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EXPERIMENTAL INVESTIGATIONS ON THE EFFECT OF CHRONIC CIGARETTE SMOKE INHALATION ON SYRIAN GOLDEN HAMSTERS AND APPLICATION OF CIGARETTE SMOKE CONDENSATE ON MOUSE SKIN*

Ever since numerous other working groups, especially Wynder and Hoffmann in the USA as well as Druckrey and Schmähl in Germany have been engaged in clarifying the question of the tumor inducing effect of cigarette smoke condensates, many investigators have tried over and over again to find ways to identify the carcinogenic or cocarcinogenic effects by fractionating the cigarette smoke condensate, to enable an elimination of harmful substances. Repeatedly, it was tried to develop methods and models in order to study the effect of whole smoke by smoke exposure in order to obtain more knowledge about the effect of whole smoke or to obtain information of more conclusive evidence by means of better bioassays.

At the conference in Lausanne (1969) and Gatlinburg (1970), and more in detail at the conference in Washington (1970) and New York (1970) we had reported on our up to that date existing results, the fundamental conception of which you know.

1.) All our endeavours are bent on the search for a way to a "safer or less harmful cigarette" in terms of definition, often explained by Wynder and others. Up to now, the condensed smoke was tested predominantly on the skin and the subcutaneous tissue.

*Lecture held at the National Cancer Institute, Bethesda/Maryland USA

2.) In order to better evaluate the biological effect we have not only performed extensive animal experiments but we have also looked for new bioassays with a higher value of evidence. All our efforts to improve the smoke exposure experiments were explained by us in detail, just as the equipment and methods we designed and resulting experiences.

3.) A special problem is the question of comparability between the epicutaneous test and the smoke exposure test. On one hand we are investigating the effect of condensate on the skin, and on the other hand the effect of fresh whole smoke in the respiratory tract, i.e. at a site where it also can become effective in man. Problems of dosage, as you know, are playing a decisive role in comparative investigations; also decisive are questions of the organotrophic effect of certain carcinogens suspected or proved in smoke. The question, whether certain nitrosamines, showing no carcinogenic effect on the skin, play a significant role in the total effect of smoke in the respiratory tract is of decisive importance, as we have often discussed.

4.) The test methods which are also required for other inhalable substances by the Food and Drug Administration in USA or by the Ministry of Health in Germany are applicable for studying new tobacco additives as well as the effect of whole smoke. The optimal test method is an effective smoke exposure experiment, i.e. that in a great number of animals alterations in organs or in the tissue are detectable. Only in a smoke exposure experiment we can study, for instance, the effect of the vapor phase. Factors, such as CO and other components of the vapor phase which are not effective on the skin, can only in this way be tested as a whole.

5.) The fundamental question is: When can a test be considered practicable and of evidence? In New York (1970) we have answered this question as follows:

A smoke exposure experiment is then effective when, with a maximum tolerable dose, in a sufficient number of animals malignant growth in the respiratory tract is induced, and this in a quantity which allows evaluation of significant differences within the experimental groups, for example differences between standard cigarettes and cigarettes from reconstituted tobacco sheets or cigarettes with sodium nitrate as additive or other cigarettes. Only, in this way, we may be able to approximately assess what we may consider "safer" or "less harmful".

The results of our second long-term experiment with 8775 mice which is in press in the Journal of Cancer Research and Clinical Oncology may be summarized as follows (table 1):

Of five used condensates from different reconstituted tobacco sheet cigarettes, two (= EG_1, EG_2 and ES) are showing a strong reduction of the tumor inducing effect on the mouse skin, calculated on the basis per gram of the administered substance. This reduction is lying below 50% compared with the activity of standard condensate. A condensate of one reconstituted tobacco sheet cigarette (EB) shows a stronger, and two condensates from reconstituted tobacco sheet cigarettes (EW and EA) show an equally strong activity compared to the condensate of the standard cigarette.

Following a detailed statistical evaluation of our experiments, performed with a great number of animals, it was found that sodium nitrate as additive to tobacco EN as well as to tobacco sheet EG_3 considerably reduced the tumor inducing effect, as already described by Wynder and others.

Detailed statistical evaluations of the experiment showed that in comparison with treatment of DMBA alone, a combined treatment of an initial dose of 140 γ DMBA and subsequent chronic condensate application up to 2 years revealed a distinct more-than-additive response, which may be interpreted in terms of a cocarcinogenic effect.

Of special interest are our findings as to the dimension of the diffusion area of the individual condensate drops (fig. 1 and table 2) dependent on their solubility. The differences were so distinct that we have included the diffusion area in the evaluation (table 1). This figure (1) gives you some examples of the differences. The different dimension of the diffusion area at the skin might be of decisive importance with respect to the activity of carcinogens and cocarcinogens. This should be understood in terms of the "impact" theory of carcinogenesis by Timoféeff.

We were, of course, interested whether all results observed up to now in the epicutaneous experiment would become apparent in the same way also in the smoke exposure experiment. This question cannot be clearly answered, even after having obtained the results.

In the following tables (3 and 4) you may see experimental conditions for smoke exposure. The experiment comprised 3600 Syrian golden hamsters, to which another 840 hamsters have to be added which were used for hematological or biochemical examinations. In total, 4440 hamsters were used in the smoke inhalation experiment.

This table (5) lists some questions which arose in connection with the smoke inhalation experiment:

1.) Is the method applied reproducible in comparison to the results of the already published pilot-test?
2.) Are the results comparable when using animals of other colonies (pilot test: hamsters from colony Seeboth, Germany; long-term inhalation experiment: hamsters from colony Zucca, USA, or from colony Coombehurst, England, for biochemical examinations)?
3.) Is there proof for a dose-response-relationship?
4.) Is the number of animals and the dose administered sufficient to evaluate significant differences?

5.) Is the test predicative of chronic toxicity, especially of carcinogenic toxicity?

6.) Do skin painting and inhalation experiments show similar results?

7.) Which results are
   a) caused by smoke exposure only?
   b) enhanced by smoke exposure?
   c) dependent or enhanced by carcinogenic additives?
   d) not caused by experimental treatment?

All findings were evaluated by means of electronic data processing (Prof. Schneider, Institute for Biometry and Documentation, Hannover). The reader of the whole paper will see that all possible correlations were evaluated.

In the following, we want to discuss the results of the smoke inhalation experiment. The question of reproducibility, even if animals from different colonies are used, can be definitely answered in the affirmative and is explained by the following findings:

The dose-response-relationship is evident in various findings:

1.) In the survival time:
You will see in this table (6) that in comparison to the controls, the mean survival time is distinctly reduced in those animals having received increased doses of smoke and in those animals having received an additional treatment of DMBA.

2.) In the development of body weight:
This table (7) demonstrates that the highest decrease of body weight is observed in the group having received the highest amount of smoke. The loss in body weight is also evident in comparison to the controls.

3.) In alterations of the larynx:
This will be discussed in the following:

The number of animals used as well as the dose administered is sufficient for statistical evaluation; this is apparent from statistical evaluation of significance in the original paper given for publication.

As optimal dose may be considered the dose II, i.e. 30 cigarettes twice daily or 10 min. smoke exposure twice daily. Owing to the marked difference of the two sexes as to mortality and incidence of certain diseases, the use of male and female animals was necessary.

We have already mentioned some of the alterations provoked by chronic smoke exposure extended throughout the whole lifespan. They are

1.) the findings in the larynx,
2.) the inhibition of body weight development,
3.) the reduction of survival time and, moreover,

the increase of Hb and of erythrocytes should be mentioned, which may be explained as consequence of the high dose of smoke offered without intervals and as a result of strong increase of the CO-Hb. This result is distinctly influenced by the method, as already explained, and, therefore, does not permit any conclusions as to the smoking habits of man. The test gives us the following information:

1.) In 800 control animals and in 160 animals treated with the vapor phase of the standard cigarettes, laryngeal leucoplakia of stage 1 is found relatively seldom, and stage 2 of laryngeal leucoplakia was observed only in one control animal. Similar observations were made in the group of animals treated with nitrosamines only; there, too, only stage 1 of laryngeal alterations was found. The group of 160 hamsters treated once with DMBA shows an exception. Besides 4 cases of stage 1 and 1 case of stage 2 of laryngeal leucoplakia, 3 cases of the papillomatous stage 4 were found.

2.) The various stages of laryngeal alterations appear in an

order of time, i.e. they are dependent on dose-time factors. This may be demonstrated by some examples (table 9 and 10), giving also information about the time of appearance, e.g. of stages 5 and 6 which in group 1 appeared distinctly earlier than, for instance, in the comparable group 5. Here already, the more-than-additive effect of the smoke is apparent, i.e. the effect cannot be only explained as summation of the effect of dose II = 2 x 30 cigarettes and DMBA.

3.) In general, animals which died early or animals having received cigarettes with lower activity have more frequently stages of lower degree, e.g. stages 2 - 4. Cigarettes with lower activity clearly show more rarely the stages of higher degree, that is stage 5 and carcinomas (stage 6).

The following tables (11 and 12) distinctly demonstrate the difference of stages within the groups. In order to offer a clear overall picture, we have summarized the most important findings in this table (13). It is evident that a reduction of condensate by using $NaNO_3$ as additive or reconstituted tobacco sheets or filters reduced alterations, especially the incidence of stage 5 and 6 (cancer) in the larynx. This is also concerned for the black cigarette showing a very low condensate yield due to the mixture used in this experiment. A significant reduction of the biological effect is demonstrated also under consideration of different numbers of puffs and period of smoke exposure. This becomes very impressive when expressed in terms of R = relative potency. Here, we believe to find a <u>way towards a safer cigarette</u> which should inspire and influence our future work.

For almost 25 years we have been engaged in questions of defining and evaluating the term of precanceroses or preliminary stages of cancer. Precanceroses or precanceroses in a narrower or broader sense of the word, were classified by Miescher into "obligatory" and "facultative" precanceroses and are considered like this in many countries up to this date.

In "facultative" precanceroses (table 14) there is probability of malignant degeneration which we rate today just as we did in 1966. The same is true for the "obligatory" precanceroses.

For our classification of stages we have chosen the Atlas of the Armed Forces Institute of Pathology, because classification of laryngeal alterations fully corresponds to our conception, i.e. to a large degree, same is in conformity with our experiences in man and animal.

We would like, for instance, to classify the stages 2, 3 and 4 as "facultative" precanceroses and to compare the stages 3 and 4 with papillomas of the mouse skin. Also in practice, we are classifying papillomas and carcinomas in animals and man differently, partly for reasons of morphology, partly for reasons of experience. We do not yet see in all precancerous lesions the "evidence" for a carcinogenic effect of substances.

Stage 5 should be considered as "obligatory" precanceroses because very often it is difficult to differentiate same from preinvasive carcinomas, i.e. the so-called carcinoma in situ. Our classification of stage 5 is also in conformity with the mentioned American Atlas, defining the lesions as carcinoma-like. Carcinomas are called those tumors showing criteria which are also basis of diagnostics in human pathology.

The following figures as well as some slides of the findings in the larynx will demonstrate this.

The lacking infiltration of small carcinomas of the larynx into the cartilage is not surprising. We have observed the same phenomenon during experiments in the same area following application of nitrosamines and polycyclic aromatic hydrocarbons. In 100 mice, for example, we have induced with high doses of 3.4-benzopyrene, carcinomas of often enormous size of the auricle, and we hardly ever observed an infiltration of the tumor into the cartilage.

The tumor grew round the cartilage and generally was not infiltrating. The lack of metastases is no absolute criteria either, as animals following chronic smoke exposure rarely died of laryngeal alterations but of other causes; this is confirmed by the evaluation of findings upon autopsy of the animals with laryngeal carcinomas. Inflammations of the oral and nasal cavity as well as of the larynx did not occur more frequently in smoke-exposed animals than in controls as you will see from this table (15).

The very rare appearance of lung carcinomas - there was only one case following the combined treatment of DMBA and smoke - may be explained by the methodically induced accumulation of the smoke components in the larynx. This figure shows a typical squamous cell carcinoma. Mucous-secreting bronchial adenomas, as described by SAFFIOTTI, were observed only twice, one in group 2 (DMBA) and one in group 5 (dose II of smoke exposure).

The clearly more-than-additive effect of the combined treatment of DMBA and smoke compared to DMBA alone or to smoke alone (dose II) demonstrates this table (16).

We consider this as a confirmation of results of many epicutaneous tests which show that factors become effective to be interpreted as cocarcinogenic factors. According to the findings obtained, DMBA seems to attack the same areas of the respiratory tract as smoke particles, which may lead to the conclusion that in the total effect, great importance may be attributed to polycyclic aromatic hydrocarbons of the smoke.

The effect of combined treatment with smoke and diethylnitrosamine was surprising. We intentionally did not administer the nitrosamine at the beginning, because following initial treatment in earlier experiments, the animal mortality rate was too high, due to high incidence of papillomas in the respiratory tract.

The following results should be emphasized in connection with the question on the "effect of nitrosamines".

1.) the additional nitrosamine effect does not enhance the "smoke effect" (table 12)
2.) $NaNO_3$ as additive does not enhance tumor induction in the larynx (table 13)
3.) Following nitrosamine application, papillomas of other morphological structure and localisation in the larynx occurred than following smoke exposure alone.
4.) Cigarettes treated with a high dose of sodium nitrate showed no findings explicable as nitrosamine effect. These are only found in the area of the bronchi and trachea in animals treated with DENA and DMBA (table 18).

Which findings have been enhanced by smoke exposure?
The incidence of the so-called smoke cells which, as already CONNING replied to OTTO in Lausanne, are no smoke cells. In smoke-exposed and also in other groups this type of cells is increased. In controls, the frequency was, for instance, 9.9 - 15%, in smoke-exposed animals 28 - 70%. An increase of the so-called "adenomatoid lesions" could not be clearly proved in smoke-exposed animals.

Which findings may be attributed to simle treatment with DMBA only?
This will be clearly demonstrated in some of the following tables:

1.) The increase of pharyngeal tumors (table 19)
2.) the increase of tumors in the oral cavity (table 20)
3.) the tumors of the esophagus and stomach, especially of the papillomas (table 21)
4.) the increase of liver tumors (table 22)
5.) the early induction of tumors of the hemopoietic or lymphoreticular system (table 23)
6.) the increase of ovary cysts in controls (= 4.6%) and in animals treated with DMBA (= 20 - 30%).

Which findings are not in relationship with the treatment? There is no evident relationship between treatment and induction of tumors in the soft tissue and subcutaneous tissue of the skin (table 24), in the nasal cavity (table 25) and in the urinary bladder. Only one bladder carcinoma appeared in the group 18A. The animals of this group were treated with DENA. The incidence of adrenal tumors was age-dependent, and the distribution of sexes with regard to tumor types was very different (table 26).

The incidence of lung thrombi, pneumonia and bronchitis was similar in all groups. Smoke-exposed animals did not exhibit lung emphysema more frequently (table 27), and this could be confirmed by two quantitative measuring methods:

1 - by densimetric measurements of the lung of old, young, smoke-exposed and control animals (table 28)

2 - by determination of the number of alveoli in smoke-exposed and control animals (table 29).

Also the incidence of gastric ulcer was not increased in smoke-exposed animals (table 30).

We have intensively been engaged in studying the incidence of heart diseases and cardiovascular diseases in smoke-exposed animals.

The results show (table 31) that

1 - diseases of heart valves could not be demonstrated more frequently in smoke-exposed animals

2 - inflammatory vascular diseases occurred more frequently in female than in male animals. They are, however, in no relationship to smoke-exposure.

3 - arteriosclerotic alterations could be demonstrated only once as calcification of the media.

This finding is worth mentioning, as animals with severe amyloidosis of the kidney, i.e. stage III - the so-called amyloid cirrhosis of the kidney - showed also hypertension. (table 32 and figure).

Additonally, it should be pointed out, that, regarding the subject of arteriosclerosis, the chronic CO-Hb increase which was dependent on the method and which was expressed in a low increase of Hb and erythrocytes, obviously did not become effective in the vessels.

Moreover, it should be pointed out that the entire biochemical findings (tables 33 and 34), especially insofar as the fat metabolism is concerned, did not show any pathological alterations.

Finally, it should be added that extensive examinations of the testicles (tables 35 and 36) did not give any indication that smoke-exposure is a cause of the severe testicle atrophy of the hamster, which could often be found at an early age.

Since it would take far too long to go into all other findings, we have mentioned those of greatest importance.

In summary it can be said that the method designed gives findings which can be evaluated and reproduced. A number of findings which could be expected, such as the increase of gastric ulcer, vascular diseases, the influence of fat metabolism and lung emphysema or bladder tumors, did not occur. The findings following combined treatment with DMBA and nitrosamine give a number of informations and further suggestions.

Finally, as a summary of this paper, I should like to express our opinion that, on the basis of further international collaboration in such a good way, the way to a "safer cigarette" can possibly be found soon. This is the purpose of all our scientific endeavours.

In conclusion, I would like to express my thanks to my collaborators, Dr. Chevalier, Dr. Harke, Dr. Lafrenz and Mr. Reckzeh, who have essentially participated in the experiments. Moreover, I would like to express my thanks for your kind attention to my presentation.

Bibliographical references may be obtained on request.

TABLE 1 COMPARISON OF STANDARDIZED PERCENTAGE RESPONSE AT THE END OF EXPERIMENT WITH (TS) OR WITHOUT (SH) CONSIDERATION OF THE DIFFUSION AREA

SMOKE CONDENSATE	DOSE LEVEL	CARCINOMAS SH	CARCINOMAS TS	TUMOURS SH	TUMOURS TS
STANDARD CIGARETTE E_2	1/2	6.7	6.7	16.4	16.4
	1	16.5	19.1	27.6	31.6
	2	14.1	19.9	25.3	39.1
RECONSTITUTED TOBACCO SHEETS EW	1	15.7	16.8	25.6	27.2
	2	18.9	26.7	31.6	43.0
RECONSTITUTED TOBACCO SHEETS EB	1	26.4	33.4	39.2	49.3
	2	15.5	23.2	31.1	44.2
RECONSTITUTED TOBACCO SHEETS EA	1	19.2	24.7	30.1	37.8
	2	15.7	23.5	34.2	48.2
RECONSTITUTED TOBACCO SHEETS ES	1	7.2	9.2	15.0	18.9
	2	3.5	5.1	11.7	16.8
RECONSTITUTED TOBACCO SHEETS EG_1	1	3.4	4.0	8.0	9.4
	2	2.5	3.7	9.6	13.5
RECONSTITUTED TOBACCO SHEETS EG_2	1	2.5	3.2	8.2	10.2
	2	3.6	5.3	8.9	12.9
RECONSTITUTED TOBACCO SHEETS EG3	1	1.9	–	3.4	4.3
	2	–	–	3.4	5.2
$E_2 + NaNO_3$ EN	1	1.0	1.4	7.6	10.4
	2	0.9	1.5	8.2	13.3

TABLE 4

DIFFUSION AREA OF 0,2 ml SMOKE-CONDENSATE ON FILTER-PAPER (S & S 595)

SMOKE CONDENSATE	DOSE LEVEL	DIFFUSION AREA ON FILTER-PAPER cm^3
STANDARD CIGARETTE E_2	1/2 1 2	20.4 14.6 9.8
RECONSTITUTED TOBACCO SHEET EW	1 2	17.7 9.3
RECONSTITUTED TOBACCO SHEET EB	1 2	11.6 8.3
RECONSTITUTED TOBACCO SHEET EA	1 2	11.6 8.3
RECONSTITUTED TOBACCO SHEET ES	1 2	12.2 9.3
RECONSTITUTED TOBACCO SHEET EG_1	1 2	14.5 9.6
RECONSTITUTED TOBACCO SHEET EG_2	1 2	12.9 9.3
RECONSTITUTED TOBACCO SHEET EG_3	1 2	12.6 8.3
[illegible]	1 2	10.4 8.6

TABLE

CHRONIC INHALATION EXPERIMENTS ON SYRIAN GOLDEN HAMSTERS

GROUP	TYPE OF CIGARETTE	SMOKING CYCLE	TREATMENT BEFORE EXPOSURE TO SMOKE	NUMBER OF ANIMALS ♀	NUMBER OF ANIMALS ♂
1	E_2 (STANDARD CIGARETTE)	2 x 30 CIG. DAILY	500 γ DMBA IN CMC INJECTED INTRATRACHEALLY	80	80
2	–	CONTROL	500 γ DMBA IN CMC INJECTED INTRATRACHEALLY	80	80
3	–	CONTROL	–	100	100
K	–	CONTROL	–	300	300
4	E_2 (STANDARD CIGARETTE)	1 x 30 CIG. DAILY	–	80	80
5	E_2 (STANDARD CIGARETTE)	2 x 30 CIG. DAILY	–	80	80
6	E_2 (STANDARD CIGARETTE)	3 x 30 CIG. DAILY	–	80	80
7	E_2 (STANDARD CIGARETTE)	GAS-PHASE FROM 2x30 CIG. DAILY	–	80	80
8	–	2x10 MIN. AIR DAILY	–	80	80
9	EN (E_2 + 8% $NaNO_3$)	2x30 CIG. DAILY	–	80	80
10	EG_3 (RECONST. TOBACCO SHEET FROM E_2 + 6.1% $NaNO_3$ ACCORDING TO GERLACH-PROCESS)	2x30 CIG. DAILY	–	80	80
11	EG_1 (RECONST. TOBACCO SHEET FROM E_2 ACCORDING TO GERLACH-PROCESS)	2x30 CIG. DAILY	–	80	80

TABLE E 11

CHRONIC INHALATION EXPERIMENTS ON SYRIAN GOLDEN HAMSTERS

GROUP	TYPE OF CIGARETTE	SMOKING CYCLE	ADDITIONAL TREATMENT OF ANIMALS	NUMBER OF ANIMAL ♀	♂
12	E_2 (STANDARD CIGARETTE)	2 x 30 CIG. DAILY	500 γ ASBESTOS IN CMC INJECTED INTRATRACHEALLY BEFORE EXPOSURE TO SMOKE	80	80
13	–	NOT EXPOSED TO SMOKE	500 γ ASBESTOS IN CMC INJECTED INTRATRACHEALLY	80	80
14	"BLACK CIGARETTE" = Z	2 x 30 CIG. DAILY	–	80	80
15	STANDARD CIGARETTE WITH ACETATE FILTER = A	2 x 30 CIG. DAILY	–	80	80
16	STANDARD CIGARETTE WITH CELLUOSE FILTER = D	2 x 30 CIG. DAILY	–	80	80
17	STANDARD CIGARETTE WITH CHARCOAL FILTER = K	2 x 30 CIG. DAILY	–	80	80
18	E_2 (STANDARD CIGARETTE)	2 x 30 CIG. DAILY	4 x 1 mg DENA/100 g BODY WEIGHT ADMINSTERED IN 52. AND 53. WEEK AFTER START OF EXPERIMENT	80	80
18-A	–	NOT EXPOSED TO SMOKE	4 x 1 mg DENA/100 g BODY WEIGHT ADMINSTERED IN 52. AND 53 WEEK AFTER START OF EXPERIMENT	45[K]	45[K]

TABLE 5

CONSIDERING THE INHALATION EXPERIMENTS TO FOLLOWING QUESTIONS ARISE :

1. IS THE METHOD APPLIED REPRODUCIBLE IN COMPARISON TO THE RESULTS OF THE ALREADY PUBLISHED PILOT TEST ?

2. ARE THE RESULTS COMPARABLE WHEN USING ANIMALS OF OTHER COLONIES (PILOT TEST: HAMSTERS FROM COLONY SEEBOTH, GERMANY; MAIN EXPERIMENT: HAMSTERS FROM COLONY ZUCCA, USA, OR COOMBEHURST, ENGLAND) ?

3. IS THERE PROOF FOR A DOSE-RESPONSE-RELATIONSHIP

4. IS THE NUMBER OF ANIMALS AND THE DOSE ADMINSTERED SUFFICIENT TO EVALUATE SIGNIFICANT DIFFERENCES ?

5. IS THE TEST PREDICATIVE OF CHRONIC TOXICITY ESPECIALLY OF CARCINOGENIC TOXICITY ?

6. ARE THERE SIMILAR FINDINGS IN SKIN PAINTING TEST AND INHALATION EXPERIMENTS ?

7. WHICH RESULTS ARE
   a. CAUSED BY SMOKE EXPOSURE ONLY ?
   b. ENHANCED BY SMOKE EXPOSURE ?
   c. DEPENDENT OR ENHANCED BY CARCINOGENIC ADDITIVES ?
   d. NOT CAUSED BY EXPERIMENTAL TREATMENT ?

TABLE 6

MEAN SURVIVAL TIME

CONTROLS (C) > DMBA > ST./III

	SEX	n	$\bar{x}$	s	$s_{\bar{x}}$
DMBA +ST./II	♀	80	45.37	16.98	1.90
	♂	80	52.95	28.53	3.19
DMBA	♀	80	46.17	17.48	1.95
	♂	80	58.64	28.72	3.21
C	♀	100	57.34	17.16	1.72
	♂	100	85.81	29.39	2.94
ST./I	♀	80	47.54	23.66	2.64
	♂	80	63.22	31.57	3.53
ST./II	♀	80	47.72	22.92	2.56
	♂	80	64.31	39.56	4.42
ST./III	♀	80	46.00	22.66	2.53
	♂	80	53.56	34.96	3.91

TABLE 16

ALTERATION OF BODY WEIGHT

	SEX	n	$\bar{x}$	s	$s_{\bar{x}}$
DMBA +ST./II	♀	80	-8.64	14.72	1.65
	♂	80	-5.43	19.49	2.18
DMBA	♀	78	+6.45	21.06	2.38
	♂	80	+2.65	21.22	2.37
C	♀	100	+7.22	18.21	1.82
	♂	100	+25.57	27.81	2.78
ST./I	♀	80	+7.00	21.59	2.41
	♂	80	+11.60	20.66	2.31
ST./II	♀	80	-2.44	14.10	1.58
	♂	80	+1.64	21.81	2.44
ST./III	♀	80	-0.01	16.42	1.84
	♂	80	-2.40	19.47	2.18

MOST PRONOUNCED REDUCTION IN BODY WEIGHT AT THE END OF EXPERIMENT WAS OBSERVED IN THE GROUPS: DMBA+ST./II AND ST./III

TABLE 8

INCIDENCE OF LEUCOPLAKIA IN CONTROL ANIMALS ETC.

I. INCIDENCE OF LEUCOPLAKIA IN 800 CONTROL ANIMALS :

STAGE 1 :	12 CASES	=	1.5 %
STAGE 2 :	1 CASE	=	0.13%

II. INCIDENCE OF LEUCOPLAKIA IN 160 ANIMALS EXPOSED TO VAPOR PHASE

STAGE 1 :	9 CASES	=	5.6 %

III. INCIDENCE OF LEUCOPLAKIA IN 160 ANIMALS ONCE TREATED WITH DMBA WITHOUT EXPOSURE TO SMOKE :

STAGE 1 :	4 CASES	=	2.5 %
STAGE 2 :	1 CASE	=	0.6 %
STAGE 4 :	3 CASES	=	1.9 %

IV. INCIDENCE OF LEUCOPLAKIA IN ANIMALS TREATED WITH 4 x 1 mg DENA / 100 g BODY WEIGHT (IN 52. AND 53. WEEK), ANIMALS NOT BEING EXPOSED TO SMOKE :

STAGE 1 :	3 CASES	=	3.5 %

TABLE (9)

RELATION BETWEEN AGE AND STAGE TO LEUKOPLAKIA OF LARYNX

GROUP 4 (♂ + ♀)

TREATMENT PERIOD (WEEKS)	STAGES						
	1	2	3	4	5	6	TOTAL
0 - 25	7		1				8
26 - 50	18	2	1	1			22
51 - 75	17	20	25	11	5		78
76 - 100	7	11	15	7	10	1	51
> 100	2	6	8	1	3		20
	51	39	50	20	18	1	179

$X^2 = 65.3$ P = 0.52

GROUP 5 (♂ + ♀)

TREATMENT PERIOD (WEEKS)	STAGES						
	1	2	3	4	5	6	TOTAL
0 - 25	10	1	2	1			14
26 - 50	23	9	12		1		45
51 - 75	9	17	8	7	13	4	58
76 - 100		4	10	9	18	5	46
> 100		3	18	4	16	8	49
	42	34	50	21	48	17	212

$X^2 = 117.2$ P = 0.60

GROUP 6 (♂ + ♀)

TREATMENT PERIOD (WEEKS)	STAGES						
	1	2	3	4	5	6	TOTAL
1 - 25	7		3	2			12
26 - 50	15	6	4	4	3		32
51 - 75	13	11	14	13	23	4	78
76 - 100		6	15	8	20	6	55
> 100		1	4	1	3	1	10
	35	24	40	28	49	11	187

X^2 = 57.9 P = 0.40

TABLE 10

RELATION BETWEEN AGE AND STAGE TO LEUCOPLAKIA OF LARYNX

GROUP 1 (♂ + ♀)

TREATMENT PERIOD (WEEKS)	STAGES						
	1	2	3	4	5	6	TOTAL
0 - 25	7		4	2			13
26 - 50	16	6	13	23	11	5	74
51 - 75	3	5	7	41	47	21	124
76-100			1	11	13	5	30
>100			1	2	2	1	6
	26	11	26	79	73	32	247

$X^2 = 82.15$ P = 0.50

GROUP 5 (♂ + ♀)

TREATMENT PERIOD (WEEKS)	STAGES						
	1	2	3	4	5	6	TOTAL
0 - 25	10	1	2	1			14
26 - 50	23	9	12		1		45
51 - 75	9	17	8	7	13	4	58
76-100		4	10	9	18	5	46
> 100		3	18	4	16	8	49
	42	34	50	21	48	17	212

$X^2 = 117.2$ P = 0.60

TABLE 11

INCIDENCE OF LEUCOPLAKIA AND CARCINOMA (LARYNX)

STAGE	1	2	3	4
Control	K ♀♂ 1.0%	K ♀♂ 0.2%	K ♀♂ 0.0%	K ♀♂ 0.0%
DMBA + standard cig./II	1 ♀♂ 16.3%	1 ♀♂ 6.9%	1 ♀♂ 16.3%	1 ♀♂ 43.8%
DMBA	2 ♀♂ 2.5%	2 ♀♂ 0.6%	2 ♀♂ 0.0%	2 ♀♂ 1.3%
Control	3 ♀♂ 3.0%	3 ♀♂ 0.0%	3 ♀♂ 0.0%	3 ♀♂ 0.0%
Standard cig./I x30	4 ♀♂ 31.9%	4 ♀♂ 24.4%	4 ♀♂ 31.3%	4 ♀♂ 12.5%
Standard cig./II x30	5 ♀♂ 26.3%	5 ♀♂ 21.3%	5 ♀♂ 31.3%	5 ♀♂ 13.1%
Standard cig./III x30	6 ♀♂ 21.9%	6 ♀♂ 15.0%	6 ♀♂ 25.0%	6 ♀♂ 17.5%
Vapor Phase of standard cig./II	7 ♀♂ 5.6%	7 ♀♂ 0.0%	7 ♀♂ 0.0%	7 ♀♂ 0.0%
Fresh air (Placebo)	8 ♀♂ 3.1%	8 ♀♂ 0.0%	8 ♀♂ 0.0%	8 ♀♂ 0.0%
Standard cig./II + $NaNO_3$	9 ♀♂ 15.6%	9 ♀♂ 10.6%	9 ♀♂ 26.9%	9 ♀♂ 23.1%
Reconst. Tobacco Sheet II + $NaNO_3$	10 ♀♂ 15.0%	10 ♀♂ 8.1%	10 ♀♂ 33.8%	10 ♀♂ 31.3%
Reconst. Tobacco Sheet/II	11 ♀♂ 14.4%	11 ♀♂ 11.3%	11 ♀♂ 33.8%	11 ♀♂ 21.9%
Standard cig./II + asbestos	12 ♀♂ 6.3%	12 ♀♂ 3.1%	12 ♀♂ 78.1%	12 ♀♂ 15.6%
Asbestos	13 ♀♂ 0.0%	13 ♀♂ 0.0%	13 ♀♂ 0.0%	13 ♀♂ 0.0%
"Black cig."/II	14 ♀♂ 10.0%	14 ♀♂ 20.6%	14 ♀♂ 66.9%	14 ♀♂ 4.3%
Standard cig./II with acetate filter	15 ♀♂ 6.3%	15 ♀♂ 18.1%	15 ♀♂ 68.1%	15 ♀♂ 9.1%
Standard cig./II with cellulose filter	16 ♀♂ 10.0%	16 ♀♂ 15.6%	16 ♀♂ 63.7%	16 ♀♂ 5.6%
Standard cig./II with charcoal filter	17 ♀♂ 8.1%	17 ♀♂ 6.9%	17 ♀♂ 68.8%	17 ♀♂ 11.3%
Standard cig./II + DENA	18 ♀♂ 12.5%	18 ♀♂ 7.5%	18 ♀♂ 68.1%	18 ♀♂ 20.0%

TABLE 19

INCIDENCE OF LEUKOPLAKIA AND CARCINOMA

STAGE	3	4	5	6
Control	K ♀♂ 0.0%	K ♀♂ 0.0%	K ♀♂ 0.0%	K ♀♂ 0.0 %
DMBA + standard cig./ II	1 ♀♂ 16.3%	1 ♀♂ 49.4%	1 ♀♂ 45.6 %	1 ♀♂ 20.0%
DMBA	2 ♀♂ 0.0%	2 ♀♂ 1.9%	2 ♀♂ 0.0 %	2 ♀♂ 0.0 %
Control	3 ♀♂ 0.0%	3 ♀♂ 0.0%	3 ♀♂ 0.0 %	3 ♀♂ 0.0 %
Standard cig./ I	4 ♀♂ 31.3%	4 ♀♂ 12.5%	4 ♀♂ 11.3 %	4 ♀♂ 0.6 %
Standard cig./ II	5 ♀♂ 31.3%	5 ♀♂ 13.1%	5 ♀♂ 30.0 %	5 ♀♂ 10.6%
Standard cig./ III	6 ♀♂ 25.0%	6 ♀♂ 17.5%	6 ♀♂ 30.6 %	6 ♀♂ 6.9 %
Vapor Phase of standard cig./ II	7 ♀♂ 0.0%	7 ♀♂ 0.0%	7 ♀♂ 0.0 %	7 ♀♂ 0.0 %
Fresh air (Placebo)	8 ♀♂ 0.0%	8 ♀♂ 0.0%	8 ♀♂ 0.0 %	8 ♀♂ 0.0 %
Standard cig./ II + $NaNO_3$	9 ♀♂ 26.9%	9 ♀♂ 23.1 %	9 ♀♂ 15.6 %	9 ♀♂ 2.5 %
Reconst. Tobacco Sheet II + $NaNO_3$	10 ♀♂ 33.8%	10 ♀♂ 31.3%	10 ♀♂ 14.4 %	10 ♀♂ 1.3 %
Reconst. Tobacco Sheet/ II	11 ♀♂ 33.8%	11 ♀♂ 21.9%	11 ♀♂ 11.9 %	11 ♀♂ 0.0 %
Standard cig./ II + asbestos	12 ♀♂ 78.1%	12 ♀♂ 15.6%	12 ♀♂ 28.8 %	12 ♀♂ 7.5 %
Asbestos	13 ♀♂ 0.0%	13 ♀♂ 0.0%	13 ♀♂ 0.0 %	13 ♀♂ 0.0 %
"Black cig."/ II	14 ♀♂ 66.9%	14 ♀♂ 4.4%	14 ♀♂ 10.0 %	14 ♀♂ 1.3%
Standard cig./ II with acetate filter	15 ♀♂ 68.1 %	15 ♀♂ 9.4%	15 ♀♂ 13.1 %	15 ♀♂ 0.6 %
Standard cig./ II with cellulose filter	16 ♀♂ 63.7%	16 ♀♂ 6.3%	16 ♀♂ 11.9 %	16 ♀♂ 2.5%
Standard cig./ II with charcoal filter	17 ♀♂ 68.6%	17 ♀♂ 11.3%	17 ♀♂ 25.0 %	17 ♀♂ 2.5 %
Standard cig./ II + DENA	18 ♀♂ 68.1%	18 ♀♂ 20.0%	18 ♀♂ 13.8 %	18 ♀♂ 1.3%

TABLE 13

TYPE OF CIGARETTE	GROUP		NUMBER OF PUFFS	TIME-FACTOR	SMOKE CONDENSATE (DRY) mg	CONDENSATE FACTOR	LARYNX ♀ ♂ STAGE 5	LARYNX ♀ ♂ STAGE 6
ST/II	E_2	5	10	1.0	33.7	1.0	30.0 % R = 1	10.6 % R = 1
ST/II + $NaNO_3$	EN	9	9	0.9	22.4	0.66	15.6 % R = 0.52	2.5 % R = 0.24
R/II + $NaNO_3$	EG_3	10	6	0.6	20.8	0.62	14.4 % R = 0.48	1.25 % R = 0.12
R/II	EG_1	11	7	0.7	27.3	0.81	11.9 % R = 0.40	0.0 % R = 0
ST/FI/II ACETATE	A	15	10	1.0	23.5	0.70	13.1 % R = 0.44	0.62 % R = 0.058
ST/FI/II CELLULOSE	D	16	11	1.1	22.7	0.67	11.9 % R = 0.40	2.5 % R = 0.24
ST/FI/II CHARCOAL	K	17	10	1.0	26.2	0.79	25.0 % R = 0.83	2.5 % R = 0.24
BLACK CIG./II	Z	14	8	0.8	20.9	0.62	10.0 % R = 0.33	1.25 % R = 0.12

R = RELATIVE POTENCY

TABLE 14

CLASSIFICATION OF PRECANCEROSES (ACCORDING TO MIESCHER)

PRECANCEROSES IN A NARROWER SENSE.

(DISEASES FROM WHICH MALIGNANT DEGENERATION CAN BE EXPECTED WITH 20 - 100 % PROBABILITY.)

- POLYPOSIS INTESTINI
- MORBUS BOWEN
- ERYTHROPLASIA
- MELANOTIC PRECANCEROSIS (DUBREUILH)
- KERATOACANTHOMA
- CORNU CUTANEUM
- KERATOMA SENILE (SENILE HYPERKERATOSIS)
- LEUKOPLAKIA VERRUCOSA
- CARCINOMA IN SITU OF PORTIO UTERI

PRECANCEROSES IN A BROADER SENSE.

(CHANGES OF TISSUE STRUCTURE INITIATING CANCER FORMATION WITH A PROBABILITY OF 3 - 20 %)

- LIGHT-, ARSENIC-, TAR- AND X-RAY DERMATOSES
- IRRADIATED LUPUS
- PHOTOATROPHIE
- LEUCOPLAKIA
- KRAUROSIS VULVAE (PENIS)
- BALANITIS XEROTICA OBLITERANS
- ANACID GASTRITIS (ATROPHIC)
- ULCERATIONS AND FISTULAE (STOMACH, LARGE INTESTINE ETC.)
- PROLIFERATING MASTOPATHY
- CIRRHOSIS OF THE LIVER
- NEUROFIBROMATOSIS
- OSTITITS DEFORMANS

TABLE 15

INCIDENCE OF INFLAMMATION

	LARYNX	ORAL CAVITY	NASAL CAVITY
Control	K ♀♂ 7.7%	K ♀♂ 7.8%	K ♀♂ 3.2%
DMBA + standard cig./II	1 ♀♂ 5.6%	1 ♀♂ 10.0%	1 ♀♂ 6.9%
DMBA	2 ♀♂ 14.4%	2 ♀♂ 8.8%	2 ♀♂ 3.1%
Control	3 ♀♂ 10.0%	3 ♀♂ 17.0%	3 ♀♂ 5.5%
Standard cig./I	4 ♀♂ 3.1%	4 ♀♂ 7.5%	4 ♀♂ 8.8%
Standard cig./II	5 ♀♂ 4.4%	5 ♀♂ 11.3%	5 ♀♂ 11.9%
Standard cig./III	6 ♀♂ 2.5%	6 ♀♂ 9.4%	6 ♀♂ 3.8%
Vapor Phase of standard cig./II	7 ♀♂ 9.4%	7 ♀♂ 13.8%	7 ♀♂ 1.9%
Fresh air (Placebo)	8 ♀♂ 6.9%	8 ♀♂ 14.4%	8 ♀♂ 1.3%
Standard cig./II + $NaNO_3$	9 ♀♂ 2.5%	9 ♀♂ 10.0%	9 ♀♂ 3.1%
Reconst. Tobacco Sheet II + $NaNO_3$	10 ♀♂ 6.3%	10 ♀♂ 13.8%	10 ♀♂ 5.0%
Reconst. Tobacco Sheet/II	11 ♀♂ 4.4%	11 ♀♂ 13.8%	11 ♀♂ 1.9%
Standard cig./II + asbestos	12 ♀♂ 6.9%	12 ♀♂ 24.4%	12 ♀♂ 5.0%
Asbestos	13 ♀♂ 5.0%	13 ♀♂ 15.0%	13 ♀♂ 5.0%
"Black cig."/II	14 ♀♂ 6.9%	14 ♀♂ 14.4%	14 ♀♂ 12.5%
Standard cig./II with acetate filter	15 ♀♂ 3.8%	15 ♀♂ 12.5%	15 ♀♂ 6.9%
Standard cig./II with cellulose filter	16 ♀♂ 3.8%	16 ♀♂ 13.1%	16 ♀♂ 6.9%
Standard cig./II with charcoal filter	17 ♀♂ 4.4%	17 ♀♂ 19.4%	17 ♀♂ 5.0%
Standard cig./II + DENA	18 ♀♂ 3.8%	18 ♀♂ 11.3%	18 ♀♂ 3.8%

TABLE 16

OVERADDITIVE EFFECT OF TOBACCO SMOKE INHALATION AND INITIAL DMBA TREATMENT

	STAGE 5 ♀ / ♂	STAGE 6 ♀ / ♂
INITIAL DOSE WITH DMBA AND SMOKE EXPOSURE 2 x 30 CIG. DAILY (= DOSE LEVEL II)	45.6 %	20.0 %
INITIAL DOSE WITH DMBA IN CMC INTRATRACHEALLY	0.0 %	0.0 %
SMOKE EXPOSURE 2 x 30 CIG. DAILY (= DOSE LEVEL II)	30.0 %	10.6 %

TABLE

17

INCIDENCE OF LARYNGEAL PAPILLOMAS (LOWER PART)

Control	K	♀	
		♂	
DMBA + standard cig./II	1	♀	
		♂	
DMBA	2	♀	
		♂	
Control	3	♀	
		♂	
Standard cig./I	4	♀	
		♂	
Standard cig./II	5	♀	
		♂	
Standard cig./III	6	♀	
		♂	
Vapor Phase of standard cig./II	7	♀	
		♂	
Fresh air (Placebo)	8	♀	
		♂	
Standard cig./II + $NaNO_3$	9	♀	
		♂	
Reconst. Tobacco Sheet II + $NaNO_3$	10	♀	
		♂	
Reconst. Tobacco Sheet/II	11	♀	
		♂	
Standard cig./II + asbestos	12	♀	
		♂	
Asbestos	13	♀	
		♂	
"Black cig."/II	14	♀	
		♂	
Standard cig./II with acetate filter	15	♀	
		♂	
Standard cig./II with cellulose filter	16	♀	
		♂	
Standard cig./II with charcoal filter	17	♀	
		♂	
Standard cig./II + DENA	18	♀ 2.5	%
		♂ 23.75	
DENA	18A	♀ 11.1	%
		♂ 22.2	

TABLE

18
18

INCIDENCE OF BRONCHIAL AND TRACHEAL PAPILLOMAS

Control	K	♀		%	
		♂			
DMBA + standard cig./II	1	♀	3.75	%	
		♂	3.75		
DMBA	2	♀		%	
		♂	0.25		
Control	3	♀			
		♂			
Standard cig./I	4	♀			
		♂			
Standard cig./II	5	♀			
		♂			
Standard cig./III	6	♀			
		♂			
Vapor Phase of standard cig./II	7	♀			
		♂			
Fresh air (Placebo)	8	♀			
		♂			
Standard cig./II + $NaNO_3$	9	♀			
		♂			
Reconst. Tobacco Sheet II + $NaNO_3$	10	♀			
		♂	1		
Reconst. Tobacco Sheet/II	11	♀			
		♂			
Standard cig./II + asbestos	12	♀			
		♂			
Asbestos	13	♀			
		♂			
"Black cig."/II	14	♀			
		♂			
Standard cig./II with acetate filter	15	♀			
		♂			
Standard cig./II with cellulose filter	16	♀			
		♂			
Standard cig./II with charcoal filter	17	♀			
		♂			
Standard cig./II + DENA	18	♀	10.0	%	
		♂	26.75		
DENA	18A	♀	2.22	%	
		♂	27.5		

TABLE

19

INCIDENCE OF PHARYNGEAL PAPILLOMAS

Control	K	♀		%	Reconst. Tobacco Sheet II + $NaNO_3$	10	♀	
		♂	0.33				♂	
DMBA + standard cig./ II	1	♀	32.5	%	Reconst. Tobacco Sheet/ II	11	♀	
		♂	13.75				♂	
DMBA	2	♀	33.75	%	Standard cig./ II + asbestos	12	♀	
		♂	22.5				♂	
Control	3	♀		%	Asbestos	13	♀	
		♂	1.0				♂	
Standard cig./ I	4	♀			"Black cig."/ II	14	♀	
		♂					♂	
Standard cig./ II	5	♀		%	Standard cig./ II with acetate filter	15	♀	
		♂	1.25				♂	
Standard cig./ III	6	♀	2.5	%	Standard cig./ II with cellulose filter	16	♀	
		♂					♂	
Vapor Phase of standard cig./ II	7	♀			Standard cig./ II with charcoal filter	17	♀		%
		♂					♂	1.25	
Fresh air (Placebo)	8	♀			Standard cig./ II + DENA	18	♀		%
		♂					♂	1.25	
Standard cig./ II + $NaNO_3$	9	♀			DENA	18A	♀	
		♂					♂	

TABLE

20

INCIDENCE OF PAPILLOMAS IN THE ORAL CAVITY

Control	K	♀			
		♂			
DMBA + standard cig./II	1	♀	7.5	%	
		♂	5.0		
DMBA	2	♀	5.0	%	
		♂	8.75		
Control	3	♀		%	
		♂	1.0		
Standard cig./I	4	♀			
		♂			
Standard cig./II	5	♀			
		♂			
Standard cig./III	6	♀			
		♂			
Vapor Phase of standard cig./II	7	♀			
		♂			
Fresh air (Placebo)	8	♀			
		♂			
Standard cig./II + $NaNO_3$	9	♀			
		♂			
Reconst. Tobacco Sheet II + $NaNO_3$	10	♀			
		♂			
Reconst. Tobacco Sheet/II	11	♀		%	
		♂	1.25		
Standard cig./II + asbestos	12	♀		%	
		♂	1.25		
Asbestos	13	♀			
		♂			
"Black cig."/II	14	♀	1.25	%	
		♂			
Standard cig./II with acetate filter	15	♀			
		♂			
Standard cig./II with cellulose filter	16	♀			
		♂			
Standard cig./II with charcoal filter	17	♀			
		♂			
Standard cig./II + DENA	18	♀		%	
		♂	1.25		
DENA	18A	♀	1.25	%	
		♂			

TABLE 21

INCIDENCE OF PAPILLOMAS AND CARCINOMAS

	ESOPHAGUS - PAPILLOMAS	STOMACH - PAPILLOMAS	STOMACH - CARCINOMAS
Control	K ♀ ♂	K ♀ ♂ 4.5 %	K ♀ ♂ 0.2 %
DMBA + standard cig./II	1 ♀ ♂ 5.0 %	1 ♀ ♂ 68.1 %	1 ♀ ♂ 3.1 %
DMBA	2 ♀ ♂ 2.5 %	2 ♀ ♂ 73.8 %	2 ♀ ♂ 2.5 %
Control	3 ♀ ♂	3 ♀ ♂ 7.0 %	3 ♀ ♂ 0.5 %
Standard cig./I	4 ♀ ♂	4 ♀ ♂ 4.4 %	4 ♀ ♂
Standard cig./II	5 ♀ ♂	5 ♀ ♂ 5.0 %	5 ♀ ♂
Standard cig./III	6 ♀ ♂	6 ♀ ♂ 6.3 %	6 ♀ ♂
Vapor Phase of standard cig./II	7 ♀ ♂	7 ♀ ♂ 8.1 %	7 ♀ ♂
Fresh air (Placebo)	8 ♀ ♂	8 ♀ ♂ 4.4 %	8 ♀ ♂
Standard cig./II + $NaNO_3$	9 ♀ ♂	9 ♀ ♂ 5.0 %	9 ♀ ♂
Reconst. Tobacco Sheet II + $NaNO_3$	10 ♀ ♂	10 ♀ ♂ 3.1 %	10 ♀ ♂ 0.6 %
Reconst. Tobacco Sheet/II	11 ♀ ♂	11 ♀ ♂ 3.1 %	11 ♀ ♂ 0.6 %
Standard cig./II + asbestos	12 ♀ ♂	12 ♀ ♂ 11.9 %	12 ♀ ♂ 1.3 %
Asbestos	13 ♀ ♂	13 ♀ ♂ 5.6 %	13 ♀ ♂ 0.6 %
"Black cig."/II	14 ♀ ♂	14 ♀ ♂ 5.6 %	14 ♀ ♂ 0.6 %
Standard cig./II with acetate filter	15 ♀ ♂	15 ♀ ♂ 8.1 %	15 ♀ ♂
Standard cig./II with cellulose filter	16 ♀ ♂	16 ♀ ♂ 4.4 %	16 ♀ ♂
Standard cig./II with charcoal filter	17 ♀ ♂	17 ♀ ♂ 5.6 %	17 ♀ ♂ 0.5 %
Standard cig./II + DENA	18 ♀ ♂	18 ♀ ♂ 4.4 %	18 ♀ ♂

TABLE 22

INCIDENCE OF LIVER TUMOURS

GROUP	K		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		18A	
SEX	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
LIVER CELL CARCINOMA		1				1																				1												
CARCINOMA OF THE BILE DUCT	1			1		1				1																												
HAEMANGIO - ENDOTHELIOMA	1	1	1			1																						1										
HAEMANGIOMA		1	1			1		1								1												1										
ADENOMA OF THE BILE DUCT								1				1														2												1

TABLE 2

INCIDENCE OF TUMOURS OF THE HAEMATOPOIETIC AND LYMPHORETICULAR SYSTEM

GROUP	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	18.
LEUKEMIA MYELOIC	1	1																	
LEUKEMIA LYMPHATIC		2		2	1												1		
LYMPHOSARCOMA TYPE I	3	1	2		2	1		1	2		2	1	1				1		2
LYMPHOSARCOMA TYPE II	3	3	3		2	2	2		1	1	1				1		2		2
LYMPHOSARCOMA TYPE III			2		1		1			1					1	1	1		2
PLASMOCYTOMA		1	3	2				1	1	1		1	1	1		1	1		
MYELOSARCOMA	1																		
TOTAL NUMBER	8	8	10	4	6	3	3	2	4	3	3	2	2	1	2	2	6	-	6
MEAN INDUCTION PERIODS (WEEKS)	41.4	57.9	103.1	77.5	98.3	76.0	85.7	76.0	76.8	104.3	77.7	108.5	68.5	86.0	68.0	79.0	77.7	-	75.

TABLE 24

SKIN • SOFT TISSUE • SUBCUTANEOUS TISSUE

GROUP / SEX	K ♂	K ♀	1 ♂	1 ♀	2 ♂	2 ♀	3 ♂	3 ♀	4 ♂	4 ♀	5 ♂	5 ♀	6 ♂	6 ♀	7 ♂	7 ♀	8 ♂	8 ♀	9 ♂	9 ♀	10 ♂	10 ♀	11 ♂	11 ♀	12 ♂	12 ♀	13 ♂	13 ♀	14 ♂	14 ♀	15 ♂	15 ♀	16 ♂	16 ♀	17 ♂	17 ♀	18 ♂	18 ♀
FIBROSARCOMA	1				1																				1						1				1			
ROUND-CELL SARCOMA									1																													
POLYMORPH.. SARCOMA			1				1								1		1																					
OSTEOBLAST. SARCOMA																			1								1											
HAEMANGIO-ENDOTHELIOMA																															1							
SPINDLE-CELL SARCOMA	1																																					
MELANOSARCOMA (EYE)	1																																					
MELANOMA (EYE)	1																																					
MELANOMA (SKIN)			1		1																																	
MELANOSARCOMA (SKIN)					1														1																			
BASALIOMA																					1																	
SQUAMOUS CELL CARC. (SKIN)					1																																	
CYSTADEN. PAPILL.					1																																	
PAPILLOMA																					1																	

TOTAL = ♂ 15 SARCOMAS AND 1 CARCINOMA
♀ 2 SARCOMAS

INCIDENCE OF ADENOMAS IN THE NASAL CAVITY

Control	K	♀		%		
		♂	0.67			
DMBA + standard cig./II	1	♀		%		
		♂	1.25			
DMBA	2	♀				
		♂				
Control	3	♀		%		
		♂	1.0			
Standard cig./I	4	♀		%		
		♂	1.25			
Standard cig./II	5	♀		%		
		♂	2.5			
Standard cig./III	6	♀				
		♂				
Vapor Phase of standard cig./II	7	♀				
		♂				
Fresh air (Placebo)	8	♀				
		♂				
Standard cig./II + $NaNO_3$	9	♀				
		♂				
Reconst. Tobacco Sheet II + $NaNO_3$	10	♀				
		♂				
Reconst. Tobacco Sheet/II	11	♀				
		♂				
Standard cig./II + asbestos	12	♀	1.25			
		♂				
Asbestos	13	♀				
		♂				
"Black cig."/II	14	♀				
		♂	1.25			
Standard cig./II with acetate filter	15	♀				
		♂	1.25			
Standard cig./II with cellulose filter	16	♀				
		♂	1.25			
Standard cig./II with charcoal filter	17	♀				
		♂	1.25			
Standard cig./II + DENA	18	♀				
		♂	3.75			
DENA	18A	♀				
		♂				

TABLE 26

INCIDENCE OF ADRENAL TUMOURS

	"SPINDLE-CELL"	"ROUND-CELL"	CARCINOMA
Control	K ♀♂ 3.7 %	K ♀♂ 12.2%	K ♀♂ 0.3 %
DMBA + standard cig./II	1 ♀♂	1 ♀♂ 8.1%	1 ♀♂
DMBA	2 ♀♂ 3.1 %	2 ♀♂ 11.9%	2 ♀♂
Control	3 ♀♂ 5.0 %	3 ♀♂ 21.0%	3 ♀♂ 1.0 %
Standard cig./I	4 ♀♂ 4.4 %	4 ♀♂ 10.0%	4 ♀♂ 0.6 %
Standard cig./II	5 ♀♂ 6.9 %	5 ♀♂ 6.9%	5 ♀♂
Standard cig./III	6 ♀♂ 1.9 %	6 ♀♂ 6.3%	6 ♀♂
Vapor Phase of standard cig./II	7 ♀♂ 5.6 %	7 ♀♂ 8.6%	7 ♀♂
Fresh air (Placebo)	8 ♀♂ 5.0 %	8 ♀♂ 13.8%	8 ♀♂
Standard cig./II + $NaNO_3$	9 ♀♂ 5.6 %	9 ♀♂ 11.3%	9 ♀♂
Reconst. Tobacco Sheet II + $NaNO_3$	10 ♀♂ 1.9 %	10 ♀♂ 9.4%	10 ♀♂
Reconst. Tobacco Sheet/II	11 ♀♂ 4.4 %	11 ♀♂ 10.6%	11 ♀♂
Standard cig./II + asbestos	12 ♀♂ 5.0 %	12 ♀♂ 12.5%	12 ♀♂
Asbestos	13 ♀♂ 6.9 %	13 ♀♂ 18.1%	13 ♀♂
"Black cig."/II	14 ♀♂ 3.1 %	14 ♀♂ 10.6%	14 ♀♂
Standard cig/II with acetate filter	15 ♀♂ 4.4 %	15 ♀♂ 13.8%	15 ♀♂
Standard cig/II with cellulose filter	16 ♀♂ 5.6 %	16 ♀♂ 7.5%	16 ♀♂
Standard cig/II with charcoal filter	17 ♀♂ 4.4 %	17 ♀♂ 10.6%	17 ♀♂ 0.6 %
Standard cig./II + DENA	18 ♀♂ 6.9 %	18 ♀♂ 10.0%	18 ♀♂

TABLE

INCIDENCE OF THE LUNG EMPHYSEMA

Control	K	♀	0.3 %	Reconst. Tobacco Sheet II + $NaNO_3$	10	♀	
		♂				♂	2.5
DMBA + standard cig./II	1	♀		Reconst. Tobacco Sheet/II	11	♀	2.5
		♂				♂	
DMBA	2	♀		Standard cig./II + asbestos	12	♀	
		♂				♂	1.3
Control	3	♀	1.0 %	Asbestos	13	♀	6.3
		♂				♂	1.3
Standard cig./I	4	♀		"Black cig."/II	14	♀	
		♂				♂	
Standard cig./II	5	♀	1.3 %	Standard cig./II with acetate filter	15	♀	2.5
		♂				♂	1.3
Standard cig./III	6	♀	1.3 %	Standard cig./II with cellulose filter	16	♀	
		♂				♂	
Vapor Phase of standard cig./II	7	♀	2.5 %	Standard cig./II with charcoal filter	17	♀	
		♂				♂	
Fresh air (Placebo)	8	♀	1.3 %	Standard cig./II + DENA	18	♀	
		♂				♂	2.5
Standard cig./II + $NaNO_3$	9	♀	1.3 %	DENA	18A	♀	
		♂	2.5			♂	2.5

TABLE

MEASUREMENTS OF LIGHT TRANSMISSION OF LUNGS

MALE	GROUP K	GROUP 3	GROUP 5
NUMBER OF ANIMALS	10	20	20
NUMBER OF MEASUREMENTS	100	100	100
LIGHT TRANSMISSION IN % MEAN:	80.63	80.62	81.29
THE DIFFERENCES ARE NOT STATISTICALLY SIGNIFICANT (P > 5%)			

FEMALE	GROUP K	GROUP 3	GROUP 5
NUMBER OF ANIMALS	10	20	20
NUMBER OF MEASUREMENTS	100	100	100
LIGHT TRANSMISSION IN % MEAN:	79.38	79.84	79.11
THE DIFFERENCES ARE NOT STATISTICALLY SIGNIFICANT (P > 5%)			

TABLE 29

DETERMINATION OF THE NUMBER OF ALVEOLI PER MEASURING UNIT.

MALE	TREATMENT PERIOD (WEEKS)	NUMBER OF ANIMALS	NUMBER OF MEASUREMENTS	ALVEOLI PER MEASURING UNIT MEAN :
GROUP 3 CONTROLS	104 th – 129 th	20	100	176.27
GROUP 6 SMOKE EXPOSED ANIMALS	71 st – 111 th	20	100	170.96

THE DIFFERENCES ARE NOT STATISTICALLY SIGNIFICANT (P > 0.05)

TABLE

80

INCIDENCE OF GASTRIC ULCER

Control	K	7.7 %	Reconst. Tobacco Sheet II + $NaNO_3$	10	8.1 %
DMBA + standard cig./II	1	7.5 %	Reconst. Tobacco Sheet/II	11	5.0 %
DMBA	2	16.9 %	Standard cig./II + asbestos	12	10.0 %
Control	3	6.5 %	Asbestos	13	15.0 %
Standard cig./I	4	3.8 %	"Black cig."/II	14	6.9 %
Standard cig./II	5	2.5 %	Standard cig./II with acetate filter	15	9.4 %
Standard cig./III	6	8.8 %	Standard cig./II with cellulose filter	16	10.0 %
Vapor Phase of standard cig./II	7	10.0 %	Standard cig./II with charcoal filter	17	10.6 %
Fresh air (Placebo)	8	8.1 %	Standard cig./II + DENA	18	5.0 %
Standard cig./II + $NaNO_3$	9	7.5 %	DENA	18A	5.9 %

TABLE 9D II

INCIDENCE OF INFLAMMATION

		CORONARY ARTERY			PERIPHERAL ARTERY		
Control	K	♀	1.0	%	K	♀	0.67
		♂	0.67			♂	0.33
DMBA + standard cig./II	1	♀	6.25	%	1	♀	2.5
		♂	1.25			♂	
DMBA	2	♀	3.75	%	2	♀	2.5
		♂				♂	
Control	3	♀	2.0	%	3	♀	2.0
		♂				♂	
Standard cig./I	4	♀	3.75	%	4	♀	2.5
		♂				♂	1.25
Standard cig./II	5	♀	3.75	%	5	♀	7.5
		♂				♂	
Standard cig./III	6	♀	6.25	%	6	♀	5.0
		♂	1.25			♂	
Vapor Phase of standard cig./II	7	♀	5.0	%	7	♀	1.25
		♂	1.25			♂	
Fresh air (Placebo)	8	♀			8	♀	5.0
		♂				♂	
Standard cig./II + $NaNO_3$	9	♀	3.75	%	9	♀	1.25
		♂	1.25			♂	
Reconst. Tobacco Sheet II + $NaNO_3$	10	♀	6.25	%	10	♀	6.25
		♂				♂	
Reconst. Tobacco Sheet/II	11	♀	6.25	%	11	♀	1.25
		♂				♂	
Standard cig./II + asbestos	12	♀	6.25	%	12	♀	3.75
		♂	1.25			♂	1.25
Asbestos	13	♀	1.25	%	13	♀	
		♂	1.25			♂	
"Black cig."/II	14	♀	11.25	%	14	♀	1.25
		♂	5.0			♂	
Standard cig./II with acetate filter	15	♀	13.75	%	15	♀	6.25
		♂	1.25			♂	1.25
Standard cig./II with cellulose filter	16	♀	11.25	%	16	♀	3.75
		♂	2.5			♂	
Standard cig./II with charcoal filter	17	♀	8.75	%	17	♀	1.25
		♂				♂	
Standard cig./II + DENA	18	♀	11.25	%	18	♀	2.5
		♂	2.5			♂	
DENA +	19	♀	4.4	%	19	♀	2.2

TABLE 2

INCIDENCE OF AMYLOIDOSIS OF THE KIDNEY

STAGE	1	2	3
Control	K ♀♂ 17.0%	K ♀♂ 37.7%	K ♀♂ 6.0%
DMBA + standard cig./II	1 ♀♂ 18.8%	1 ♀♂ 36.3%	1 ♀♂ 8.8%
DMBA	2 ♀♂ 15.0%	2 ♀♂ 38.1%	2 ♀♂ 6.9%
Control	3 ♀♂ 20.5%	3 ♀♂ 43.5%	3 ♀♂ 6.5%
Standard cig./I	4 ♀♂ 14.4%	4 ♀♂ 33.8%	4 ♀♂ 7.5%
Standard cig./II	5 ♀♂ 16.9%	5 ♀♂ 28.1%	5 ♀♂ 7.5%
Standard cig./III	6 ♀♂ 13.1%	6 ♀♂ 19.4%	6 ♀♂ 20.0%
Vapor Phase of standard cig./II	7 ♀♂ 10.6%	7 ♀♂ 40.6%	7 ♀♂ 13.8%
Fresh air (Placebo)	8 ♀♂ 9.4%	8 ♀♂ 45.6%	8 ♀♂ 13.8%
Standard cig./II + $NaNO_3$	9 ♀♂ 11.3%	9 ♀♂ 27.5%	9 ♀♂ 16.3%
Reconst. Tobacco Sheet II + $NaNO_3$	10 ♀♂ 10.6%	10 ♀♂ 35.0%	10 ♀♂ 16.9%
Reconst. Tobacco Sheet/II	11 ♀♂ 11.3%	11 ♀♂ 36.3%	11 ♀♂ 15.6%
Standard cig./II + asbestos	12 ♀♂ 8.8%	12 ♀♂ 43.1%	12 ♀♂ 23.8%
Asbestos	13 ♀♂ 13.8%	13 ♀♂ 58.8%	13 ♀♂ 11.3%
"Black cig."/II	14 ♀♂ 8.8%	14 ♀♂ 41.9%	14 ♀♂ 20.6%
Standard cig./II with acetate filter	15 ♀♂ 7.5%	15 ♀♂ 41.3%	15 ♀♂ 23.8%
Standard cig./II with cellulose filter	16 ♀♂ 5.0%	16 ♀♂ 34.4%	16 ♀♂ 13.3%
Standard cig./II with charcoal filter	17 ♀♂ 10.0%	17 ♀♂ 30.6%	17 ♀♂ 18.1%
Standard cig./II + DENA	18 ♀♂ 4.4%	18 ♀♂ 37.5%	18 ♀♂ 20.0%
DENA	18A ♀♂ 5.9%	18A ♀♂ 76.5%	18A ♀♂ 10.6%

TABLE

BIOCHEMICAL AND HAEMATOLOGICAL DATA	TREATMENT	DURATION OF EXPERIMENT	NUMBER OF ANIMALS	MEAN	S.D.	RANGE OF OBSERVATION
ERYTHROCYTES ($X 10^6/mm^3$)	CONTROLS	0-46 WKS.	350	7.36	±0.54	5.13 - 9.01
	PLACEBO	0-14 "	90	7.58	±0.66	5.59-8.72
	SMOKING	10-46 "	290	7.88	±0.61	6.00-9.70
LEUCOCYTES (TOTAL) ($X 10^3/mm^3$)	CONTROLS	0-46 "	410	8.20	±2.55	2.60-20.10
	PLACEBO	0-14 "	90	8.65	±2.43	5.30-14.60
	SMOKING	10-46 "	290	7.67	±2.02	4.0 -10.8
HAEMOGLOBIN (g/100 ml)	CONTROLS	0-46 "	350	15.67	±1.37	11.2-18.4
	PLACEBO	0-14 "	90	16.68	±1.18	13.6-18.8
	SMOKING	10-46 "	290	15.61	±1.27	13.6-19.9
HEMATOCRIT (% v/v)	CONTROLS	0-14 "	250	47.72	± 3.50	37-57
	PLACEBO	14-15 "	90	48.46	± 3.69	38-56
	SMOKING	14-15 "	210	50.26	± 3.87	32-59
PROTHROMBIN TIME (sec)	CONTROLS	0-14 "	250	9.15	±1.06	6.5-12.5
	PLACEBO	14-15 "	90	8.73	±1.09	5.0-11.5
	SMOKING	14-15 "	210	9.00	±0.78	6.0-11.5
RETICULOCYTES (% OF ERYTHROCYTES)	CONTROLS	0-14 "	190	18.67	± 7.48	1 - 44
	PLACEBO	14-15 "	90	21.96	± 7.44	8-40
	SMOKING	14 15 "	210	22.70	± 7.08	9-39
THROMBOCYTES ($X 1000/mm^3$)	CONTROLS	0-14 "	190	244.02	± 52.40	125-417
	PLACEBO	14-15 "	90	250.84	± 59.40	114-408
	SMOKING	14-15 "	210	259.54	± 70.92	118-776
SODIUM (mVal / l SERUM)	CONTROLS	0-14 "	190	147.02	± 5.73	133-158
	PLACEBO	14-15 "	60	143.56	± 5.68	132-158
	SMOKING	14-15 "	173	145.13	± 5.80	132-189
POTASSIUM (mVal / l SERUM)	CONTROLS	0-14 "	190	5.56	±0.47	4.8-8.0
	PLACEBO	14-15 "	60	5.61	±0.45	4.8-7.1
	SMOKING	14-15 "	180	5.66	± 0.48	4.8-7.0
TOTAL PROTEIN (g/100 ml SERUM)	CONTROLS	0-14 "	220	6.13	±0.51	4.8-7.6
	PLACEBO	14-15 "	60	6.18	±0.31	5.4-6.8
	SMOKING	14-15 "	180	6.07	±0.41	4.8-6.9
TOTAL BILIRUBIN (mg/100 ml SERUM)	CONTROLS	0-14 "	190	0.4249	±0.1170	0.18-0.82
	PLACEBO	14-15 "	60	0.4485	±0.1253	0.14-0.62
	SMOKING	14-15 "	180	0.4433	±0.1200	0.21-1.21
SGOT (m U/ml SERUM)	CONTROLS	0-14 "	230	207.83	±92.09	80->500
	PLACEBO	4-15 "	100	197.92	±89.61	81 - 466
	SMOKING	4-15 "	220	193.03	±90.83	81 - 494

TABLE 9B/1

BIOCHEMICAL AND HAEMATOLOGICAL DATA	TREATMENT	DURATION OF EXPERIMENT	NUMBER OF ANIMALS	MEAN	S.D.	RANGE OF OBSERVATION
SGPT (m U/ml SERUM)	CONTROLS	0-14 WKS.	190	16.89	± 7.62	5.0 - 41.9
	PLACEBO	14-15 "	60	12.43	± 4.49	5.5 - 41.9
	SMOKING	14-15 "	180	12.55	± 4.80	3.1 - 31.3
TOTAL CHOLESTEROL (mg/100 ml SERUM)	CONTROLS	0-14 "	230	206.57	± 57.30	91-379
	PLACEBO	4-15 "	100	227.02	± 73.47	72-387
	SMOKING	4-15 "	220	181.56	± 62.93	84-530
FREE CHOLESTEROL (mg/100 ml SERUM)	CONTROLS	0-14 "	230	59.63	± 20.37	16-150
	PLACEBO	4-15 "	100	50.85	± 15.00	18 - 79
	SMOKING	4-15 "	220	51.90	± 14.04	16-100
FREE FATTY ACIDS (mVal/l SERUM)	CONTROLS	0-14 "	230	1.41	± 0.76	0.20-6.90
	PLACEBO	4-15 "	100	1.41	± 0.69	0.40-5.02
	SMOKING	4-15 "	220	1.66	± 0.78	0.08-4.10
FATTY ACIDS (mVal/l SERUM)	CONTROLS	0-14 "	230	307.19	± 94.08	49 - 705
	PLACEBO	4-15 "	100	340.53	± 101.04	95-732
	SMOKING	4-15 "	220	355.23	± 92.31	192-761
ALKALINE PHOSPHATASE (mU/ml SERUM)	CONTROLS	0-14 "	190	159.68	± 27.94	91-218
	PLACEBO	14-15 "	60	152.31	± 30.47	91-248
	SMOKING	14-15 "	180	162.00	± 31.04	81-300
NEUTRAL FAT (mg/100 ml SERUM)	CONTROLS	0-14 "	230	159.83	± 63.29	26-476
	PLACEBO	4-15 "	100	147.40	± 59.95	33-499
	SMOKING	4-15 "	220	145.42	± 52.21	23-451

TABLE 95 (96)

INCIDENCE OF OVARIAN CYSTS AND ATROPHY OF THE TESTICLE

	OVARIAN CYSTS	ATROPHY OF THE TESTICLE
Control	K ♀/♂ 4.0 %	K ♀/♂ 32.3 %
DMBA + standard cig./II	1 ♀/♂ 20.0 %	1 ♀/♂ 47.5 %
DMBA	2 ♀/♂ 30.0 %	2 ♀/♂ 55.0 %
Control	3 ♀/♂ 6.0 %	3 ♀/♂ 41.0 %
Standard cig./I	4 ♀/♂	4 ♀/♂ 35.0 %
Standard cig./II	5 ♀/♂	5 ♀/♂ 40.0 %
Standard cig./III	6 ♀/♂ 1.3 %	6 ♀/♂ 31.3 %
Vapor Phase of standard cig./II	7 ♀/♂ 1.3 %	7 ♀/♂ 50.0 %
Fresh air (Placebo)	8 ♀/♂ 5.0 %	8 ♀/♂ 36.3 %
Standard cig./II + $NaNO_3$	9 ♀/♂ 1.3 %	9 ♀/♂ 35.0 %
Reconst. Tobacco Sheet II + $NaNO_3$	10 ♀/♂ 5.0 %	10 ♀/♂ 56.3 %
Reconst. Tobacco Sheet/II	11 ♀/♂ 2.5 %	11 ♀/♂ 43.8 %
Standard cig./II + asbestos	12 ♀/♂ 3.8 %	12 ♀/♂ 51.3 %
Asbestos	13 ♀/♂ 3.8 %	13 ♀/♂ 55.0 %
"Black cig."/II	14 ♀/♂	14 ♀/♂ 51.3 %
Standard cig./II with acetate filter	15 ♀/♂ 1.3 %	15 ♀/♂ 57.5 %
Standard cig./II with cellulose filter	16 ♀/♂	16 ♀/♂ 38.8 %
Standard cig/II with charcoal filter	17 ♀/♂	17 ♀/♂ 35.0 %
Standard cig./II + DENA	18 ♀/♂	18 ♀/♂ 31.3 %

TABLE 93

WEIGHT OF TESTICLE

GROUP	n	$\bar{x}$	s	MIN.	MAX.
1	60	0.7684	0.7033	0.12	2.59
2	65	0.7702	0.7848	0.14	3.11
3	93	1.1668	0.8815	0.14	3.25
4	59	1.2000	1.0201	0.15	3.21
5	58	0.9698	0.8026	0.15	2.73
6	53	1.1360	0.9254	0.12	3.31
7	66	0.7827	0.7356	0.16	2.93
8	60	1.3497	1.2132	0.15	4.30
9	48	0.8635	0.7851	0,17	2.80
10	62	0.7498	0.8518	0.15	3.69
11	58	0.8286	0.8583	0.15	3.48
12	65	0.8548	0.9391	0.15	3.40
13	74	1.0107	1.0198	0.16	3.42
14	65	0.8045	0.7527	0.17	2.95
15	62	0.7406	0.8577	0.15	3.68
16	50	0.9798	0.9212	0.17	3.17
17	60	1.2320	1.0705	0.17	3.70
18	61	1.0872	0.8650	0.19	3.23
18A	40	1.0190	0.9233	0.23	3.70