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Nicotine Yield as Determinant of Smoke Exposure Indicators and Puffing Behavior

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HÖFER, I., R. NIL AND K. BÄTTIG. *Nicotine yield as determinant of smoke exposure indicators and puffing behavior.* PHARMACOL BIOCHEM BEHAV **40**(1) 139–149, 1991.—Relationships between machine smoking nicotine yield and different smoke exposure indicators were investigated in a cross-sectional study. For each of the four yield classes H (1.0–1.2 mg), M (0.7–0.9 mg), L (0.4–0.6 mg) and U (0.1–0.3 mg) 18 male and 18 female subjects were recruited. The experimental design (2×2) included smoking with lip contact or with a flowmeter holder, natural smoking of one cigarette or forced smoking (30 puffs). The analysis of presmoking measures revealed for plasma nicotine H>L,U; M>U, for plasma cotinine H,M>U, and no differences for respiratory CO. Pre- to postsmoking boosts of CO and nicotine increased with yield, but the differences were smaller than those in yield. This partial compensation can be attributed to puffing behavior as revealed by the differences between yield classes with respect to flowmeter measures (puff volume, flow parameters, number of puffs). Contact condition hardly influenced the results. Forced puffing revealed down regulation mechanisms in smoke absorption and, less pronounced, in puffing behavior. Cardiovascular and subjective effects were widely independent of yield. Plasma cotinine appeared as the best smoke exposure indicator, due both to its high retest reliability and its relationship to nicotine yield.

Cross-sectional study Cigarette yield Smoke absorption Respiratory carbon monoxide Plasma nicotine Plasma cotinine Puffing topography Nicotine compensation Retest reliability

WHETHER and to what extent smokers compensate for changes in the machine determined nicotine, condensate and CO yield by adequate puffing, inhalation, and/or daily consumption has been the object of numerous studies in the past. The main slogans of this research are "upregulation" for intensifying smoking of "lighter" cigarettes, "down regulation" for reducing smoking intensity with "stronger" cigarettes, and "nicotine titration" for the presumed underlying mechanism.

Semichronic switching to lighter cigarettes has been reported to be associated with modest upregulation or no change, and switching to stronger cigarettes produced in a more pronounced and consistent fashion down regulation, as reviewed by (30, 31, 33, 35, 45). However, the yield of the habitual brand, the magnitude of the change in yield as well as the duration of the switching period all affected the outcome, thus complicating final conclusions. Furthermore, most of these studies were carried out within intermediate to higher nicotine yield values, allowing no firm conclusions for the lower yield ranges.

A number of cross-sectional studies, as summarized in Table 1, compared different indicators of smoke absorption across smokers habituated to different yields. Although these studies differ in manifold methodological aspects (subject sample, yield range, time of blood sampling, smoking conditions, calculations of dependent variables, etc.), there are some commonalities across the results. Compensation through the self-reported number of cigarettes smoked per day (CPD) is mostly absent or minimal. CO absorption as a gross indicator of inhalation (measured in blood or respiratory air after smoking, or independently of smoking, in the table referred to as pre-CO) hardly differed across yields or tended to indicate modest upregulation for low yields. Plasma nicotine and cotinine values revealed mostly partial upregulation for light cigarettes. The few studies analysing the increase in CO or nicotine from pre- to postsmoking don't allow final conclusions. The different relationships of the different smoke exposure indicators are confirmed by two recently published reports (6,7) which analyse the data of an earlier study (8) in more detail.

The present cross-sectional study was done in an attempt to add to these findings by combining the dependent measures used in the various previous studies (respiratory CO, plasma nicotine and cotinine measured pre- and postsmoking, butt length, amount of nicotine retained in the filter, heart rate as a possible indicator of the pharmacological action of nicotine, subjective ratings), by relying on a sample equally stratified across sex and yield classes, including in particular a group of smokers of "ultra-low" yield cigarettes (0.1–0.3 mg nicotine yield) which were underrepresented in the studies summarized in Table 1, and by including the number of cigarettes smoked per day and puffing parameters as dependent measures, in order to detect possible mechanisms of compensation. Further, repeated measurements were used to assess the stability of the dependent measures over time (test-retest reliability), as well as to assess the impact of lip

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TABLE 1

NICOTINE YIELD AND CONCENTRATION OF SMOKE CONSTITUENTS IN BLOOD/BREATH (CROSS-SECTIONAL STUDIES): METHOD OF INVESTIGATION AND SUMMARY OF RESULTS

Study	Sample	Cig. Yield	Design
Bättig (2)	67 M 43 F, unsuccessful quitters	0.1–1.7	ad lib, 2 × breath-cig-breath (holder)
Benowitz (3)	I: 149 M+F II: 123 M+F smoking treatment	0.1–1.9	I: ad lib, 1–6.30 p.m.: blood II: 8–12 h depriv., 8 a.m.: blood
Benowitz (5)	7 M+5 F, hospit. for 9 days	0.8–1.8 filter+plain	pre cig. blood every 2/4 h over 24 h, stand. smoking
Bridges (8)	108 M	0.28–1.10	ad lib, 8 a.m.: cig. +5 min-blood
Burling (9)	23 M+37 F, stop smoking program	T: 10.5 ± 5.6	ad lib, 5–8 p.m.: breath
Ebert (16)	43 M+33 F, stop smoking program	0.1–1.5	ad lib, afternoon: cig+<5min-blood, breath
Folsom (20)	2561 M+F, coronary risk study	T: <5–>20	blood
Gori (21)	41 M 52 F	0.05–1.12	5 h stand.smoking, 12 a.m.: blood, breath
Gori (22)	397 M+468 F	0.1–1.5	ad lib, midafternoon: cig+10min-blood, breath
Hatsukami (23)	5 M+ 5 F, hospit. for 7 days	0.60–1.15	ad lib, afternoon 4 × blood-cig-blood (holder)
Herning (24)	8 M+3 F	1.03 ± 0.18 exp.: 0.4/2.5	2 × 10 h depr., 8 a.m.: 2 × blood-cig-blood (1. usual, 2. exp., holder)
Hill (25)	450 M +F	mean >1.0	30–90 min after last cig.: blood
Hill (26)	7 M+2 F	0.09–1.33	10 × ad lib, 9 a.m.: blood-cig
Jaffe (28)	72 M 128 F	0.1–>1.0	15–60 min after last cig. 12 a.m.–4 p.m.: breath
Maron (32)	330 M+383 F	<.2–>1.0	breath, blood
Nil (36)	69 M+48 F	0.80 ± 0.27	breath-cig-breath (holder)
Petitti (38)	7706, Medical care program	<1.0	questionnaire
Rawbone (39)	268 representative	LT: <10; MT: <17–22	butts over 24 h
Rickert (41)	<240 (51–140)	0.30–1.40	blood, saliva, breath
Russell (42)	124 M 206 F	0.6–2.0 filter+plain	afternoon: cig-blood
Russell (43)	10	1.2–1.6 exp: 0.14/3.2	4 × 10–11.30 a.m.: blood-5 h smoking-blood, (2× usual, 2× exp.)
Stepney (46)	78 M+F	L: 0.86 ± 0.12 M: 1.52 ± 0.12	2–3 × morning (1.cig): breath-cig-breath
Sutton (47)	55	0.5–1.5	afternoon,evening: cig-blood

Entries are: Study: first author and reference; Sample: size, sex (Male/Female), special characteristics; cigarette yield: range or mean (±SD) of nicotine or tar (T) yield, in case of classification for Low/Medium yield; Design: repetitions (on different days), presampling requirements (deprivation, ad lib), time of sampling, repetitions within a session, smoking conditions, sampled substance.

vs. flowmeter holder smoking and the unrestricted smoking of a single cigarette vs. standardized puffing of 30 puffs.

Toward these goals all subjects participated in two sessions, one with lip and the other one with flowmeter smoking (randomized order across subjects), and they smoked in each session firstly a cigarette in a nonrestricted natural fashion and, after a fixed interval, 30 puffs (10 times 3 puffs from a half-cut cigarette) under otherwise nonrestricted conditions.

METHOD

Subjects

Seventy-two men and 72 women regularly smoking perforation ventilated American Blend cigarettes with a nicotine yield between 0.1 and 1.2 mg [machine smoking according to CORESTA standard method No.10 (12)] participated in the study. They were equally stratified in four classes according to the nicotine deliveries of the brands: 0.1–0.3 mg (Ultra low=U), 0.4–0.6 mg (Low=L), 0.7–0.9 mg (Medium=M), and 1.0–1.2 mg (High=H), resulting in eight groups with 18 subjects each. Additionally, 18 men and 18 women smoking channel-ventilated cigarettes (nicotine yield: 0.2 mg) were also examined; the results for these subjects will be communicated separately. Subjects were recruited by newspaper advertisement, and they were paid SFr 100 for participation. All subjects reported being in good health.

Apparatus

Biochemical parameters. CO concentrations were measured with a CO analyzer (Beckman Instruments model 866) until stable readings were obtained. Concentrations were determined from expired tidal air collected in a 30-litre polyethylene bag during normal breathing. This procedure yields measures of tidal air CO rather than of end expiratory CO [for details see (36,40)].

Nicotine and cotinine concentrations in plasma were determined at the Institut für Klinische Chemie, Universitätsspital Zürich, by a GC-MS method (14, 15, 19, 48). Ten-millilitre venous blood samples were collected into anticoagulant vacutainers and kept on ice until centrifugation; after separation plasma was aliquoted and stored at −80°C until analysis.

The amount of nicotine in the filter was determined in the Laboratoire Cantonal, Epalinges, by a GC method (11). The

TABLE 1 (continued)

Results								
	CO		Nicotine			Boost		
CPD	Pre	Post	Pre	Post	Cotinine	CO	Nicotine	Remarks
.06	−.03	—	—	—	—	.10/.17	—	for 1./2. cig.
.03	−.02	—	—	—	—	.02/.17	—	topography, TV: −.17/−.36 (M/F)
—	—	—	—	—	.15	—	—	
—	—	—	—	—	.06	—	—	
—	−.28	—	.07	—	—	—	—	maximum over 24 h
—	—	.11	—	.17	.26	—	—	topography, TV: r = −.41
—	.30	—	—	—	—	—	—	with CO yield
−.14	—	.03	—	.25	—	—	—	
.03	—	—	—	—	—	—	—	with tar yield, SCN: r = .12, adj. for log(CPD), sex
—	<.16	<.16	<.16	<.16	—	—	—	5 h smoking
—	<.16	<.16	<.16	<.16	—	—	—	
n.s.	—	n.s.	—	.37	.23	—	—	
—	—	—	—	—	—	—	−.26	individual means
—	—	—	—	—	—	—	.52	mixed between/within, topography
—	.38	—	.41	—	.45	—	—	with tar yield
—	.37	—	.45	—	.45	—	—	
−.13	.26	—	—	—	.33 (.68*)	n.s.	—	mixed between/within
—	.03	—	—	—	—	—	—	
—	.03	—	—	—	—	—	—	
p<0.01 neg.	n.s.	—	—	—	—	—	—	linear trend (ANOVA), SCN: n.s.
n.s.	n.s.	—	—	—	—	—	—	topography, TV: n.s., −.31 (M/F)
p<0.05	—	—	—	—	—	—	—	contingency analysis
n.s.	—	—	—	—	—	—	—	
—	.10[+a]	—	—	—	.08[a]	—	—	[+] with CO yield SCN;.15/.04 (blood/sal.) with HCN yield
—	.18[a]	—	—	—	—	—	—	[a] all r's adj. for CPD
—	—	−.21	—	.17	—	—	—	
—	—	.05	—	.26	—	—	—	
—	—	—	—	−.04 (.35*)	—	—	—	mixed between/with, 5 h smoking
—	.14*	—	—	—	—	.33*	—	individual means
—	—	−.31	—	.10	—	—	—	topography, TV: .03

Results: correlation of yield and cigarettes per day, CO, nicotine or cotinine concentration (independent of or presmoking, postsmoking) and pre- to postsmoking boosts in CO or nicotine; Remarks: special characteristics of yield measure, smoke absorption measure, or statistics; additional smoke absorption measures (incomplete): TV: total puff volume; SCN: thiocyanate.
*Recalculations from reported data or statistics (i.h.).

butts were extinguished under oxygen withdrawal, enclosed in air-tight containers and stored at +4°C until analysis. In the forced puffing condition (see below), only the first and last butts were collected. In the laboratory, butt length (tobacco rod) was determined, and nicotine washed out from the separated filters for quantification.

Puffing behavior. Puffing behavior was recorded automatically using a flowmeter [CGC Ltd, England, cf. (13)], yielding analogue signals for flow and pressure. During smoking sessions with lip contact, puffing behavior was recorded by the experimenter by pressing a marker from the beginning to the end of each puff (observation via a TV monitor). All puffing signals were digitized and stored on a lab computer (MINC with A/D-module, DEC).

An off-line program was used for the determination of puff duration, interpuff interval, puff volume, mean and peak flow, peak pressure, and latency from beginning of puff to peak pressure. Single puffs were defined by an increase in pressure; puffs with an interpuff interval below one second were treated as single puffs (individually checked).

Physiological measures. Heart rate was recorded continuously via a photoplethysmogram (infrared-transducer) at the earlobe, stored on the lab computer and off-line averaged for 1-minute intervals.

Questionnaires. A self-constructed questionnaire for smoking history asked for the following information: age when started smoking, years of smoking, usual cigarette consumption per day (CPD), subjective inhalation depth (1 = none, 2 = low, 3 = high).

Subjective need for smoking was rated on a 100 mm analog rating scale (no need/very high). On similar scales, subjects also rated smoking satisfaction (low/very high), strength (weak/strong) and taste (bad/good), and calming, activating, nervous and dizzy making effects of smoking (not at all/totally).

Experimental Design and Procedure

Subjects came to the laboratory for two experimental sessions

TABLE 2

SAMPLE CHARACTERISTICS

	Means		ANOVA			Means			
Variable	M	F	S	Y	S×Y	U	L	M	H
General characteristics									
Age	27.10	29.24	3.52‡	2.74	7.33*	M:26.1	23.9	31.0	27.4
						F:35.2	28.8	26.0	26.9
Height (m)	1.81	1.66	131.18*	0.65	1.05	1.73	1.73	1.73	1.75
Weight (kg)	76.01	57.86	178.36*	1.33	0.67	67.1	65.6	58.7	66.5
Smoking habits									
CPD	24.13	22.37	1.32	1.32	3.91†	M:22.6	19.1	28.7	26.1
						F:20.8	25.9	22.8	20.0
Age began smoking	16.81	16.94	0.10	0.45	0.16	17.2	17.0	16.8	16.5
Years of smoking	10.24	12.29	3.10	2.28	6.89*	M:9.2	7.0	14.3	10.7
						F:17.7	11.8	9.1	10.6
Inhalation depth	2.69	2.62	0.45	3.74‡	3.06‡	2.49	2.56	2.86	2.73
Cigarette brands									
Nicotine yield (mg)	0.64	0.67	4.91‡	754.95*	3.85‡	0.23	0.49	0.80	1.11
Tar yield (mg)	7.96	8.03	0.14	885.90*	3.27‡	2.47	5.00	9.53	14.97
CO yield (mg)	8.82	9.16	2.15	453.23*	6.16†	M:3.39	5.37	11.06	15.46
						F:5.20	6.10	10.34	15.01
Ventilation (%)	40.87	39.92	0.40	234.96*	4.16†	M:68.2	54.6	32.3	8.4
						F:58.5	51.9	36.2	13.1

Entries are: Sex specific means; F-values and significance level; Yield specific means, broken by sex where appropriate.
Abbreviations: S: Sex (M: male/F: female); Y: yield class (U: ultra/L: low/M: medium/H: high).
Significance levels: *$p \leq 0.001$; †$p \leq 0.010$; ‡$p \leq 0.050$.

(2 hours each) on different days (usually 1–2 weeks apart). All sessions took place in the morning or early afternoon, whenever possible at the same time of day for each subject. Subjects were not required to abstain from smoking. Each of the two sessions consisted of two experimental periods with a 40-minute resting time in between: the first smoking period called for natural puffing (n), i.e., smoking one (already lighted) cigarette of the habitual brand in the usual way, the second period required forced puffing (f), i.e., taking ten times three puffs each on a half-cut (tobacco rod) and already burning cigarette of the habitual brand in a maximum of 13 minutes, whereby no additional instructions (puff duration, intervals, etc.) were given. The two sessions differed concerning mouth cigarette contact: one session was carried out with direct lip contact (l) and the other one with a cigarette holder (h; randomized order).

After general information concerning the experiment, subjects gave their written consent to participate in the study. First, subjects filled out questionnaires (general information, number of cigarettes smoked on the experimental day). Then the plethysmographic sensor was fixed to the earlobe for heart rate recording, and a catheter was inserted into a forearm vein. The procedure continued with the first experimental period with natural puffing, followed by a resting period of 40 minutes (questionnaire for smoking history, or reading). Then the procedure continued with the second experimental period with forced puffing, and finally deinstallation. Both experimental periods started with taking a blood sample for determination of nicotine/cotinine, a breath sample for CO analysis, subjective rating of smoking need, and registration of heart rate for one minute. During the subsequent smoking period, puffing behavior and heart rate were recorded continuously. After smoking, a second blood sample, second breath sample and subjective ratings of smoking quality and effects were required.

Data Handling and Statistical Analysis

Reported puffing behavior values refer to means or totals of the single puff values for each smoking period.

Presmoking heart rate refers to the minute immediately before smoking, postsmoking heart rate is the average of either the minute prior to, parallel to, or following the last puff, depending on which of these revealed the highest value.

Boosts were calculated as the difference between postsmoking and presmoking measures.

The effects of sex, yield class and experimental variations [lip/holder contact (l/h); natural/forced puffing (n/f)] were analysed with full factorial analyses of variance (and of covariance) with up to two grouping factors and two repeated measures factors. For the error term of the corresponding F-values, degrees of freedom usually are 136, slightly varying according to the considered model and possible missing values. For a conservative interpretation of the results, and in order to avoid confusion of the results by complex interactions which might be only occasional results, the comments are restricted to effects with $p \leq 0.010$. Significant yield class effects (and interactions) were additionally tested with a posteriori Scheffé-tests ($p = 0.050$).

Furthermore, (Pearson) correlations were calculated; in the case of significant sex effects, correlations were determined separately for the two subsamples. Significance levels correspond to two-tailed testing. All statistical analyses were computed with SPSSX or BMDP procedures on a Cyber 855 computer.

Results

The sample characteristics, as summarized in Table 2, revealed some group differences across sex and yield: The males in the M class showed higher age, years of smoking, and daily

TABLE 3

TEST-RETEST RELIABILITIES FOR SMOKE EXPOSURE INDICATORS

	Presmoking	Boost	Postsmoking
CO	75/79*	49/52*	80/78*
Nicotine	76/80*	67/68*	78/82*
Cotinine	83/84*	−09/06	83/84*
Butt length		69/65*	
Filter nicotine		75/67*	

Entries are correlations between lip and holder measures for natural/forced puffing (decimal points omitted) and significance level $*p \le 0.001$.

consumption than those in the L class (M>L); and the females in the U class showed higher age and years of smoking (U>H,M).

All these variables were subsequently controlled for their possible biasing effect on the dependent measures (analyses of covariance). As no such effects reached significance (except for cigarettes on experimental day), the details of these procedures are omitted in the further result section.

Finally, the table shows that self-reported daily cigarette consumption as a possible candidate for compensation was independent of nicotine yield.

The test-retest reliabilities (cf. Table 3), i.e., the correlations of the measures in the lip session with those in the holder session, were high for the parameters of smoke absorption, except for the pre- to postsmoking changes in cotinine, as was to be expected. Further, the reliabilities for the number of puffs, puff duration and intervals varied between r = .51 and r = .67, those for the subjective ratings between r = .22 and r = .56, and for heart rate between r = .11 and r = .18 (presmoking and boosts) and between r = .36 and r = .39 (postsmoking). Systematic distortions of these coefficients due to the fact that one measure was obtained with holder smoking and the other with natural lip smoking are unlikely, as significant interactions with contact condition were observed for the number of puffs only (see below).

The results for the smoke exposure measures obtained before smoking in the laboratory are summarized in section a of Tables 4 and 5. Subjects had smoked about 30 percent of their self-reported cigarettes per day (cf. Table 2) before arriving at the lab. Males in the M class had smoked more than those in the L class (M>L), and this tended to reflect the differences in CPD (ANCOVA: $p = 0.140$). Yield affected plasma nicotine (H>L,U, M>U) and plasma cotinine (H,M>U), but not respiratory CO, indicating that U smokers and, in part, L smokers absorb less nicotine than H and M smokers. Correspondingly, nicotine yield contributed considerably to variance explanation for plasma nicotine and cotinine, but only marginally for respiratory CO. Contact condition did not affect any of the presmoking variables, either by main or by interaction effects. As was to be expected according to the fixed order and the time interval between natural and forced puffing, presmoking measures increased over time in both sessions, although only marginally for nicotine.

The results for the measures of smoke exposure during a single smoking period, i.e., the pre- to postsmoking boosts in plasma nicotine, cotinine and respiratory CO and the putative indicators butt length and filter nicotine, are summarized in section b of Tables 4 and 5. The CO boosts increased with nicotine yield, both with natural puffing (M>L,U) and even more pronouncedly with forced puffing (H,M>L,U). They were higher with forced than with natural puffing, and there was an additional interaction with contact condition. The plasma nicotine boosts were higher for men than for women, and higher with forced than with natural puffing. They increased with nicotine yield, and this increase was more pronounced with forced (H,M>L,U) than with natural puffing (H>L,U, M>U). Furthermore, there were slight sex differences in the increase of the boosts across the yield classes, marginally significant at $p = 0.021$.

Butt length differed, as was to be expected, between natural and forced puffing, since with forced puffing three puffs were required from half-cut cigarettes. It increased with nicotine yield (H>U for natural puffing; H,M,L>U, H>L for forced puffing), indicating that lower yield cigarettes were smoked more intensively. Nicotine retained in the filter was higher with forced than with natural puffing, but it remained unaffected by nicotine yield.

The correlational relationships with nicotine yield reached significance for CO and nicotine boosts, and for butt length. For the boosts, higher variance explanations were observed under forced puffing, and for nicotine boost in the male subsample. The results for butt length indicate that a lower amount of tobacco was smoked from the higher yield cigarettes, suggesting less intensive smoking and lower smoke exposure, as also emerges from the filter nicotine results.

Analysing the postsmoking measures with respect to their correlational relationships to nicotine yield revealed variance explanations for CO and cotinine which are comparable to those obtained for the presmoking or boost measures in the case of cotinine (r = .32) and CO (r = .23/.30 for n/f), and slightly higher for plasma nicotine (M: r = .57/.61; F: r = .39/.54 for n/f; cf. Table 5).

The results for heart rate are summarized in section c of Tables 4 and 5. Presmoking heart rate was higher among the men in the U class (U>M,H); correspondingly, a weak negative correlation with nicotine yield was obtained for the male subsample. The presmoking heart rate increased from natural to forced puffing (fixed order). From pre- to postsmoking the heart rate increased on the average by 4.95 bpm, but the trend toward greater boosts with increasing nicotine yields failed to reach significance, and none of the experimental conditions affected this measure.

The results for the subjective ratings are summarized in section d of Tables 4 and 5. The subjective ratings of cigarette strength increased with increasing nicotine yield (H>L,U), and they were greater after forced than natural puffing and after lip than holder smoking. All other subjective ratings were not influenced by nicotine yield. They generally were more negative after forced than natural puffing, and in part after holder than lip smoking, with interactions of the two experimental conditions for some of these variables. Only minor parts of the variance of these variables were explained by nicotine yield.

The results for the puffing behavior parameters are summarized in section e of Tables 4 and 5. The number of puffs decreased marginally with increasing nicotine yield when lip contact was allowed (Scheffé n.s.), and more pronouncedly when holder contact was required (U>M,H), also indicating that subjects increased the number of puffs when smoking through a holder as compared to lip smoking, especially in the lower yield classes. The mean puff durations were generally shorter with forced than with natural puffing, particularly for holder smoking. Mean puff duration showed opposite relationships with nicotine yield during natural vs. forced puffing, indicating that subjects shortened the puff duration with forced smoking, especially in the higher yield classes (difference n − f: H>L,U). Total puff duration as a composite measure of puff frequency and duration differed between forced vs. natural puffing and lip vs. holder contact, but relations to nicotine yield were weak. The puff intervals increased linearly with increasing nicotine yield in women

TABLE 4

MEANS OF DEPENDENT VARIABLES BROKEN BY YIELD CLASS, SEX, EXPERIMENTAL CONDITION

Variable		U	L	M	H	M/F	ln	hn	lf	hf
a. Presmoking Measures										
No. cigarettes	M	8.0	4.5	10.6	8.2	7.8/6.6	7.3	7.1		
on exp. day	F	6.8	7.5	5.4	6.6					
CO (ppm)		10.0	9.9	11.8	12.2	10.8/11.1	10.6	10.3	11.6	11.3
Nicotine (ng/ml)		8.2	10.0	12.0	14.2	11.1/11.0	10.8	10.9	11.5	11.1
Cotinine (ng/ml)		177	198	256	270	231/219	226	220	231	224
b. Pre- to Postsmoking Boosts										
CO (ppm)	n	2.1	2.1	3.2	3.0	3.4/4.1	2.6	2.5	5.4	4.4
	f	3.7	4.1	6.0	5.9					
Nicotine (ng/ml)	Mn	4.4	8.7	13.0	15.7	12.4/8.9	9.1	8.5	12.8	12.0
	Fn	5.1	6.3	8.4	9.1					
	Mf	6.1	12.3	19.7	19.1					
	Ff	7.1	7.8	12.8	14.5					
Cotinine (ng/ml)		0.6	0.7	0.0	1.9	0.9/0.7	0.0	0.2	1.6	1.4
Butt length (mm)	n	11.9	15.4	14.9	16.6	13.8/15.7	14.9	14.5		
	f[a]	15.7	18.9	20.2	22.5	18.3/20.3			19.9	18.7
Filter nicotine (mg)	n	0.92	0.78	0.76	0.74	0.86/0.75	0.75	0.85		
	f[b]	2.02	1.85	1.99	1.84	2.21/1.64			1.92	1.93
c. Heart Rate										
Presmoking (bpm)	M	85.2	80.7	76.4	78.5	80.3/80.0	79.9	78.4	81.6	80.6
	F	79.7	77.2	81.1	82.0					
Boost (bpm)		3.22	4.24	5.90	6.07	4.78/4.85	4.23	4.97	5.07	5.04
d. Subjective Ratings										
Smoking need		67.1	65.1	65.9	62.9	66.8/63.6	67.4	66.1	66.7	60.7
Strength		45.0	49.4	54.6	61.0	51.1/53.9	49.9	36.5	67.4	56.1
Taste		47.7	43.1	44.0	42.0	43.6/44.8	65.6	42.6	37.2	31.3
Satisfaction		48.8	45.1	43.0	39.8	44.5/43.8	66.0	45.8	34.0	30.9
Activation		39.5	39.5	33.8	32.5	34.9/34.6	36.0	33.6	34.4	34.9
Calming		42.9	44.2	38.8	36.0	42.1/38.9	51.9	43.7	34.3	32.0
Nervousness		22.2	23.6	31.2	28.5	27.6/25.2	16.4	18.1	37.2	33.8
Dizziness		20.0	21.1	33.0	31.0	25.8/30.6	14.7	18.2	36.8	34.9
e. Puffing Behavior										
No. Puffs (n only)	l	12.3	11.8	11.4	10.9	11.8/12.9	11.6	13.1		
	h	15.6	13.6	12.2	11.1					
Puff duration (s)	n	1.97	1.95	2.03	2.19	1.96/1.81	2.04	2.04	1.79	1.66
	f	1.76	1.75	1.72	1.69					
Tot. puff duration (s)		39.9	38.5	37.2	37.0	39.3/36.9	22.7	26.0	53.6	50.2
Interval (s)	M	18.3	19.0	21.7	17.0	19.0/18.2	22.7	19.8	17.9	14.1
	F	16.1	18.2	17.6	21.0					
Volume (ml)	n	44.5	45.2	40.0	36.8	44.3/35.9		41.6		38.6
	f	45.3	41.1	38.7	29.3					
Total puff	n	678	596	467	405	934/764		536		1163
volume (ml)	f	1418	1237	1168	879					
Mean flow (ml/s)		25.2	23.5	21.7	18.5	23.5/20.9		20.8		23.6
Peak flow (ml/s)		45.5	41.0	36.3	31.3	40.9/36.1		36.9		40.1
Peak pressure (cmH_2O)		25.9	29.0	30.4	25.8	28.0/27.5		27.4		28.0
Latency (s)		0.50	0.57	0.59	0.60	0.58/0.55		0.59		0.59

[a]Mean (butt 1, butt 10); [b]10 * mean (butt 1, butt 10).

Yield specific means: in case of significant yield interactions broken by the corresponding factor.

Abbreviations: Yield class: U—ultra/L—low/M—medium/H—high; Sex: M—Male/F—Female; Contact condition: l—lip/h—holder; Puffing condition: n—natural/f—forced.

women (H>U) but not in men (M>H). The intervals were shorter during holder than lip smoking and during forced vs. natural puffing.

Most puff volume and flow indices were higher in men than in women, differed between natural and forced puffing and between the yield classes. Mean puff volume decreased slightly

TABLE 5

SUMMARY OF ANOVA RESULTS, AND CORRELATIONS WITH NICOTINE YIELD

Variable		ANOVA S	Y	S×Y	C	Y×C	P	Y×P	C×P	Correlation With Yield r	r^2
a. Presmoking Measures											
No. cig. on exp. day		2.13	1.07	4.00†	0.67	0.48				M 15	2
										F −06	<1
CO (ppm)		0.22	2.57	0.99	1.37	2.29	76.16*	2.75‡	0.00	21‡	4
Nicotine (ng/ml)		0.01	8.17*	2.31	0.25	1.71	5.73‡	3.78‡	3.54	36*	13
Cotinine (ng/ml)		0.44	5.44*	1.57	1.02	1.88	28.10*	0.51	0.07	32*	10
b. Pre- to Postsmoking Boosts											
CO (ppm)		4.33‡	9.12*	0.67	12.95*	0.82	214.12*	3.99†	12.19†	22†/33*[a]	5/11
Nicotine (ng/ml)		19.09*	27.15*	3.72‡	3.28	3.33‡	96.88*	5.42*	0.02	M 59*/57*[a]	34/32
										F 33†/47*[a]	11/22
Cotinine (ng/ml)		0.07	2.53	1.17	0.00	0.36	6.45‡	0.47	0.17	04	<1
Butt length (mm)	n	3.83	4.03†	0.27	1.14	3.10‡				n 28*	8
	f[1]	10.59*	20.76*	2.09	13.16*	2.91‡				f 51*	26
Filter nicotine (mg)	n	3.13	1.76	0.38	17.66*	1.66				n −22†	5
	f[2]	18.71*	0.51	0.37	0.08	2.35				f −13	2
c. Heart Rate											
Presmoking (bpm)		0.02	2.25	5.04†	1.50	1.03	9.60†	0.51	0.17	M −27‡	7
										F 12	1
Boost (bpm)		0.00	2.66	1.11	0.21	1.59	0.42	0.36	0.41	12	1
d. Subjective Ratings											
Smoking need		1.01	0.30	0.48	4.48‡	0.88	3.48	3.20‡	2.42	−06	<1
Strength		0.98	5.86*	1.07	49.06*	1.30	141.84*	0.36	0.71	25†	6
Taste		0.16	0.65	0.34	53.38*	3.73‡	130.25*	2.56	33.25*	−07†	2
Satisfaction		0.05	1.57	0.47	41.34*	2.91‡	159.03*	1.08	49.86*	−12	2
Activation		0.01	0.89	2.19	0.37	0.05	0.01	0.12	1.21	−04	<1
Calming		0.99	1.43	1.06	10.25†	0.13	83.67*	3.11‡	4.42‡	−13	2
Nervousness		0.69	2.08	0.32	0.25	2.83‡	107.72*	1.75	2.65	11	2
Dizziness		0.07	3.68‡	0.94	0.08	0.79	66.34*	1.14	1.42	21‡	4
e. Puffing Behavior											
No. Puffs (n only)		3.30	4.13†	2.68‡	26.38*	4.83†				−15/−31*[b]	2/10
Puff duration (s)		3.85	0.24	0.81	3.70	1.30	108.11*	4.81†	9.39†	13/−07[a]	2/1
Tot. puff duration (s)		2.74	0.84	0.99	0.01	3.89‡	883.64*	0.39	42.50*	−10	1
Interval (s)		0.95	1.65	4.78†	80.65*	0.12	81.38*	2.81‡	1.91	M −04	<1
										F 19	4
Volume (ml)		16.32*	6.50*	0.41			16.58*	5.91*		−24†/−42*[a]	6/18
Tot. puff volume (ml)		14.83*	13.74*	0.56			583.14*	4.13*		−43*/−43*[a]	18/18
Mean flow (ml/s)		6.75†	8.69*	1.69			90.11*	2.00		−40*	16
Peak flow (ml/s)		7.64†	13.16*	2.55			38.22*	2.17		−47*	22
Peak pressure (cmH_2O)		0.18	3.17‡	3.08‡			2.00	0.78		02	<1
Latency (s)		1.98	3.84‡	2.61			43.79*	1.83		24†	6

Entries are: F-values and significance level; correlations with nicotine yield (decimal point omitted), averaged over experimental conditions if not indicated otherwise, and explained variance (r^2).

[1]Mean (butt 1, butt 10); separate ANOVAs for natural and forced puffing; [2]10 * mean (butt 1, butt 10); separate ANOVAs for natural and forced puffing; [a]separate for natural/forced puffing; [b]separate for lip/holder smoking.

Abbreviations: S: Sex (Male/Female); Y: Yield class (Ultra/Low/Medium/High); C: Contact condition (lip/holder); P: Puffing condition (natural/forced).

Significance levels: *$p \leq 0.001$; †$p \leq 0.010$; ‡$p \leq 0.05$.

with increasing nicotine yield during natural puffing (Scheffé n.s.) and considerably during forced puffing (U,L,M>H). Total puff volume as a composite measure of mean puff volume and number of puffs showed a similar picture, with a more pronounced decrease with yield during forced than natural puffing (n: U,L>H, U>M; f: U,L,M>H). For mean and peak flow the relationships with nicotine yield were independent of puffing condition (mean: U,L>H; peak: U,L>H, U>M).

The amount of variance explained by nicotine yield varied considerably between the different parameters. Substantial amounts were found for the volume and flow indices and for the number of puffs during holder smoking. The relationships were generally negative, indicating that low yield cigarettes were smoked with larger volumes and with more puffs.

TABLE 6

TEST-RETEST RELIABILITIES FOR SMOKE EXPOSURE INDICATORS

Study	N	k	CO	Nic.	Cot.	CO-boost	Remarks
Adams (1)	9	4	—	—	—	.04	1 cig[1]*
Bättig (2)	43M	2	—	—	—	−.05	1 cig, same day
	67F	2	—	—	—	.43	1 cig, same day
Hill (26)	9	10	.74	—	.45	—	pre 1 cig[1]
McBride (29)	9(36)	2	.96	.55	—	.38	pre 1 cig, same day† nic. boost: .68
Russell (43)	10	4	.78–.93	—	—	.97[1]	pre 5 h smoking
Russell (44)	10	4	—	.72	—	—	postsmoking
Stepney (46)	78	2	.81	—	—	.73	pre 1 cig

Entries are: first author and reference; N = Sample size (number of subjects, cases); k = number of repeated measures; Test-retest reliabilities.

[1]Reliability (for one measure) reanalysed from published data (mean ± SE, figure) according to variance analytical model (50).

*Possibly underestimated, as reported values are normalised for CO yield of brands.

†Four repetitions on different days, 2 × usual brand, 1 × low yield, 1 × medium yield.

DISCUSSION

Our results generally support the hypothesis that lower yield cigarettes are associated with reduced smoke absorption, although to varying degrees across the different smoke exposure indicators considered.

A first point of interest can be seen in a comparison of the correlational relationships between yield and smoke exposure measures in the present study with those in earlier studies as summarized in Table 1. For CO levels, most earlier investigations obtained very low coefficients (2, 8, 16, 21, 22, 28, 32, 36, 41, 42, 46), as did the present study with r≈.20. Substantial positive correlations emerged only in two investigations (9,25), and some doubts may arise concerning the latter ("relative correlation from linear regression analysis"; correlation with tar yield or tar availability?). The values of r≈.35 for plasma nicotine and of r≈.30 for plasma cotinine as obtained in the present study are somewhat higher than those obtained in earlier reports [(5, 8, 16, 21, 22, 25, 42, 43); (3, 8, 22, 25, 26, 41)], which might be due to the equal sample sizes in the present study. Furthermore, our results correspond to a recently published report (6) that confirms the different relationships of CO, plasma nicotine and cotinine with nicotine yield.

With respect to the boost measures, the correlations obtained in our study amounted to r≈.20 for CO and r≈.45 for nicotine, which is at the upper end of those reported in the literature [(2, 26, 46); (23,24)], which refer to individual means (23,46) or repeated measures (26), in part mixing habitual and experimental cigarettes (24), or to a highly selective sample (2).

The observed low to moderate correlations are hardly a result of insufficient methodological reliability. The test-retest correlations in the present study amounted for all smoke exposure indicator concentrations to values >.75 and for the boosts to values >.50. The reliabilities for the concentrations are similar to the few reports available from the literature [(26, 29, 43, 44, 46); cf. Table 6], with the exception of the only figure reported so far for cotinine (26), which was lower than in the present study. The majority of the reliabilities reported for boost measures refer to CO (1, 2, 29, 43, 46), and their great variability suggests that they depend considerably on the particular sampling circumstances.

Given this background, a comparison between the yield classes as presented in Fig. 1 is the next point of interest. The figure shows the means for the yield classes, differentiated for presmoking and boost measures, and for natural vs. forced puffing and sex as far as different relations were obtained for these factors in the statistical analysis. The presmoking values for CO, nicotine and cotinine were unaffected by sex and the subsequent smoking condition (lip vs. holder, natural vs. forced), except for the slight increase from the first to the second measurement. Therefore, they can be considered as relevant for the real life situation. Comparing the corresponding values in Fig. 1, H and M smokers show comparable concentrations, whereas L smokers and especially U smokers show lower concentrations. With respect to the pre- to postsmoking boosts, a similar picture emerges. These comparisons suggest that, at least for the range of the U yield class and in part also for that of the L yield class, nicotine absorption is definitely reduced as compared to H and M cigarettes, whereas a reduction in respiratory CO is less evident. The reports in the literature, too, reveal reduced nicotine and cotinine concentrations in subjects smoking cigarettes with a nicotine yield up to about 0.5 mg as compared to those with a yield over 1.0 mg (6, 16, 21), whereas reduced CO concentrations could rarely be confirmed (6, 16, 21, 28, 32). Certainly the great majority of the U and L smokers are smokers who have switched to these light classes, as such cigarettes were hardly on the market when they started smoking. However, as the range of smoke absorption in the U and L classes is included in the wider range of absorption in the M and H classes, it remains open whether this switching was accompanied by a lowering of absorption or not. The possibility that the L and U smokers were already "low absorbers" when they previously smoked stronger cigarettes cannot be excluded.

Although cigarettes with lower nicotine yield result in reduced absorption, these biological differences are less pronounced than would be expected from the machine determined yields. Taking the H cigarettes as reference point, the reduction of cigarette yield in U cigarettes by about 80 percent is reflected in a reduction of respiratory CO concentration by 18 percent presmoking and 22 percent postsmoking, of plasma nicotine by 42 percent presmoking and about 50 percent postsmoking, and in plasma cotinine by 35 percent. These figures correspond to those that can be derived from the literature: between 10 and 25 percent for CO concentrations (6, 16, 21, 28, 32), 20 to 45 per-

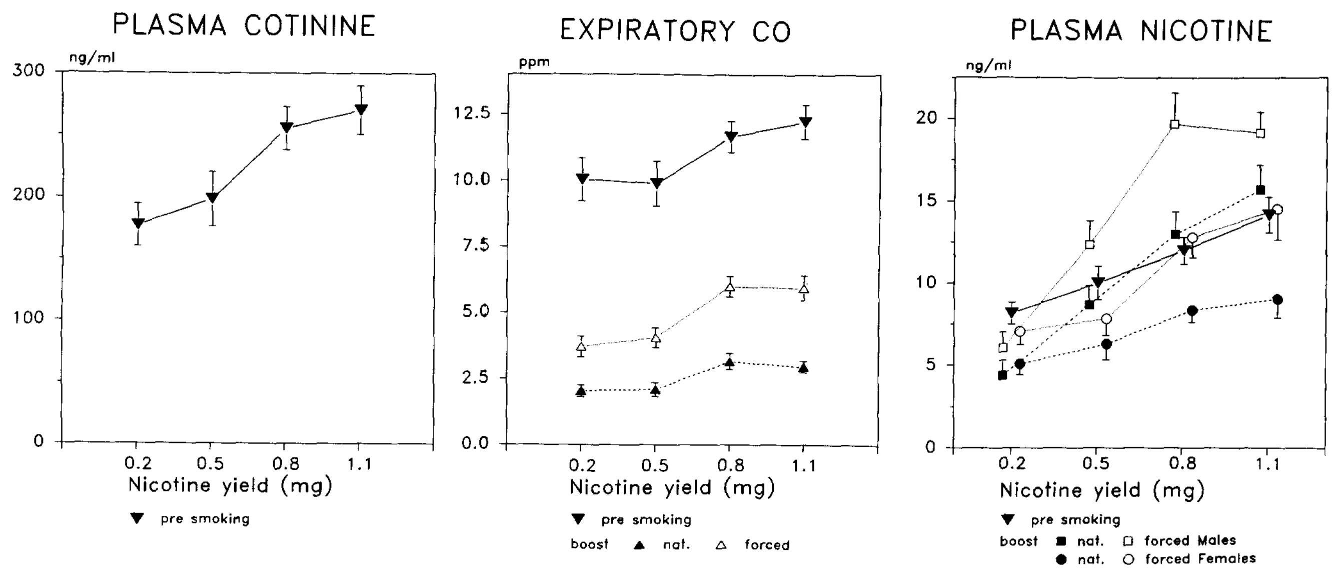

FIG. 1. Biochemical smoke absorption indicators as related to nicotine yield: Mean ± SEM for concentrations presmoking (individual means of all 4 measures) and boost with natural and forced puffing (individual means of lip contact and holder measure), for plasma nicotine broken by sex (SEM referring to n = 36 or n = 18, respectively).

cent for nicotine (6, 16, 21), and 35 percent for cotinine concentrations (6). The reductions for single cigarette boosts observed in the present study were somewhat higher, with 30 percent for respiratory CO and 70/45 percent (males/females) for plasma nicotine. So with respect to all these measures, the reduction of the absorption with U cigarettes is smaller than that in yield, indicating a partial compensational effect when smoking low yield cigarettes.

The possible mechanisms of compensation, which enable a smoker to regulate smoke or nicotine absorption within certain limits, are a further topic of interest. In this respect, a smoker can change the daily consumption, the number, the duration or the volume of the puffs, the pressure/flow profiles, or the way (s)he inhales.

The daily consumption of cigarettes shows no increasing trend for lower yield cigarettes, and this appears from the present results as well as from those reported in the literature [(2, 16, 20, 22, 26, 36, 39); cf. Table 1].

With respect to puffing behavior, the number of puffs and the puff duration are widely independent of cigarette yield, at least under natural smoking conditions. However, holder smoking reveals that the volume and flow measures are considerably higher for low yield cigarettes. The mean volume is 20 percent greater and the total volume 67 percent greater in the U class as compared to the H class (natural puffing); mean and peak flow are about 40 percent higher. The greater difference for total than for mean volume reflects the synergistic effect for the number of puffs with holder smoking (U 40% higher than H).

The literature mostly reports correlations of total puff volume with nicotine yield of about r≈ −.30 [(2, 7, 8, 36); cf. Table 1], which corresponds to our results. Nonsignificant correlations are reported from two investigations where low yield smokers are underrepresented (36,47). So the fact of higher puff volumes with lower yield cigarettes seems rather well established. Relationships between puffing behavior and smoke absorption are rather consistent when the puffing behavior is experimentally controlled [e.g., by within subject design; (29, 49, 51); own data for forced puffing, not shown, cf. (27)]. In cross-sectional studies, however, comparable effects seem difficult to detect even if multivariate models (regression or path analysis) are considered. The multivariate relationships are rather inconsistent over different studies, and the variance in smoke absorption is explained only to a minor portion [(7, 24, 47); own data for natural puffing, not shown, cf. (27)].

As a further possible mechanism of compensation, the change in the amount of tobacco smoked (complement to butt length) might be considered. As can be derived from the butt length results (assuming a tobacco rod length of 63 mm), about ten percent more tobacco was smoked from the U than from the H cigarettes.

Thus the compensational effect with low yield cigarettes is mainly due to increased puff volume. However, it remains open to what extent the observed effect might be transferred to normal lip smoking.

Smoking with a cigarette holder instead of normal lip contact changes some aspects of smoke absorption, puffing behavior, and subjective effects of smoking, but these changes are widely comparable over the whole range of nicotine yield. Yield specific holder effects emerged with respect to the number of puffs only. From lip to holder smoking, the number of puffs was increased more with low than high yield cigarettes, although these differences were less obvious for total puff duration. However, CO and nicotine boosts were independent of the contact condition.

Forced smoking of 30 puffs considerably increased the covariations of nicotine yield with CO and nicotine boosts and postsmoking measures, as compared to the corresponding measures under natural puffing. This indicates that the forced puffing procedure shifts human smoking in the direction of standardised machine smoking.

As expected, forced puffing, corresponding to smoking two to three cigarettes at once, led to higher total puff durations and volumes, to higher boosts in CO and nicotine, and to higher strength ratings. On the other hand, forced puffing was associated with shorter mean puff duration and volume, especially in high yield cigarettes, indicating some down regulation. The number of puffs increased from natural to forced puffing by 145 percent on the average. In parallel, total volume increased by

120 percent and total puff duration by 110 percent, CO boost by 90 percent and finally nicotine boost by 40 percent only. This indicates a considerable down regulation, apparently much less due to changes in puffing behavior than to changes in inhalation. However, these results must be interpreted with some caution, as the order of natural and forced puffing was fixed.

The sex differences in nicotine boosts are consistent with the sex differences in puff volume. However, neither presmoking plasma nicotine nor cotinine showed comparable sex differences, nor are corresponding results reported in the literature (21). If these differences are reproducible, they might reflect sex specific differences in the absorption, pharmacokinetics or metabolism of nicotine, and they might indicate a more complete compensation in female as compared to male smokers. The observed sex differences in puffing behavior, especially volume and flow parameters, are consistent with other investigations (2,10). Sex differences in puff duration (2,17), however, could not be confirmed in our study.

The failure to obtain a positive relationship between cigarette yield and heart rate might have been expected for ad lib smokers as a consequence of the well-established phenomenon of acute tolerance (4, 18, 37). The low retest reliabilities may well be due to the variable emotional load caused by the implanted intravenous catheter.

The subjective ratings were related to cigarette yield for subjective cigarette strength and marginally for dizziness. The other ratings, however, were independent of nicotine yield, indicating that smokers get equal satisfaction and effects from cigarettes with different nicotine yield. This might also indicate that the nicotine content of a cigarette is less important for the subjective evaluation and appreciation, as was reported from switching experiments which compared cigarettes with different nicotine yield and taste (34).

Comparing the validity of different measures for real-life smoke absorption reveals that both nicotine yield and daily cigarette consumption are only rough indicators. Nicotine yield explains between 4 and 33 percent of the variance of the absorption parameters (considering absolute concentrations with respect to natural puffing; cf. Table 5 and results for postsmoking values). Daily cigarette consumption as an additional predictor increases the amount of explained variance by 7 to 18 percent [data not shown, cf. (27)], but there remains a large amount of unexplained variance. Comparable results emerged in other multivariate analyses (6, 24, 47). Therefore, biochemical measures are absolutely necessary in order to assess the smoke exposure of the individual smoker. Filter nicotine, sometimes used as mouth uptake estimate, seems to be an inadequate measure, as the differences in filter efficiency result in a negative covariation with nicotine yield, which is contradictory to all other results. CO measures should be used with caution, as they are relatively weakly related to yield (and CPD; total explained variance <17%), thus confirming that CO concentrations are highly influenced by nonsmoke related variables (physical activity, environment). Although plasma nicotine seems a good indicator, it is highly influenced by the sampling time relative to the last cigarette, and therefore appears rather as a useful indicator to quantify smoke absorption due to a single cigarette. Cotinine concentrations seem to be the best indicator for long-term smoke exposure both because of their high stability (test-retest reliability, half-life) and their relatively strong relationship with yield (and CPD; total explained variance 23–28%). The fact that CO and nicotine/cotinine measures show different relationships to yield, although the respective yields as well as tar yield are highly correlated, should serve as a caveat against generalizing to tar exposure.

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