file Personal Concerns

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CQB/EPB

7th April 1982.

W.L. Telling, Esq.,
Brown & Williamson International Tobacco,
1600 West Hill Street,
Louisville,
Kentucky 40232,
U.S.A.

Dear Bill,

Smoker Compensation Study

Colin Pendry has asked if I would reply to your letter requesting the report on the above subject.

The report gave some useful indications of the capability of an individual to compensate for changing from one delivery level to another. However, the delivery levels are somewhat out of context with today's products since the low, medium and high delivery cigarettes used for the study were respectively 16 mg, 23 mg and 36 mg tar.

However, I enclose a paper from one of our recent Product Knowledge Seminars which contains a summary of the work and a number of the tables from the report. David Creighton from Ca & DC was the author of both this paper and the original report. If you still wish to have a copy of the original report please drop me a line and I will be delighted to order a copy to be sent to you.

With kind regards,
Yours sincerely,

C.D. EDMONDS

Group Secretary & Legal Director Deputy Secretary Assistant Secretary

PAPER 16 - HUMAN SMOKING BEHAVIOUR

HUMAN SMOKING BEHAVIOUR

The deliveries of cigarettes are measured by collecting the smoke under standard smoking conditions. The machine that smokes the cigarette is designed to smoke all cigarettes in the same way, irrespective of factors that might influence a human smoker. For example, pressure drop, strength, irritation. The delivery data, which may be listed as a league table, therefore form a comparative basis on which the constancy of delivery of a brand may be checked, when changes are made to the blend or materials used to construct the cigarette. What the standard machine data does not tell you is what a human smoker will give himself when he smokes a particular brand.

Some simple observations indicate that some people light a cigarette and leave it burning on an ashtray, others will smoke a cigarette with high intensity, and yet others will puff with high intensity while listening, but not at all while talking. The same cigarette might be used in all these situations, but clearly a high intensity of smoking will deliver more material to the smoker than the subject who took a single puff and allowed the rest of the cigarette to burn away in the ashtray.

A further observation is that smokers inhale smoke and exhale smoke, whereas the standard machine collects all the smoke drawn from a cigarette. Therefore not all the smoke drawn from a cigarette by a human smoker is retained.

In order to study the smoking patterns of smokers under different conditions and to find out what they actually draw from a cigarette, it was necessary to construct and develop special apparatus. This equipment was known as the Puff Analyser and Data Logger and the Puff Duplicator.

The purpose of the Puff Analyser and Data Logger is to

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record, as accurately as possible, the pressures and flows in a cigarette holder. It is still necessary for the smoker to use a cigarette holder, which is a difference between normal smoking and laboratory smoking. From these pressure and flow data, and a time clock, it is possible to calculate:

1. Peak pressure.
2. Peak flow.
3. Puff shape.
4. Puff volume per puff and per cigarette.
5. Duration of puff.
6. Interval between puffs.
7. Number of puffs.
8. Amount of 'rod' used to smoke the cigarette.

Additionally:

Average lip pressure drop.

Puff spacing.

Total time alight.

Volume of smoke per minute.

The data are recorded on a magnetic tape in computer compatible form, but can be recalled either onto a printer or onto a paper tape. The paper tape is used to control the Puff Duplicator so that 'slave' cigarettes can be smoked in exactly the same way as the original, which should mean that the butt length left by the machine is exactly the same as left by the man. In fact butt length matching is within ±2mm which demonstrates that even selected cigarettes are not identical. The smoke from the puff duplicator is collected on a Cambridge filter pad, as in a standard smoking machine, and the gas phase is collected in a Latex balloon.

The use of large apparatus and a cigarette holder in a laboratory may well be criticised as artificial and not typical of

the way smokers normally smoke. This aspect has been checked out by the use of 'Surreptitious Monitoring'. We designed and built a hand held control - about the size of a cigarette lighter - that contained a microphone, oscillator and switches, which was linked to a pocket sized tape recorder. This equipment was used by pressing a switch and holding it in while the subject puffed and releasing when the puff finished. In this way, puff number, puff duration, and intervals between puffs were recorded. We used this equipment to record the smoking patterns of about 50% of the GREDC smokers after lunch in the coffee lounge. These results were compared with those recorded on the puff analyser. It was found that butt lengths were slightly shorter and puff numbers slightly higher when people were smoking cigarettes through the holder in the laboratory. This is probably due to the fact that most smokers use smoking as an unobtrusive accompaniment to other activities (chatting in the coffee lounge) rather than as the main activity (smoking alone in a laboratory).

We also investigated the effects of stress on smoking pattern by measuring the smoking patterns of smokers who were taking part in an experiment in evoked brain wave patterns (EEG). This was a new experience to our smokers who had 20 or more electrodes stuck on their heads, and since anything to do with the brain is rather emotive, the situation was rather stressful. In this situation the intensity of smoking increased quite dramatically - 30% increase in total volume of smoke drawn, 16% shorter intervals between puffs and 20% more puffs, but a 5% longer butt.

These investigations indicated that the laboratory conditions we used were sufficiently realistic to allow the comparison of cigarette designs.

An example of an experiment to investigate compensation is where a panel of 10 smokers smoked a typical UK brand of cigarette

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which has a standard machine smoked delivery of 1.4mg nicotine and 16mg tar. Ten recordings were made of each subject smoking this brand over a period of one month. Half of the panel were then changed to a brand with a higher standard machine smoked delivery: 1.8mg nicotine and 26mg tar and the other half of the panel to a lower delivery brand with 1.0mg nicotine and 13mg tar. A further ten recordings of smoking pattern were made over the next month for each subject.

An examination of the smoking pattern data showed that the higher delivery product was smoked with lower intensity (that is, fewer puffs, smaller volume per puff and longer intervals between puffs) than the control brand which was smoked for the first month. The lower delivery product was smoked with higher intensity than the control brand.

When the smoking patterns of the subjects who smoked these different brands were reproduced on the puff duplicator, the results showed that the weights of tar and nicotine taken from the higher delivery brand and the control brand were almost the same but the weights of tar and nicotine taken from the lower delivery brand were significantly less than taken from the control.

Further findings from these results were that the modified smoking patterns used to smoke the changed delivery brands were maintained for the month during which they were smoked. This shows that there was no adaptation during that time and that smokers will need longer than a month to become used to a product with changed delivery. It was also known that smokers did not alter the number of cigarettes smoked per day when they changed to either the higher or lower delivery brand. This means that compensatory changes are made in the way in which individual cigarettes are smoked, rather than smoking all cigarettes in the same way and altering the number of cigarettes smoked per day.

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Although these results show that on a group basis smokers do compensate for changed delivery they do not indicate whether the smokers were compensating for the tar delivery, the nicotine delivery or both. It was difficult to design experiments to answer this question as most commercial cigarettes in the UK at that time delivered very similar proportions of tar and nicotine. There is some indication from work in Southampton that normal nicotine delivery (around 1 mg) with low tar delivery is as unacceptable to many habitual smokers as a low nicotine and low tar product.

It is generally accepted that a large number of habitual smokers are influenced in their smoking habit by the amount of nicotine that they draw from a cigarette. Over a period of time, during which they are learning how to smoke effectively - that is so that they do not make themselves feel ill, but do derive pleasure and satisfaction from smoking - they probably build up an association in their minds between the mouth sensations such as flavour, irritation and 'impact' and the amount of smoke that gives them the satisfactions of smoking. This is a similar mechanism to Pavlov's dogs. If one of the major sensations of smoking is missing there will be a subconscious correction to the smoking pattern to try to adjust it back to the familiar level. By making such a correction the smoker will upset the other levels so that the product seems unsatisfactory.

Nicotine is the most pharmacologically active constituent in tobacco smoke and so probably the most usual factor responsible for the maintenance of the smoking habit. Psychologists have shown that the acts and rituals of smoking are of importance. Although these acts play a part in the smoking habit it is possible to consider alternatives which have at least financial advantages. It is possible to place a cigarette in the mouth and puff on it without lighting it, or to chew a pencil but such activities do not satisfy most smokers.

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similarly it is possible to buy non-tobacco cigarettes made from lettuce leaf (Bravu Smokes of USA) and other herbal mixtures with quite pleasant aroma but such products again are of little interest to habitual smokers and have been commercial failures. The main difference between tobacco and other shredded vegetable products is nicotine.

When smoke is inhaled by the smoker nearly all the nicotine is transferred from the smoke in the lungs to the blood stream. This transfer to the blood is very rapid and nicotine is circulated to all parts of the body within seconds. Nicotine has pharmacological effects both in the brain and other parts of the body. Some of these effects are due to nicotine itself whereas others are due to nicotine causing a release of other substances within the body such as adrenaline. Nicotine is metabolised in the body to a substance called cotinine within a comparatively short time - typically 20 minutes for the level of nicotine in the blood to fall to half its original concentration. Cotinine is almost pharmacologically inactive when compared with nicotine. The smoker who is therefore looking for the effects of nicotine must either smoke regularly in order to maintain a relatively constant nicotine level in his body or if he smokes infrequently will have a less constant, spiky nicotine level in his body.

These smokers, who smoke very frequently, or only occasionally may be considered as extreme cases who fall into different groups. The majority of smokers are between these two extremes. The smoker from the first group who smokes to maintain a constant blood level of nicotine is most likely trying to avoid the unpleasant sensations that he feels when he is not smoking. Without a cigarette he will become nervous, irritable and likely to make mistakes in his work. Such a smoker is likely to compensate for changed delivery if given a cigarette brand with different standard machine smoked deliveries to his usual

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brand so that as far as possible he maintains a constant blood level of nicotine.

Nicotine can only act as a stimulant when taken into the body at the levels available to smokers, yet smokers smoke during times of stress because they say it calms their nerves but the same smokers may also smoke when they are bored or tired because they say it gives them stimulation. The occasional smoker is therefore the subject of a remarkable paradox: or he uses the same product to achieve opposite effects. Smokers who smoke occasionally to level their emotional state will not necessarily compensate for changed delivery as long as the cigarette that they are smoking provides enough nicotine to make the anxious smoker calm or to elevate the emotional state of a bored smoker. The mechanism by which the leveling of emotional state taken place can be explained simply by imagining the shape of the brain emotional activity curve to be an inverted 'u'shape (i.e. ∧). Psychologists refer to this as an arousal curve. If a smoker is in a 'normal' state of arousal he will be on the left hand limb of the inverted U somewhere about the middle (i.e. ∧). If he is bored and depressed he will be lower on the left hand limb or if he is stressed and anxious high up on the left hand limb or on the top of the curve (i.e. ∧). A dose of nicotine will act as a stimulant, so the bored smoker will be moved up to the normal region and the over anxious smoker will move over the peak and down the right hand limb to a region of lower arousal, hence lower brain activity and effective calming (i.e. ∧).

Many smokers will fall between these two extremes and their smoking patterns suggest that they wish to maintain a certain blood level of nicotine but to add occasional spikes to it. Thus there is an element of habituation and adjustment of emotional levels. From this we can therefore predict that there will be a general trend for

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smokers to compensate, but individually some may show perfect equalisation of delivery from different products but others may not show any compensation at all.

There are several features of a cigarette design which would be expected to reduce the amount of smoke that a smoker might take from a cigarette. For example a cigarette with high draw resistance, i.e. a cigarette from which it is hard to draw smoke, or a cigarette that has high irritation levels that would cause the smoker pain. Cigarettes with unpleasant taste or flavour, or cigarettes that burn very fast during the smoulder period between puffs. Such features are not desirable characteristics as far as the smoker is concerned and are likely to cause the smoker to change to an alternative brand which he perceives as more pleasant or easier to smoke.

It is possible to consider nicotine as the component of cigarette smoke that controls the amount of smoke that a smoker takes from a cigarette. Nicotine taken in just the right amount by a smoker is pleasant and desirable yet in excess is aversive and unpleasant to the senses. The evidence for this can be seen when comparing the results of a number of studies in which cigarettes with different standard machine smoke nicotine deliveries have been smoked by people. Cigarettes with deliveries of 0.1, 0.4, 0.7 and 0.9mg nicotine have been smoked by panels in Southampton, and similar high smoking intensities were observed for all of these products (all the cigarettes were King Size Filter tipped). This suggested that they were all being smoked at maximum intensity by the smokers. Cigarettes with standard machine smoked deliveries of 1.4, 1.8 and 2.4mg of nicotine were smoked with decreasing intensity. From the latter series of three cigarettes the smokers took on average 2.0mg nicotine. Compensation may, therefore, be looked upon as a way of reducing the nicotine intake of a product which has the potential to deliver more than the smoker requires.

when a product is smoked which either has only just enough nicotine to satisfy the smoker when smoked at maximum intensity or cannot be smoked to deliver enough nicotine to satisfy the smoker then there will be less evidence of compensation.

These findings have been confirmed by recent studies at the University of Cambridge, where GRADC are working on some experiments in collaboration with Professor Mills. The results indicate that with low delivery smokers and middle tar smokers took similar amounts of smoke from experimental low delivery products, whether of normal tar to nicotine ratio or low tar to nicotine ratio.

The simple answer would seem to be to offer the smoker a product with comparatively high nicotine deliveries so that with a minimum of effort he could take the dose of nicotine suitable to his immediate needs. There is no lower limit to the amount of smoke a smoker might take from a cigarette but there is a maximum. The problem with this approach is that for most grades of tobacco the tar and nicotine deliveries are close to a constant ratio and the selective filtration of tar is not yet a practical proposition. This means that cigarettes with high nicotine deliveries are also strong in flavour and tend to be high in irritation. Most smokers would not be satisfied with a product that gave them their nicotine in only 2 or 3 small puffs because they not only require the nicotine to adjust their blood levels to a level avoid the unpleasant effects of not smoking or to adjust their emotional state, but it does not allow enough margin of error to avoid overshooting the optimum level and suffering the giddiness, nausea and pallor of excessive nicotine intake. (The sensations described by a naive smoker.) It is also true to say that most smokers enjoy smoking and like to take 6-12 puffs on a cigarette.

It is difficult to ignore the advice of the Health Authorities who advise smokers to give up smoking or change to a lower delivery

brand but there is now sufficient evidence to challenge the advice to change to a lower delivery brand, at least in the short-term. In general a majority of habitual smokers compensate for changed delivery, if they change to a lower delivery brand than their usual brand. If they choose a lower delivery brand which has a higher tar to nicotine ratio than their usual brand (which is often the case with unventilated lower delivery products) the smokers will in fact increase the amounts of tar and gas phase that they take in, in order to take the same amount of nicotine. More realistic advice to smokers would be to choose a brand with a lower tar to nicotine ratio which gives them the satisfaction that they require in the lowest amount of smoke taken in. However, as mentioned earlier, there are problems for smokers to learn to smoke cigarettes with lower tar to nicotine ratios to avoid the unpleasant effects of over-shooting nicotine intake.

In the longer term the general trend throughout the world is for more lower delivery products to be introduced onto the market. It is possible that smokers who start smoking a low delivery product will be satisfied with it - for example all the market leader brands in Germany have low levels by comparison with the U.K. It is difficult for the established smoker to make a sudden change to a different product but if subliminal changes (less than 20%) are made to a product over a number of years it is likely that a manufacturer could slowly reduce delivery levels without upsetting his customers. If delivery levels are reduced too quickly or eventually to a level which is so low that the nicotine is below the threshold of pharmacological activity then it is possible that the smoking habit would be rejected by a large number of smokers. It is not known where this threshold between just acceptable and rejection lies.

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TPM TO NICOTINE RATIOS FOR

CIGARETTES SMOKED BY PUFF DUPLICATOR

		PHASE I	PHASE II	PHASE III
SUBJECTS	DELIVERY IN PHASE II	TPM:NICOTINE	TPM:NICOTINE	TPM:NICOTINE
MALE	HIGH	14 • 4	13 • 5	15 • 0
MALE	LOW	15 • 2	13 • 6	14 • 3
FEMALE	HIGH	12 • 2	10 • 6	11 • 6
FEMALE	LOW	12 • 7	11 • 1	11 • 7
ALL	HIGH	13 • 3	12 • 0	13 • 3
ALL	LOW	13 • 3	12 • 0	13 • 0

MACHINE SMOKING
CONTROL [illegible] mg
HIGH 15.0 mg
LOW 1[illegible] mg

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EFFECT OF CHANGED DELIVERY ON

AVERAGE CARBON MONOXIDE DELIVERY BY DUPLICATION

SUBJECTS	DELIVERY IN PHASE III	PHASE I AVERAGE CO		PHASE II AVERAGE CO		PHASE III AVERAGE CO	
		mg	%	mg	%	mg	%
MALE	HIGH	30.4	4.23	28.7	4.78	33.1	4.60
MALE	LOW	31.5	4.12	25.0	2.68	33.5	4.04
FEMALE	HIGH	24.4	3.92	22.4	4.55	26.3	4.31
FEMALE	LOW	2 .3	3.61	15 .2	2.17	21.6	3.10
ALL	HIGH	27.4	4.03	25.6	4.67	29.7	4.45
ALL	LOW	26.4	3.82	20.2	2.53	29.1	4.32

MACHINE SMOKING	CONTROL	25.5	4.5
MACHINE SMOKING	HIGH	21.5	5.0
MACHINE SMOKING	LOW	21.0	5.4

EFFECT OF CHANGED DELIVERY ON

AVERAGE TPM DELIVERY BY DUPLICATION

		PHASE I	PHASE II	PHASE III
SUBJECTS	DELIVERY IN PHASE	AVERAGE TPM DELIVERY mg	AVERAGE TPM DELIVERY mg	AVERAGE TPM DELIVERY mg
MALE	HIGH	32 · 3	30 · 0	34 · 9
MALE	LOW	34 · 6	22 · 1	34 · 8
FEMALE	HIGH	25 · 0	23 · 2	22 · 5
FEMALE	LOW	23 · 5	10 · 8	19 · 0
ALL	HIGH	28 · 6	26 · 6	28 · 7
ALL	LOW	29 · 1	16 · 4	26 · 9

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EFFECT OF CHANGED DELIVERY ON

AVERAGE NICOTINE DELIVERY BY DURATION

		PHASE I	PHASE II	PHASE III
SUBJECTS	DELIVERY IN PHASE II	AVERAGE NICOTINE DELIVERY mg	AVERAGE NICOTINE DELIVERY mg	AVERAGE NICOTINE DELIVERY mg
MALE	HIGH	2 • 16	2 • 14	2 • 15
MALE	LOW	2 • 26	1 • 71	2 • 34
MALE	HIGH	2 • 04	2 • 17	1 • 95
FEMALE	LOW	1 • 90	0 • 98	1 • 61
ALL	HIGH	2 • 10	2 • 15	2 • 04
ALL	LOW	2 • 06	1 • 35	1 • 95

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EFFECT OF CHANGED DELIVERY ON

ESTIMATED AVERAGE NUMBER OF CIGARETTES SMOKED PER DAY

		PHASE I	PHASE II	PHASE III
SUBJECTS	DELIVERY IN PHASE II	NUMBER OF CIGS. PER DAY	NUMBER OF CIGS. PER DAY	NUMBER OF CIGS. PER DAY
MALE	HIGH	34 • 6	27 • 7	34 • 4
MALE	LOW	29 • 3	31 • 6	34 • 9
FEMALE	HIGH	31 • 8	32 • 1	32 • 2
FEMALE	LOW	30 • 1	33 • 1	30 • 9
ALL	HIGH	33 • 2	29 • 9	33 • 3
ALL	LOW	31 • 1	32 • 6	32 • 8

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EFFECT OF CHANGED DELIVERY ON

AVERAGE TOTAL PRESSURE TO DRAW PUFFS

		PHASE I	PHASE II	PHASE III
SUBJECTS	DELIVERY IN PHASE II	AVERAGE TOTAL DRAW PRESSURE cm.W.G sec.	AVERAGE TOTAL DRAW PRESSURE cm.W.G sec.	AVERAGE TOTAL DRAW PRESSURE cm.W.G sec.
MALE	HIGH	555 • 8	506 • 1	559 • 5
MALE	LOW	638 • 9	607 • 7	587 • 3
FEMALE	HIGH	458 • 8	392 • 4	439 • 5
FEMALE	LOW	469 • 5	446 • 5	435 • 2
ALL	HIGH	526 • 3	443 • 2	519 • 6
ALL	LOW	554 • 9	527 • 3	518 • 2

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STATISTICALLY SIGNIFICANT DIFFERENCES WHEN

SMOKING CHANGED DELIVERY CIGARETTES

VARIABLE	CHANGE TO HIGH DELIVERY	CHANGE TO LOW DELIVERY
PUFF NUMBER	LOWER	HIGHER
PUFF LENGTH	HIGHER	HIGHER
[illegible] PRESSURE DROP	HIGHER	LOWER
[illegible] TIME ALIGHT	LOWER	NO CHANGE
[illegible] NICOTINE	LOWER	HIGHER
[illegible] NICOTINE INTAKE	HIGHER	LOWER 2 OF 3 NO CHANGE 2 OF 3
[illegible] PRESSURE	LOWER	NO CHANGE
[illegible] PRESSURE	NO CHANGE	NO CHANGE
[illegible] VOLUME	LOWER	HIGHER
[illegible] VOLUME	LOWER	HIGHER
[illegible] RATION	LOWER	HIGHER
[illegible] DURATION	LOWER	HIGHER
[illegible] TIVAL	LOWER	NO CHANGE
[illegible] TERVAL	NO CHANGE	NO CHANGE 1 OF 3 LOWER 2 OF 3

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EFFECT OF CHANGED DELIVERY ON AVERAGE INTERVAL

SUBJECTS	DELIVERY IN PHASE II	PHASE I AVERAGE INTERVAL SEC.	PHASE II AVERAGE INTERVAL SEC.	PHASE III AVERAGE INTERVAL SEC.
MALE	HIGH	42 • 5	40 • 7	44 • 0
MALE	LOW	39 • 2	41 • 7	44 • 7
FEMALE	HIGH	34 • 4	32 • 4	34 • 5
FEMALE	LOW	33 • 8	32 • 7	37 • 0
ALL	HIGH	38 • 5	36 • 5	39 • 2
ALL	LOW	36 • 5	37 • 2	40 • 9

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EFFECT OF CHANGED DELIVERY ON

AVERAGE PUFF DURATION

SUBJECTS	DELIVERY IN PHASE II	PHASE I PUFF DURATION SEC.	PHASE II PUFF DURATION SEC.	PHASE III PUFF DURATION SEC.
MALE	HIGH	2 • 4	2 • 3	2 • 6
MALE	LOW	2 • 6	3 • 3	2 • 7
FEMALE	HIGH	2 • 1	1 • 9	2 • 1
FEMALE	LOW	2 • 3	2 • 3	2 • 1
ALL	HIGH	2 • 3	2 • 1	2 • 3
ALL	LOW	2 • 4	2 • 8	2 • 4

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ORDER OF SMOKING CIGARETTES IN EXPERIMENT TO INVESTIGATE THE EFFECTS OF CHANGED DELIVERY

SUBJECTS	PHASE I	PHASE II	PHASE III
4 MALE 4 FEMALE	EMBASSY KINGS (CONTROL)	EMBASSY EXTRA MILD (LOW)	EMBASSY KINGS (CONTROL)
4 MALE 4 FEMALE	EMBASSY KINGS (CONTROL)	EMBASSY KING SIZE (HIGH)	EMBASSY KINGS (CONTROL)

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EFFECT OF CHANGED DELIVERY ON

AVERAGE NUMBER OF PUFFS DRAWN.

		PHASE I	PHASE II	PHASE III
SUBJECTS	DELIVERY IN PHASE II	AVERAGE NUMBER OF PUFFS	AVERAGE NUMBER OF PUFFS	AVERAGE NUMBER OF PUFFS
MALE	HIGH	11 • 6	9 • 8	10 • 6
MALE	LOW	11 • 6	10 • 5	10 • 3
FEMALE	HIGH	14 • 4	13 • 1	14 • 4
FEMALE	LOW	13 • 6	13 • 6	12 • 6
ALL	HIGH	13 • 0	11 • 5	12 • 6
ALL	LOW	12 • 6	12 • 0	11 • 4

EFFECT OF CHANGED DELIVERY ON AVERAGE PUFF VOLUME

SUBJECTS	DELIVERY IN PHASE II	PHASE I AVERAGE PUFF VOLUME mℓ	PHASE II AVERAGE PUFF VOLUME mℓ	PHASE III AVERAGE PUFF VOLUME mℓ
MALE	HIGH	52 • 8	49 • 0	54 • 5
MALE	LOW	54 • 8	66 • 2	55 • 8
FEMALE	HIGH	34 • 3	30 • 3	34 • 1
FEMALE	LOW	37 • 4	40 • 3	36 • 4
ALL	HIGH	43 • 5	39 • 6	44 • 3
ALL	LOW	46 • 1	53 • 4	45 • 1

EFFECT OF CHANGED DELIVERY ON

AVERAGE TOTAL PUFF VOLUME

SUBJECTS	DELIVERY IN PHASE II	PHASE I AVERAGE TOTAL VOLUME ml	PHASE II AVERAGE TOTAL VOLUME ml	PHASE III AVERAGE TOTAL VOLUME ml
MALE	HIGH	590 • 4	469 • 7	583 • 8
MALE	LOW	640 • 8	703 • 9	590 • 3
FEMALE	HIGH	501 • 3	387 • 0	484 • 9
FEMALE	LOW	500 • 2	545 • 8	454 • 5
ALL	HIGH	545 • 8	453 • 4	534 • 4
ALL	LOW	570 • 5	624 • 8	522 • 4