Y_1 - Y_0}{Y_0}\right)$ and (11) since $\log(1+x)$ approximately equals x for small x, it can be seen that

$$I_2 \cong 1 - \frac{(B_1 - B_0)/B_0}{(Y_1 - Y_0)/Y_0} = I_1 \tag{12}$$

Thus the compensation index used by Scherer can be viewed as a reasonable approximation to the index I normally use. The advantage of the formula I use is that it implies a more simple relationship of biomarker to yield, with 1-I_2 being the slope of the line relating log B to log Y. As B is often found to be reasonably approximated by a log normal distribution, this makes I_2 estimable by simple linear regression in situations where there are more than two pairs of data points.

3. Estimating the compensation index

In a study where B and Y are determined for different cigarettes smoked by the same individual, the correct procedure for estimating the mean of the compensation index (either I_1 or I_2) is based on averaging individual subject estimates. Thus one should, theoretically, estimate I_2 by

$$\hat{I}_2 = 1 - \sum_{i=1}^{n} \left(\frac{L_{1i} - L_{0i}}{M_{1i} - M_{0i}} \right) / n \tag{13}$$

where L = log B, M = log Y, the first subscript references the cigarette and the second subscript i references individual (i=1, … n).

In practice, individual person data are not available for any of the papers cited by Scherer in his Table 4, and one has to make do with estimates of the form:

$$\hat{I}_2 = 1 - \frac{\overline{L}_1 - \overline{L}_0}{\overline{M}_1 - \overline{M}_0} \tag{14}$$

where $\overline{L}_0$ is the mean of the n readings of L_0, etc.

In some of the studies, as we will see in section 6, the yields of the two cigarettes are fixed, and estimates (1) and (2) are therefore the same. However, in other studies, where subjects switch from their own brand, which may vary, the two estimates are not identical. This is discussed further in section 6.

4. Variability of the compensation index

In brand switching studies where the subjects switch between two brands with known nicotine yields, the factor that determines the variability of the compensation index is the between-subject variance of $\log(B_1/B_0)$. Many of the papers provide information on the between-subject variance of B_1 and of B_0 separately, but this is of no use. One could imagine a study where subjects have a wide range of B_0 values, but all of them reduce by a very similar factor on brand switching so that B_1/B_0 and hence the estimated compensation index has quite small variability.

The situation is somewhat more complex when there is variation between subjects in Y as well as in B. This is discussed further in the next section.

5. A regression approach

In some studies, as discussed in section 6, some of the sets of data considered by Scherer are not independent as they involve the same subjects. Thus in the first study he considers, by Benowitz *et al*, the same subjects have data for three cigarettes, with changes between cigarette 1 and cigarette 2 considered on the first line of Table 4, and changes between cigarette 1 and cigarette 3 considered on the second line. In principle, data from one set of subjects should be used to generate a single estimate of the compensation index.

Also individual subjects may vary, not only in their biomarker level, B, but also in the value of the yield, Y, associated with the cigarette. Typically this occurs if subjects switch from the brand they usually smoke (which may vary from subject to subject) to one or more experimental cigarettes.

To address both these problems, a regression approach can be used. Suppose that there are m subjects (i=1, … m), each observed when smoking n different cigarettes (i=1, … n). We use the model (as for formula 4)

$$B_{ij} = \mu_i Y_{ij}^{1-I_2} \tag{15}$$

Note that this assumes there is a common compensation index I_2 to all subjects but that the factor μ_i varies by subject. Taking logarithms this gives us the linear regression equation

$$L_{ij} = Q_i + (1 - I_2)M_{ij} + E_{ij} \tag{16}$$

where, as before, $L = \log B$ and $M = \log Y$ and we also have $Q = \log \mu$. E_{ij} is the error term which is considered to be normally distributed and independent of *i* and *j* with variance σ^2. Note that this formulation assumes that there is error in determining the biomarker level for a given subject and cigarette, but not in determining the yield. Although there is some error in determining machine nicotine yield this will be relatively small compared to the error in determining the biomarker level.

For a single subject, *i*, the slope of the regression line, $S = 1 - I_2$ is estimated by

$$\hat{S}_i = \frac{\sum_{j=1}^{n}(M_{ij} - \overline{M}_i)(L_{ij} - \overline{L}_i)}{\sum_{j=1}^{n}(M_{ij} - \overline{M}_i)^2} \tag{17}$$

where $\overline{M}_i$ and $\overline{L}_i$ are the individual subject means of log Y and log B respectively.

The variance of the slope estimate is given by

$$\operatorname{var}\hat{S}_i = \sigma^2 / \sum_{j=1}^{n} (M_{ij} - \overline{M}_i)^2 \tag{18}$$

If an overall estimate of slope, S, is obtained from the mean of the individual slope estimates, its variance is given by

$$\operatorname{var} S = \sigma^2 \overline{U}_i / m \tag{19}$$

where $\overline{U}_i$ is the mean of the estimates of $U_i = 1/\sum_{j=1}^{n}(M_{ij} - M_i)^2$ for each subject. Clearly where the subjects all switch between the same brands, U_i will be the same for each subject. Since S = 1-I_2 the variance of I_2 will equal the variance of S.

The above suggests that if one has an estimate of the variability of the compensation index based on a study (or studies) with known sample size and known variation in yields, one can also estimate the variability of the compensation index for other studies with known sample size and known variation in yields, provided that one is prepared to accept that the (proportional) error in determining the biomarker level in each study is the same. Although this may not actually be exactly true, it gives us something to work on to assess (in the absence of any more precise information) whether compensation indices estimated for different studies are, or are not, statistically significant. It also gives us a basis for testing between study variability.

6. The individual studies

In the sections that follow, the main features and findings of the studies and data used by Scherer in his Table 4 are summarized. Among other things, we note any apparent errors we found in the data extracted by Scherer, and any information available on the variability of the ratio of biomarker levels (or yields) for the two cigarettes being compared.

6.1 Benowitz *et al* (1982)[2]

12 healthy subjects were studied in three 3-day treatment periods. In the first period they smoked their own usual brand of cigarettes (which had a nicotine yield averaging 1.23 mg, varying from 0.82 to 1.75 mg), while in the next two periods they smoked (in randomized order) either an experimental high nicotine cigarette (yield 2.5 mg) or an experimental low nicotine cigarette (yield 0.4 mg), the two experimental cigarettes having quite similar tar and CO values. On each day the subjects were instructed to smoke 30 cigarettes at a specified interval of 30 minutes and to a specified butt length. The 24 hour area under the curve for nicotine (AUC) was estimated as 707 ng/ml for the high nicotine, 574 ng/ml for the usual brand and 165 ng/ml for the low nicotine brand. It should be noted that nicotine data were only available for 8 of the 12 subjects, a point not noted by Scherer (1999). From the point of view of his table and the subsequent weighted calculations, 8 would have been a more appropriate number of subjects to include.

Detailed data presented by Benowitz *et al* include the individual subject data for usual brand nicotine yield and usual brand AUC. One does not know which of the 12 subjects were the 8 with experimental brand AUC values, or the individual AUC values themselves. However the authors do present results based on normalized AUC values by taking the ratio of the AUC to the machine delivery. They note that the "mean normalized AUC_{nic} ratio for high-nicotine to usual brand cigarettes was 0.50 ± 0.17 and that for high- to low-nicotine was 0.73 ± 0.15 (both $P<0.01$). Comparing normalized AUC_{nic} with the low-nicotine to usual brand cigarettes, the low-nicotine cigarettes were smoked slightly, but significantly, less intensively (ratio 0.84 ± 0.24)." The $\pm$ must refer to standard deviations rather than to standard errors to make the significances make sense though, as so often in published papers, this is not defined.

It should be noted that there is not a very direct correspondence between the mean normalized ratios of Benowitz *et al* to the compensation indices described above. However if there is no compensation, so that $B_1 / B_0 = Y_1 / Y_0$, their normalized ratio should take the value 1. Thus the fact that the ratio is significantly different from 1 for both the high-nicotine/usual brand and low-nicotine/usual brand argues against there being no compensation. As the compensation index increases from 0 to 1, the normalized ratio should decrease from 1 for the high nicotine/usual brand comparison and increase from 1 for the low nicotine/usual brand comparison. The fact that the normalized ratio for the second comparison is less than 1 implies reverse compensation (i.e. less intensive smoking with reduced nicotine). However, I note that with a sample size of 8, the ratio of 0.84 would have a standard error of 0.085, implying a non-significant t-statistic of 1.89, when comparing with a ratio of 1.

With complete compensation $B_1 = B_0$ and the normalized ratio should be equal to Y_0/Y_1. For the high nicotine/usual brand comparison the normalized ratio estimated by Benowitz is 0.50 (with standard error 0.06), which is similar to the ratio of (average) brand yield values of 0.49. The actual values of the compensation indices estimated from the mean AUC and yield values are $I_1 = 0.776$ and $I_2 = 0.706$, which are less than the value of about 1 suggested by the normalized ratio. Perhaps this is because there is variation in Y_0 so that estimating indices based on means is biased.

A problem with the analysis by Scherer for this study (and for some others discussed below) is that the data are treated as if they are two independent experiments on two different sets of people. In fact, of course, there was only one set of people and the results for the cigarette usually smoked were used in both analyses. As a result the two estimates are correlated. To estimate the compensation index properly one should use all the data in one analysis. Based on the data provided, I used formula (4), or the logarithmic form of it,

$$\log B = \log \mu + (1 - I_2)\log Y$$

to estimate I_2 by linear regression. The results are shown below.

Brand	Yield (Y)	AUC (B)	Fitted AUC
Low nicotine	0.40	165	180.5
Usual brand	1.23	574	454.9
High nicotine	2.50	707	815.3

Fitted equation : $\log B = 5.950 + 0.823 \log Y$ $r^2 = 0.93$

Estimated compensation index : $I_2 = 0.177$.

The fit seems moderate, and the overall data suggest little compensation. I note that, based on just the first two data pairs, I_2 is estimated as -0.110, while based on just the last two data pairs, it is estimated as 0.706.

I also note that the standard deviation of the AUC value for the usual brand was estimated as 175, suggesting a standard error based on the mean of eight readings of 61.9. The differences between the actual and fitted values of AUC are rather more than this, suggesting that the data do not fit this model all that well (though this can only be tested properly by a within-subject analysis). In contrast, fitting the model with no compensation fits still worse (fitted AUC values are 151.6, 466.2 and 947.5) and the model with full compensation is hopeless, as the AUC values clearly do vary far more than by chance.

In conclusion, this study suggests moderate, and statistically significant, compensation with little evidence of any meaningful variation over the range of nicotine values tested. The study is, of course, very small and interpretation is limited by the way the data are presented.

6.2 Fagerstrom (1982)[3]

12 healthy subjects were studied in three 4-week treatment periods. As in the previous study, the subjects smoked their own usual brand of cigarettes (details not provided) and then smoked (in randomized order) either of two cigarettes, one with 0.5 mg nicotine and one with 1.1 mg nicotine, the two cigarettes having much more similar tar and CO values. Unlike the previous study, subjects were not constrained to smoke a fixed number of cigarettes per day. The numbers of cigarettes smoked per day for the 0.5 mg and 1.1 mg nicotine cigarettes were reported as, respectively, quite similar values of 27.4 and 25.5. Cotinine was measured for the two experimental cigarettes only, and was 270 ng/ml for the 0.5 mg nicotine cigarette and 319 ng/ml for the 1.1 mg nicotine cigarette. This was based on only 7 subjects, again a point Scherer did not note.

No individual subject details are given, or estimate of the variability of the cotinine ratio for the two experimental cigarettes. Based on the mean yields and cotinine values, the compensation index can be estimated as 0.788. However this is likely to have considerable variability. The author states that the 49.0 ng/ml difference in cotinine is only 30% of the standard deviation, indicating a standard error for a mean based on 7 subjects of 62 ng/ml. The standard error of the mean difference will be less than indicated by the value of 87 ng/ml assuming independence, but could easily be 30 or 40 ng/ml I would guess. If so, the true ratio could quite well be, say, 0.65, rather than the value of 0.85 observed, which would give a compensation index estimate of 0.45 rather than the 0.79 estimated.

The data seem consistent with quite full compensation, but not with no compensation.

6.3 Russell *et al* (1982)[4]

12 volunteers attended on nine occasions over a period of 12 weeks. On occasions 1 and 3 the subjects had been smoking their usual brand (mean nicotine 1.33 mg) in their usual way, on occasion 2 they had been smoking a popular commercial brand of middle tar medium nicotine (1.3 mg) throughout the day, while on subsequent occasions they had been smoking an experimental low tar low nicotine cigarette (0.7 mg). Cotinine was only determined at the start on the usual brand (350 ng/ml) and after 10 weeks on the low nicotine brand (246 ng/ml) and then only on 8 of the 12 subjects, a point not mentioned by Scherer (1999) in Table 4. Cigarette consumption was virtually identical at these two time points, 23.8 cigs/day for usual brand and 23.9 cigs/day for low nicotine.

The authors present the individual nicotine yield values for all 12 subjects (which range only from 1.1 to 1.5 mg), and also present (graphically) the usual brand and low tar cotinine values individually for the 8 subjects where this was available. However, the two sets of values cannot be linked, so that compensation cannot be estimated for individual subjects.

From the means, I_2 can be estimated as 0.451. This is clearly significantly greater than 0, as a within-subject paired t-test showed the cotinine levels had declined significantly ($p<0.001$). It is also likely to be significantly less than 1, as none of the 8 subjects had proportional reductions in cotinine that were as large as that seen in nicotine yield (47% based on 1.33 and 0.7 mg).

6.4 Robinson *et al* (1982, 1983)[5,6]

16 heavy smokers smoked their usual brand (mean nicotine yield 0.96 mg) for two weeks, a lower yield product (0.64 mg) for 3 weeks and then a still lower yield vented product (0.38 mg) for 3 weeks. Compared to their usual brand, cigarette consumption increased by 16% and 11% for the nominal nicotine delivery brands. Cotinine values were only presented for usual brand (284 ng/ml) and the vented product (244 ng/ml).

The analyses are not presented in a way that allows any proper estimation of the compensation index or its variance. From the means, I estimate I_2 is 0.84. It is clear that the no compensation model does not fit the data, as the cotinine values are not consistent with the 60% reduction seen for the yields, but it is unclear if they are inconsistent with a full compensation model.

6.5 Haley *et al* (1985)[7]

Two groups of six subjects were involved, one smokers of low nicotine cigarettes (mean 0.73 mg) and one smokers of high nicotine cigarettes (mean 1.03 mg). In each group, subjects had 7 cotinine measurements made at wekly intervals, following *ad libitum* smoking for a week of cigarettes of varying nicotine brand. Thus in group 1, the sequence was usual brand (0.73 mg), 0.06 mg, 0.40 mg, 0.70 mg, 0.90 mg and 1.30 mg and usual brand again. In group 2, the sequence was usual brand (1.03 mg), 1.30 mg, 0.90 mg, 0.70 mg, 0.40 mg, 0.06 mg and usual brand again. Daily cigarette consumption data were also available for all occasions except the repeat usual brand at the end.

Individual subject data are not given, and Scherer treats the data as allowing independent estimates of compensation index to be made for multiple comparisons with usual brand. They also do not use all the data presented by Haley *et al* (in their figure 5). Using all the data, it is possible to do more appropriate analyses as follows:

Group 1

Yield (Y) (mg)	Cotinine (B) (ng/ml)	Fitted B (ng/ml)	Cig. consumption (cigs/day)
0.73	175	170.4	19.5
0.06	49	53.2	16.8
0.40	154	128.7	14.7
0.70	162	167.1	14.3
0.90	203	187.9	15.7
1.30	183	223.0	12.8
0.73	175	170.4	-

Fitted equation : $\log B = 5.285 + 0.466 \log Y$ $r^2 = 0.94$
Estimated compensation index : $I_2 = 0.534$
Relating consumption to yield : $I_c = 1.045$ $r^2 = 0.12$

Group 2

Y (mg)	B (ng/ml)	Fitted B (ng/ml)	Consumption (cigs/day)
1.03	253	211.2	24.5
1.30	185	220.4	22.7
0.90	214	206.0	31.2
0.70	203	196.8	28.2
0.40	154	177.6	30.8
0.06	129	125.5	30.8
1.03	220	211.2	-

Fitted equation : $\log B = 5.347 + 0.183 \log Y$ $r^2 = 0.72$
Estimated compensation index : $I_2 = 0.817$
Relating consumption to yield : $I_c = 1.070$ $r^2 = 0.35$

In the above I_c represents the compensation index based on consumption rather than cotinine, calculated in an analogous way to I_2. For both data sets I_c is quite close to 1 implying cigarette consumption is little affected by yield.

For both data sets, these conclusions regarding the compensation index (for cotinine) can be made:

(i) The fitted model indicates some compensation, $I_2 = 0.534$ and 0.817, with the fit to the model not apparently that unreasonable,

(ii) There is a clear tendency for cotinine values to vary (in particular, they are notably lower for 0.06 mg cigarettes) so $I_2 = 1$ does not explain the data,

(iii) The variation in cotinine is very clearly proportionately much less than the corresponding (20-fold) variation in yield, so $I_2 = 0$ certainly does not explain the data.

6.6 Benowitz *et al* (1986)[8]

Two groups of 11 volunteers were involved. In each group, subjects smoked their own brand of cigarettes for two days and then (in random order) a high nicotine cigarette or a low nicotine cigarette for four days. The relevant data from the two groups are shown in the table below. Scherer did not use the data from the usual brand in their Table 4 for some reason, but it seems reasonable to use the complete data to estimate compensation.

Group 1

Brand	Yield (Y)	AUC(B)	Fitted AUC	Cigs/day
Usual	1.1	478	415.8	29
High	1.0	349	407.0	30
Low	0.4	336	331.2	39

Fitted equation : $\log B = 6.009 + 0.225 \log Y$ $r^2 = 0.422$
Estimated compensation index : $I_2 = 0.775$
Relating consumption to yield : $I_c = 1.290$ $r^2 = 1.00$

Group 2

Brand	Yield (Y)	AUC(B)	Fitted AUC	Cigs/day
Usual	1.06	338	327.9	28
High	1.0	313	322.8	28
Low	0.1	174	173.9	32

Fitted equation : $\log B = 5.777 + 0.269 \log Y$ $r^2 = 0.993$
Estimated compensation index : $I_2 = 0.731$
Relating consumption to yield : $I_c = 1.057$ $r^2 = 1.00$

The data for group 2, which gave an I_2 of 0.731, fit the model well and clearly exclude $I_2 = 0$ and $I_2 = 1$ as viable alternatives.

The data for group 1 give a similar I_2 value, 0.775, but the fit to the model seems poor, because of the very different AUC values of 478 and 349 for quite similar Y values of 1.1 and 1.0. The data probably exclude $I_2 = 0$, which would give fitted values of 553,503 and 201 as against 478, 349 and 336 observed, but do not clearly seem to misfit $I_2 = 1$ where the fitted values would all be 383.

6.7 Armitage *et al* (1988)[9]

21 regular smokers of middle tar cigarettes smoked their own product for a 2-week run-in period and then, in the next three two-week periods smoked, in a balanced order, experiment cigarettes with nicotine yields of 1.7, 1.4 or 0.8 mg. Towards the end of each period, a blood sample was taken for cotinine estimation, the mean values corresponding to the three cigarettes being 313, 317 and 268 ng/ml. (It should be noted that the value of 313 ng/ml was only based on 20 of the smokers.) The mean weekly cigarette consumption was noted to be almost identical for the three cigarettes (though the actual means are not given). Scherer reports a figure of 4 days for the period during which the new brand was smoked when it should have been 14 days.

Individual subject data are not given, and Scherer (1999) give compensation data separately for the comparison of the 1.4 and 1.7 mg cigarettes and for the comparison of the 1.4 mg and 0.8 mg cigarettes. Using all the data in one analysis, we have:

Yield (Y)	Cotinine (B)	Fitted B
1.7	313	320.7
1.4	317	306.8
0.8	268	270.3

Fitted equation : $\log B = 5.650 + 0.227 \log Y$ $r^2 = 0.90$
Estimated compensation index : $I_2 = 0.773$

It is clear the data do not fit $I_2 = 0$ for which fitted cotinine values would be 409.4, 337.1 and 192.7 ng/ml. $I_2 = 1$ clearly fits the data much better, though it is unclear whether the misfit to the implied common (geometric) mean of 298.5 ng/ml is significant.

6.8 Kolonen *et al* (1988)[10]

Eight smokers who habitually smoked medium-yield cigarettes took part in a cross-over study. In each of two periods separated by 2 weeks, subjects first had a 2-day non-smoking period, then smoked 10 cigarettes per day of the specified brand for 2 days and then smoked 20 cigarettes per day of the same brand for 2 days. The two brands tested were low nicotine (0.3 mg/cig) and medium nicotine (1.0 mg/cig). Mean cotinine values during the 20 cigs/day period were 219.2 ng/ml for the low nicotine brand and 309.3 ng/ml for the medium nicotine brand.

No individual person data are given and from the means I estimate I_2 as 0.71. It is clear that the no compensation model does not fit the data – this would give fitted values of 142.6 and 475.4 ng/ml. Probably $I_2 = 1$ does not either, as the difference of 90.1 ng/ml compares with a between-subject estimate of standard error of 80.5 ng/ml which would likely be more like 30 or 40 ng/ml if based on within subject estimates (which are not available).

6.9 Zacny and Stitzer (1988)[11]

10 smokers of high-yield cigarettes (1.0 mg nicotine) were switched in random order among five different commercially available cigarette brands with nicotine yields of 0.1, 0.4, 0.7, 1.1 (altered brands) and 1.0 (usual brand). Each cigarette was smoked for 5 days. No individual person data were presented. Scherer presents the data as if there were four independent groups each comparing one of the altered brands with the usual brand. Carrying out a combined analysis, we have:

Yield (Y) (mg)	Cotinine (B)*	Fitted B	C ig. consumption (cigs/day)
0.1	151.7	147.2	34.3
0.4	188.4	200.4	31.8
0.7	220.8	226.9	28.4
1.0	252.2	245.7	28.6
1.1	259.2	250.9	27.1

(*Note that Scherer gives slightly different values of 150, 187, 216, 254 and 258 ng/ml – these were presumably estimated from Figure 1 without realising the values are given in the text on page 622)

Fitted equation : $\log B = 5.504 + 0.222 \log Y$ $r^2 = 0.964$
Estimated compensation index : $I_2 = 0.778$
Relating consumption to yield : $I_c = 1.093$ $r^2 = 0.912$

It is clear that the model fits the data well. $I_2 = 0$ is clearly a nonstarter as cotinine values do not vary by anything like the 11-fold factor by which yields vary. $I_2 = 1$ also does not fit, as the authors report within-subject analyses showing that cotinine values vary significantly by yield. The same is true for I_c, which again significantly varies by yield.

6.10 Guyatt *et al* (1989)[12]

28 smokers smoked their own commercially available cigarettes (mean tar yield >10 mg) over a 5-month period during which cotinine and number of cigarettes/day were measured monthly. They were then asked to switch to another commercially available cigarette with a tar yield at least 3 mg lower and cotinine and cigarette consumption were recorded on six further occasions at 6-week intervals. Average machine nicotine yields were noted to have fallen from 1.36 to 0.91 mg following switching. Mean cotinine values were reported as 378 ng/ml for visits 2-6 (on their original cigarette) and as 309 ng/ml for visit 7 following switching, a change which was noted to be significant ($p<0.005$) based on within-subject differences. The authors also noted that cotinine did not change significantly over visits 7-12, but only presented values graphically. Cigarettes/day were noted to be 24.9 for visits 2-6 and 28.5 for visit 7, a difference which was not statistically significant. Again, no significant change was seen within visits 7-12.

Based on the mean cotinine values, I_2 can be estimated as 0.498. I_2 is clearly <1 as significant differences were noted between the two cotinine values. It is presumably significantly greater than 0 as well as the I_2 value is close to 0.5.

6.11 Frost *et al* (1995)[13]

434 Civil Servants who smoked, and who had previously successfully switched to a brand yielding about 10% less tar than their usual brand were randomly allocated to three groups:

(a) a "fast reduction" group changing to a brand of cigarettes with a tar yield of about half their usual brand;

(b) a "slow reduction" group which reduced to the same level in steps over several months; and

(c) a "control" group which continued smoking cigarettes with a tar yield 10% lower than their usual brand.

Data were collected at five points in time, pre-randomisation (i.e. when still smoking their original brand), at randomisation (i.e. after successfully switching to the brand with 10% less tar than usual), and two months, four months and six months post randomisation. The data included tar, nicotine, and CO yield of brand smoked, number of cigarettes smoked by time of visit and on the previous day and serum cotinine level.

Scherer uses data for the fast reduction and slow reduction groups as recorded at randomisation and six months later. For the fast reduction group, based on 99 subjects, nicotine yield fell from 1.32 to 0.81 mg while cotinine fell from 305 to 269 ng/ml, giving an I_2 estimate of 0.743. (Note that Scherer gives 302 not 305 ng/ml in Table 4 of his paper.) For the slow reduction group, based on 105 subjects, nicotine yield fell from 1.31 to 0.84 mg, while cotinine fell from 289 to 271 ng/ml, giving an I_2 estimate of 0.855.

Frost *et al* present their own estimates of the Compensation index (I_1) based on a within-subject analysis of changes from the mean of the values recorded pre-randomisation and at randomisation to the value recorded six months post randomisation, with adjustment for number of cigarettes smoked. The estimates they derive are 0.813 (95% CIU 0.723-0.902) for the fast reduction group and 0.777 (0.654-0.899) for the slow reduction group. This is the only study of those considered which gives valid confidence intervals for the compensation index. The results suggest that regardless of whether I_1 or I_2 is used, and regardless of whether adjustment is made for changes in cigarette consumption, the data do not fit either the model of full compensation or no compensation (though the data clearly show very substantial compensation).

It is interesting to note that this is the only study where cigarette consumption was reported to have decreased following reduction in brand nicotine yield, though the reduction was only slight, 8% in the fast reduction group and 5% in the slow reduction group.

7. <u>Overview of findings and discussion</u>

Table 1 summarizes some of the major data from the 14 independent datasets within the 11 studies considered by Scherer. Included in the table is not only an estimate of the compensation index, I_2, but also an estimate of its 95% confidence limit. This was derived by using formula 19, coupled with an estimate of σ derived from the Frost study and individual study estimates of m and $\overline{U}$. The Frost study data allowed estimates of σ to be made of 0.157 for the fast reducers and 0.201 for the slow reducers, which were averaged to give an overall estimate of 0.179 which was then used throughout for the estimation of the 95% limits of I_2. Note that quite small studies can provide quite narrow confidence limits for I_2 provided that the range of nicotine yields tested is wide. Thus, for example, in Group 1 in the Haley study, the confidence limits for the I_2 estimate of 0.53 are as narrow as 0.48-0.59 despite being based on only six subjects. This is because estimates were made over a 21.7 fold range of nicotine yield. The ratio of cotinine values associated with this, 3.73, is clearly quite far from the predicted ratio of 1, assuming full compensation, or 21.7, assuming no compensation.

The columns headed "significantly >0?" and "significantly <1?" are based on the tentative conclusions drawn in section 6 before an attempt had been made to estimate confidence limits of I_2. The confidence limits were broadly in line with these conclusions although in some cases they gave extra assurance concerning the conclusions.

Of the estimates of I_2, all 14 are significantly greater than 0, so clearly compensation occurs. However, with one minor exception - the Fagerstrom study which had quite wide confidence limits - all the estimates of I_2 are significantly less than 1, implying compensation is only partial. Of the 14 estimates of I_2, the lowest was 0.18 (Benowitz 1982), with three about 0.5 (Russell 1982, Haley 1985 group 1, Guyatt 1989), and all the rest in the range 0.71-0.86. While the overall data suggest an average I_2 value of about 0.75 (which would predict a 16% reduction in cotinine for a 50% reduction in yield), there is clearly heterogeneity between the study estimates. In particular, the Benowitz 1982 study has an estimated I_2 of 0.18 (95% CI 0.08-0.27) which is inconsistent with values in the range 0.71-0.86, while group 1 in the Haley study has an estimate of I_2 of 0.53 (0.48-0.59) with an upper 95% limit also inconsistent with that range.

Could there be something unusual about these two studies (Benowitz 1982 and Haley group 1) which might explain their relatively low I_2 estimates? As can be seen from Table 1, there is nothing particularly unusual about the duration of these studies and though the two studies investigated a relatively wide range of nicotine yields, other studies (Benowitz 1986 group 2 and Zacny and Stitzer) also had and gave I_2 values around 0.75. Table 2 investigates the possibility that the tar/nicotine yield ratio of the brands smoked may help to explain the heterogeneity. As can be seen from the data presented, in most of the studies the tar/nicotine ratio was reasonably constant over the brands tested, with tar reducing roughly in line with the reduction in nicotine. However, the two studies with low I_2 values are very different. In the Benowitz 1982 study, smokers reduced nicotine yields by a factor of over 6, while slightly increasing tar yields, while in the Haley study, nicotine yields were reduced over 20-fold with tar yields almost constant. Whereas in all the other studies, tar/nicotine ratios were typically in the range 8 to 16, in the Benowitz 1982 study a cigarette with a ratio of 79.5 was smoked, while in the Haley study cigarettes with ratios of 28.9 and 176.7 were smoked. It seems to this author that achieving full or nearly full compensation with a cigarette with a very high tar/nicotine ratio may be very difficult, due to the huge dose of tar one would have to take in to succeed, which may make the cigarettes unpalatable.

If one excludes the results of these two studies, restricting attention to three studies which kept the tar/nicotine ratio reasonably consistent (as is the situation in the market), then the I_2 estimates are much more consistent, with a mean of 0.72 and a median of 0.77.

There are difficulties coming to a precise answer, due to the way the results have been presented in the source papers, with individual subject data not presented and appropriate statistics based on within-subject changes usually not available, but the general conclusion, that compensation is substantial, but incomplete, seems clear enough.

Scherer's review refers on page 9 to a number of other studies which have investigated nicotine uptake following brand-switching. He cites the results of six other studies which showed an increase in nicotine uptake following switching to a brand with a higher nicotine yield, and of ten other studies which showed a decrease in uptake following switching to a brand with a lower nicotine yield. He comments that "in most of the investigations, it was found that the change in uptake was less than predicted from the change in cigarette yields, suggesting partial compensation." This is consistent with the present analysis of the 11 studies Scherer had selected for estimation of compensation indices, and no attempt has been made in this report to review this additional material in detail. Interestingly, Scherer cited only two studies where nicotine uptake did not change after switching to cigarettes with different nicotine deliveries - Fagerstrom and Benowitz 1986. As shown in this review, both these studies did show a tendency for nicotine uptake to decline with decreasing nicotine yield.

It should be noted that the data considered in detail in this review concern experimental brand-switching studies. I am aware of two observational studies in Germany which also reported results relating to compensation following brand-switching.

In one study (Adlkofer *et al* 1988[14]), in which I was a co-author and involved in the statistical analysis, six blood samples were taken from each of 51 male and 51 female smokers at intervals of 4-6 weeks for serum cotinine determination. Based on the nicotine yield and cotinine values at each of the six time points, an I_2 value of 0.755 (95% CI 0.520-0.990) was estimated from a within-smoker analysis.

In the other study (Heller *et al* 1990[15]), 41 smokers were identified who had switched brands. Thirteen had spontaneously switched from a higher yield cigarette in 1984/85 to a lower yield cigarette in 1987/88. Plasma cotinine levels determined at both time points revealed a less than proportional decrease, with I_1 estimated as 0.55.

Generally the results from these studies strengthen the conclusion that compensation exists and is substantial, but is incomplete.

This report has concentrated mainly on the issue of compensation in terms of nicotine uptake rather than in terms of amount smoked. Some of the relevant information for the 11 studies reviewed here is given in Table 1. It can be seen that two of the studies (Benowitz 1982, Kolonel) constrained the smokers to smoke the same number of cigarettes/day for each cigarette tested. These do not provide any relevant information on compensation for amount smoked. Of those five studies where the range of nicotine yields tested decreased by no more than 2.2 (Fagerstrom, Russell, Armitage, Guyatt, Frost), changes in cigarette compensation were quite modest, ranging from -8% in Frost group 1 to +14% in Guyatt. Somewhat larger changes in cigarette consumption (all increases) were seen in the four studies (Robinson, Haley, Benowitz 1986, Zacny) where nicotine yield declined by a larger factor, but even then they never exceeded 36%, even for a 20 fold decrease in nicotine yield.

The review by Scherer refers to evidence from a larger number of studies than are considered in detail here. Apart from the Frost study, he reports 26 studies which found no change in consumption following brand-switching, and 18 studies which found a tendency for consumption to change in a direction compatible with compensational smoking behaviour, but he carries out no quantitative estimation. The fact that the majority of the studies did not find a significant change in consumption suggests that, as our analysis showed, any increase in consumption following a reduction in nicotine yield is quite minor.

8. Summary and conclusions

When switching to a brand with a reduced machine nicotine yield, smokers may compensate by altering how the cigarettes are smoked or the number of cigarettes smoked. This document considers the evidence in the 1999 review by Scherer relating to brand-switching studies, in which variation in nicotine uptake (as usually measured by cotinine) or daily cigarette consumption is related to variation in the nicotine yield of the brand smoked. Most attention is given to those 11 studies considered by Scherer to be most suitable for determining compensation.

Methods of estimating compensation are discussed and an index derived which takes the value 1 for full compensation (no change in intake following a change in yield) and 0 for no compensation (proportional change in intake the same as the proportional change in yield). Difficulties in estimating the compensation index from the published material are discussed; these derive mainly from failure to present individual subject data, and presentation of statistics which show between-person variability in intake for different cigarettes, but not between-person variability in change in intake.

For each of the 11 studies, the available data are reviewed, and compensation indices with approximate 95% confidence intervals are presented. Where, in a study, smokers had switched between three or more types of cigarette, Scherer had estimated compensation indices relating intake to yield for various pairwise comparisons. Here, a more appropriate single estimate of the compensation index is derived based on all the available data for a specific group of subjects. Overall the 11 studies provided 14 independent estimates of the compensation index.

All 14 estimates of the compensation index are significantly greater than 0, so clearly compensation occurs. With one minor exception, all the estimates are significantly less than 1, so compensation is not complete. With two exceptions, compensation indices are all estimated to be in the range 0.71 to 0.86. Lower compensation indices were seen in two studies where, unusually, the low nicotine yield experimental cigarettes had extremely high tar/nicotine ratios. Provided attention is restricted to studies in which tar/nicotine ratios are reasonably typical of cigarettes on the market, a compensation index around 0.75 would be an appropriate estimate. An index of 0.75 would imply that a 50% reduction in machine nicotine yield would result in a 16% reduction in nicotine intake and that a 90% reduction in yield would result in a 44% reduction in intake.

The conclusion that compensation is substantial, but certainly not complete seems consistent with evidence from other brand-switching studies cited by Scherer and from limited observational studies of changes in intake within smokers.

Compensation in terms of increased cigarette consumption is also discussed, but in less detail. The evidence suggests that it is quite minor, with even a 10 fold reduction in yield being associated with an increase in consumption of only around 20%.

9. References

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TABLE 1 Summary of findings from the 11 studies

Study	True sample size	Duration (days)	Range of nicotine yields tested	Change in cig.consumption on reduction in nicotine yield	Estimated I_2 (95% CI)	Significantly >0?	<1?
Benowitz *et al* (1982)	8	3	2.5/0.4 = 6.25	None, by design	0.18 (0.08-0.27)	Yes?	Yes
Fagerstrom (1982)	7	28	1.1/0.5 = 2.2	+7%	0.79 (0.55-1.03)	Yes	No
Russell *et al* (1982)	8	70	1.33/0.7 = 1.9	<1%	0.45 (0.18-0.72)	Yes	Yes
Robinson *et al* (1982,1983)	16	21	0.96/0.38 = 2.5	+11%	0.84 (0.71-0.97)	Yes	?
Haley *et al* (1985) - 1	6	42	1.30/0.06 = 21.7	+31%	0.53 (0.48-0.59)	Yes	Yes
- 2	6	42	1.30/0.06 = 21.7	+36%	0.82 (0.76-0.87)	Yes	Yes
Benowitz *et al* (1986) - 1	11	10	1.1/0.4 = 2.75	+34%	0.78 (0.68-0.95)	Yes	?
- 2	11	10	1.06/0.1 = 10.6	+14%	0.73 (0.68-0.79)	Yes	Yes
Armitage *et al* (1988)	21	14	1.7/0.8 = 2.13	Very little	0.77 (0.64-0.91)	Yes	?
Kolonel *et al* (1988)	8	2	1.0/0.3 = 3.33	None, by design	0.71 (0.56-0.86)	Yes	Yes ?
Zacny & Stitzer (1988)	10	5	1.1/0.1 = 11.0	+27%	0.78 (0.72-0.83)	Yes	Yes
Guyatt *et al* (1989)	28	42	1.36/0.91 = 1.49	+14%	0.50 (0.26-0.73)	Yes	Yes
Frost *et al* (1995) - 1	99	180	1.32/0.81 = 1.63	-8%	0.74 (0.64-0.85)	Yes	Yes
- 2	105	180	1.31/0.84 = 1.56	-5%	0.86 (0.75-0.96)	Yes	Yes

TABLE 2 Tar, nicotine and tar/nicotine ratios of brands smoked in the 11 studies, together with their associated cotinine (C) or nicotine (N) values

	Tar (mg)	Nicotine (mg)	Tar/nicotine ratio		Cotinine/ nicotine
Benowitz *et al* (1982)	29.6	2.50	11.8	N	707
	-	1.23	-		574
	31.8	0.40	79.5		165
Fagerstrom (1982)	5.8	1.10	5.3	C	319
	4.8	0.50	9.6		270
Russell *et al* (1982)	17.4	1.33	13.4	C	350
	10.9	0.70	15.6		246
Robinson *et al* (1982,1983)	17.6	0.96	18.3	C	284
	4.1	0.38	10.8		244
Haley *et al* (1985)	11.2	1.30	8.6	C	<u>183</u>, 185
	-	1.03	-		253, 220
	10.9	0.90	12.1		<u>203</u>, 214
	-	0.73	-		<u>175</u>, <u>175</u>
	11.1	0.70	15.9		<u>162</u>, 203
	11.5	0.40	28.9		<u>154</u>, 154
	10.6	0.06	176.7		<u>49</u>, 129
Benowitz *et al* (1986)	-	1.1	-	N	<u>478</u>
	-	1.06	-		338
	15.4	1.0	15.4		<u>349</u>, 313
	4.6	0.4	11.5		<u>336</u>
	0.8	0.1	8.0		174
Armitage *et al* (1988)	16.9	1.7	9.9	C	313
	11.2	1.4	8.0		317
	9.1	0.8	11.4		268
Kolonel *et al* (1988)	15.6	1.0	15.6	C	309
	4.5	0.3	15.0		219
Zacny and Stitzer (1988)	16.0	1.1	14.5	C	259
	16.0	1.0	16.0		252
	10.0	0.7	14.3		221
	5.0	0.4	12.5		188
	1.0	0.1	10.0		152
Guyatt *et al* (1989)	15.1	1.36	11.1	C	378
	9.3	0.91	10.2		309
Frost *et al* (1995)	14.0	1.32	10.6	C	<u>305</u>
	14.1	1.31	10.8		289
	8.3	0.84	9.9		271
	7.8	0.81	9.6		<u>269</u>

Note: For the Haley *et al* (1985), Benowitz *et al* (1986) and Frost *et al* (1995) studies, underlined cotinine or nicotine values refer to group 1 and non-underlined values to group 2.