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EXPERIMENTALLY INDUCED IRRITATING EFFECTS OF ACROLEIN ON MAN

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ABSTRACT

Summary. In order to investigate the acute irritation effects of acrolein on men, healthy subjects were exposed in a climatic chamber to different acrolein concentrations in the range between 0 and 0.60 ppm. Three experimental series were carried through: (a) 40 min exposure of 54 subjects to a continuously increasing acrolein concentration, (b) four 1 1/2 min exposures of 42 subjects to different acrolein concentrations and (c) 60 min exposure of 46 subjects to a constant concentration of 0.3 ppm acrolein.
Subjective irritations and annoyance as well as eye blinking rate and respiratory frequency were determined periodically during the exposures.
Subjective irritations, annoyance and eye blinking rate increased as a function of acrolein concentration, as well as of exposure duration up to a certain degree. Respiratory frequency decreased with increasing acrolein concentration. The changes were significant in the range between 0.09 and 0.30 ppm acrolein.
Acute irritations during exposure to 0.3 ppm acrolein proved to be considerable after 10 and 20 min already; from this angle, the actual US threshold limit value of 0.3 ppm for exposures of 15 min should be re-examined.
The effects of pure acrolein are small compared to those produced by the side stream of cigarette smoke with the same acrolein concentration: therefore, acrolein is only to a minor extent responsible for the irritations caused by the side stream smoke.

Key words: Acrolein – Irritations – Annoyance – Eye blinking rate – Respiratory frequency – Passive smoking

Introduction

Acrolein is an irritating substance which may occur in numerous industries, in roadside air, and in tobacco smoke, in more or less high concentrations. In industry, acrolein is formed as an air-polluting byproduct in the production of drying oils, high pressure polyethylene, in the vulcanization of rubber, and in the refining of fatty acids and soaps (ref.12, 3). Besides this, acrolein plays a significant part in organic chemistry, above all for the synthesis of plastics, resins, and biochemical substances as well as numerous intermediate products (ref. 3). Acrolein has been found in concentrations

between 2 and 4 ppm in the exhaust gases from diesel engines (ref. 12, 6). The mainstream smoke -- therefore the part of tobacco smoke that is inhaled by the smoker when drawing -- contains (in the gas phase) 45 to 228 µg of acrolein/cigarette, depending on the brand, i.e. between 69 and 350 ppm acrolein (ref. 7, 1). In the sidestream smoke also -- the smoke produced in the smoldering zone of the cigarette -- acrolein is also formed; therefore after smoking 5 and 10 cigarettes in an climate chamber of 30 m^3 size with a very low air exchange rate, we have measured 0.05 and 0.11 ppm acrolein, respectively (ref. 18).

The relative involvement of acrolein in the effects of the air pollution caused by cigarette smoke in a room was the primary concern of the present investigations. They were intended to record the subjectively perceived irritations in the eyes and now, the subjective judgments of air quality and the blinking rate, in the same manner as for the irritating effects measured by us that were caused by the sidestream smoke of cigarettes (ref. 16). In addition we also investigated the respiratory rate, since acrolein has been demonstrated to influence various respiratory functions in numerous animal experiments (ref. 6, 10, 15, 5).

This question of the involvement of acrolein in the irritating effects of cigarette smoke is of particular importance from the standpoint of the problem of passive smoking at the workplace

and in public places. As is known, this problem is frequently debated more emotionally than factually. The clarification of the questions raised here should make a material contribution to the evaluation of passive smoking.

2. Methodology

Acroleiln metering

The trials were conducted in a large climatic chamber of 30 m^3 size with an hourly air exchange rate of 0.1.

In order to meter the acrolein in the room air, we used the apparatus described in (ref. 17). For this purpose acrolein was injected with a µl syringe, vaporized, and blown into the test room via a carrier gas stream. The acrolein concentrations obtained in this way, which were measured continually during the entire trial, were highly reproducible. The concentrations measured at the end of the experiments with continuous metering-in had the following values:

mean value: 0.60 ppm acrolein

standard deviations: ± 0.023 (3,8%)

Chemical analysis

We modified the Technicon Air Monitor IV System for the determination method of Cohen and Altshuller (ref. 4) for the quantitive registration of the acrolein. The reaction of acrolein with 4-hexylresorcinol in an ethanol-trichloroacetic acid solution in the presence of mercury chloride produces a blue colored

product with an absorption maximum at 605 nm. The process thus devised produces a continuous automatic analysis of the room air.

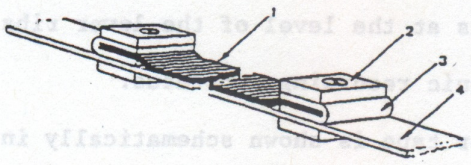


Fig. 1. Extensometric tape for recording respiratory movements. 1=semiconductor tape (Scotch 13 EPR), 2=Pressure plate, 3=contact grid, 4=elastic carrier tape.

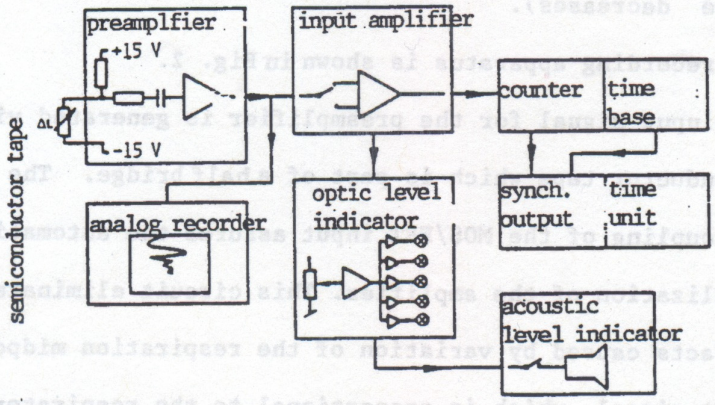


Fig. 2. Recording apparatus.

Psychological and physiological measuring procedures

During the trials, the following measurements were performed: subjectively perceived irritations and annoyances (with the aid of a graded question form, see (ref. 17), blink rate, see (ref. 17), respiratory rate.

Apparatus for recording respiratory activity

To investigate the respiratory rate and curve, on the one hand we developed an extensometer tape for recording the respiratory movements at the level of the lower ribs, and on the other, an electronic recording apparatus.

The extensometer tape is shown schematically in Fig. 1. Between 2 pressure plates with contact grids a semiconductor tape (ethylene propylene rubber) is mounted. This tape has a negative coefficient of stretching (when stretched, the electrical resistance decreases).

The recording apparatus is shown in Fig. 2.

The input signal for the preamplifier is generated via the semiconductor tape which is part of a half bridge. The DC voltage coupling of the MOS/FET input assures the automatic self equalization of the amplifier. This circuit eliminates the artifacts caused by variation of the respiration midpoint. The output signal, which is proportional to the respiratory movements, is sent for recording on an analog recorder. This recording permits a qualitative evaluation of the respiratory movements.

The imput amplifier of the counter makes it possible to use the negative or positive flanks of a signal optionally for triggering the counter. The optical and acoustical level monitor is coupled to the input amplifier.

The 6 position electronic measuring counter totals the positive pulses during the time preassigned by the time base. At the end of the measuring time the total of the respiratory movements is displayed on the parallel BCD output.

The time base of the Elesta counter CMM was expanded by 1 decimal so that measurement intervals of 999 seconds (16.65 minutes) could be set until the first printout. The next measurement cycle is triggered automatically.

The frequencies of 100, 10 and 1 kHz, 100, 10, 1, 0.1, 0.01 and 0.001 Hz are optionally available for the synchronization of other instruments at a special output.

The 6 position low-noise thermal printer receives the total of the respiratory movements from the BCD output of the measurement counter. At the same time either the time of day or the current test time is printed out in hours and minutes. Whenever the measuring system is hooked up to a computer, the printer can be blocked off without losing the time information.

The extensometer tape was placed on the subjects over the clothing in the lowest thoracic region. The respiration was registered during the entire trial, during which the subjects sat quietly in a reclining chair. In our trials we used the mean value over periods of 3 minutes as the respiratory rate.

Test arrangement and subjects

We performed 3 series of trials:

a. a continuous exposure with a constantly rising acrolein concentration,

b. several exposures of brief duration to successively increasing acrolein concentrations,

c. a long term exposure (1h) to a constant acrolein concentration

Continuous

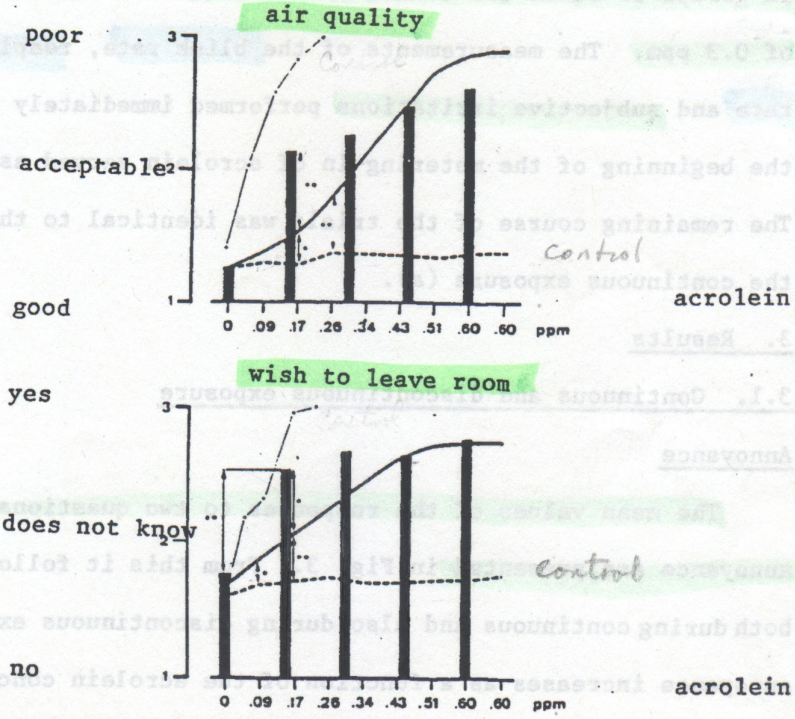
a. 53 healthy college students (31 men and 22 women) in groups of threes participated in the continuous exposure. One trial was performed with acrolein and also one control trial under identical conditions but without acrolein was performed with each subject. The duration of the test was 40 min., during which the acrolein concentration rose in the first 35 min from 0 to 0.60 ppm and remained constant for the last 5 min.

The subjects had to fill out the question form every five minutes. Immediately afterward the blink rate was measured on two of the subjects of each group of three. The respiratory rate was recorded continuously from the third subject during the entire duration of the test.

Discontinuous

b. 42 healthy college students (17 men and 25 women) participated in the discontinous exposure. The subjects in groups of 4 were each exposed 5 times for 1½ minutes to variously high acrolein concentrations (0, 0.15, 0.30, 0.45, and 0.60 ppm). After one minute of exposure they were presented with the question form. Between two exposures the subjects were

allowed to recover in a well ventilated room for 8 min. The first exposure in the well ventilated chamber served as the control.



- continuous acrolein exposure (duration 40 min)

-- control test (duration 40 min)

▬ discontinuous acrolein exposure (1½ min each)

- side stream smoke (duration 25 min)

• $p < 0.05$ •• $p < 0.01$

Fig. 3. The annoying effect of acrolein.

Long term

c. 46 healthy college students participated in the long term exposure (21 men and 25 women). The subjects were exposed in groups of three for 60 min to a constant acrolein concentration of 0.3 ppm. The measurements of the blink rate, respiratory rate and subjective irritations performed immediately before the beginning of the metering-in of acrolein served as controls. The remaining course of the trials was identical to that of the continuous exposure (a).

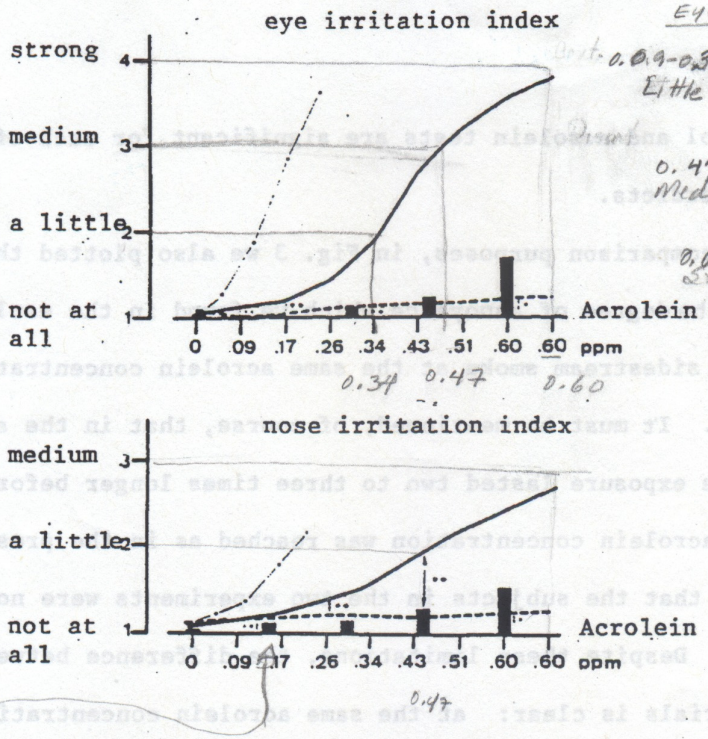
3. Results

3.1. Continuous and discontinuous exposure

Annoyance

The mean values of the responses to two questions regarding annoyance are presented in Fig. 3. From this it follows that both during continuous and also during discontinuous exposure, the annoyance increases as a function of the acrolein concentration.

Between the continuous and discontinuous exposure at the same acrolein concentration a significant difference exists only at 0.15 ppm. The annoyance is significantly higher during discontinuous exposure than during continuous ($p<0.01$ for the evaluation of the air quality, $p<0.05$ for the wish to leave the room). We assume that in the first phase of the tests, a certain adaptation to the irritant had taken place which disappears again at higher concentrations.



— continuous acrolein exposure (duration 40 min)

-- control test (duration 40 min)

▮ discontinuous acrolein exposure (1½ min each)

_ side stream smoke (duration 25 min)

•• $p < 0.01$

Fig. 4. Irritating effects of acrolein on eyes and nose. For convenience of presentation the upper steps of irritation on the ordinate were omitted.

The control trial without acrolein shows (in comparison to continuous acrolein exposure) that neither of the two criteria is significantly changed. Otherwise the differences between

the control and acrolein tests are significant for each of the two verdicts.

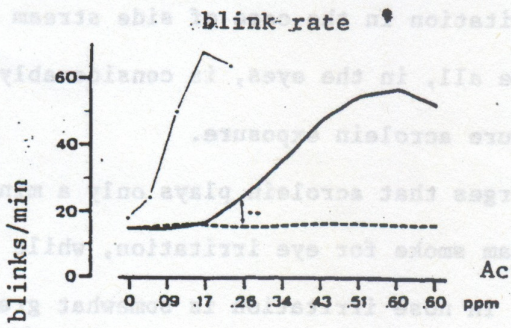
For comparison purposes, in Fig. 3 we also plotted the curve of the degree of annoyance which we found in the earlier study with sidestream smoke at the same acrolein concentration (ref. 16). It must be mentioned, of course, that in the smoke trial, the exposure lasted two to three times longer before the same acrolein concentration was reached as in the present trial and that the subjects in the two experiments were not the same. Despite these limitations, the difference between the two trials is clear: at the same acrolein concentration, the sidestream smoke causes a significantly stronger annoyance than acrolein alone. The degree of involvement of acrolein in the annoyance caused by the sidestream smoke thus appears to be minor.

Eye, nose and throat irritation

As in earlier studies (ref. 17, 16) we formed the corresponding indices from the responses to several questions regarding eye, nose and throat irritations. Fig. 4 shows the mean values of the eye and nose indices as functions of the acrolein concentrations.

In both trials, the two irritation indices increased significantly with rising acrolein concentration. The eyes were more sensitive than the nose.

Eye 0.09
Nose 0.15
Throat 0.43



blink rate starts at 0.26 ppm

— continuous acrolein exposure (duration 40 min)

-- control trial (duration 40 min)

- sidestream smoke (duration 25 min) •• $p < 0.01$

Fig. 5. Blink rate as a function of acrolein concentration.

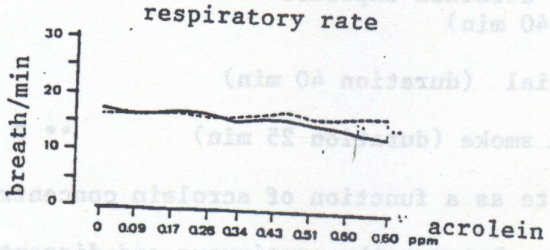
The difference between the continuous and discontinuous exposure is striking: in the eyes as well as in the nose the irritation is significantly stronger in the case of continuous exposure, indicating an increase in the sensitivity of both organs as a function of the exposure time.

The differences between the control test and the continuous acrolein exposure are statistically confirmed for the eye and nose irritations. In the control trial, to be sure, the irritation increases slightly and after 35 minutes of exposure significantly ($p<0.05$), which is presumably ascribable to a placebo effect.

The comparison of the irritations in the eyes and nose in the present experiment with the earlier side stream smoke experiment (ref. 16) reveals the following: at the same acrolein

concentration the irritation in the case of side stream smoke in the nose and, above all, in the eyes, is considerably stronger than in the case of pure acrolein exposure.

From this it emerges that acrolein plays only a minor part in the side stream smoke for eye irritation, while its degree of involvement in nose irritation is somewhat greater.



– continuous acrolein exposure (duration 40 min)

-- control test (duration 40 min)

• $p < 0.05$

•• $p < 0.01$

Fig. 6. Respiratory rate as a function of acrolein concentration.

The throat irritation was found in both trials to be a less sensitive criterion: in the continuous test, it increased significantly only at 0.43 ppm acrolein; in the discontinuous test no change occurred.

Blink Rate

The mean values of the blink rate of 34 subjects in the continuous trial are presented in Fig. 5 as a function of the acrolein concentration.

The blink rate increases as a function of the acrolein concentration after 0.17 ppm; the increase is significant at 0.26 ppm acrolein ($p<0.01$). The mean initial value of the blink rate doubles at ca. 0.3 ppm.

Here also a comparison with the previous side stream smoke experiment shows that the degree of involvement of acrolein in the increase in the blink rate caused by the side-stream smoke is minor.

The calculation of the Kendall rank correlation coefficient τ between the blink rate and the eye irritation index produced statistically confirmed values only at the acrolein concentrations of 0.34 and 0.43 ppm ($\tau=0.30$ and $\tau= 0.34$, $p< 0.05$ and $p<0.01$ respectively). In all other concentration ranges no significant relationship exists between blink rate and eye irritation index.

Respiratory rate

Fig. 6 shows the curve of the average respiratory rate of 19 subjects as a function of the acrolein concentration.

The respiratory rate decreases slightly with increasing acrolein concentration. Compared to the control test, this decrease is statistically secured at 0.6 ppm acrolein; at this concentration the decrease in the respiratory rate reaches an average of 4 breaths/min, which corresponds to a decrease of about 25%.

The recording of the length variation of the extensometer tape permitted us to make a qualitative pronouncement concerning the depth of the respiration and the "breathing behavior". Thus in 11 of the 19 subjects we observed, in comparison to the control trial, an increasing irregularity in the depth of respiration which, in part, appeared very soon after the addition of acrolein but usually in the second half or last third of the exposure time. Again approximately half of the subjects displayed a more or less pronounced tendency to lengthen the expiration cycle or -- more rarely -- the inspiration cycle byholding the breath toward the end of the acrolein exposure.

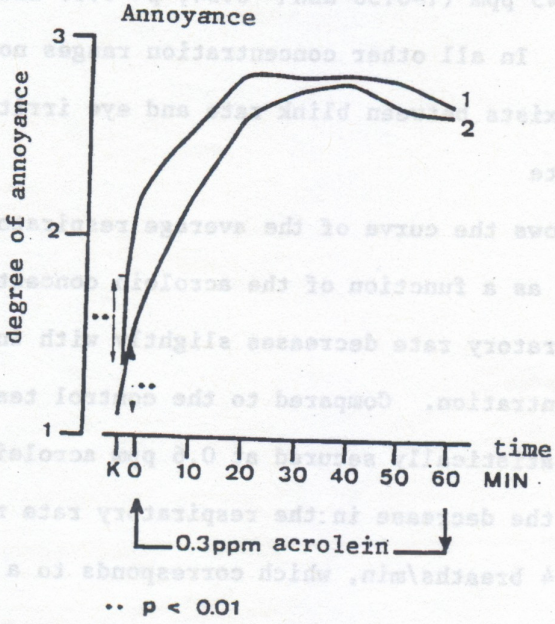


Fig. 7. Effect of one hour acrolein exposure to 0.3 ppm on annoyance. Curve 1 corresponds to the curve of the responses to the question of air quality, curve 2 to the desire to leave the room. The numbers 1, 2, and 3 on the ordinate correspond to the degree of annoyance (see Fig. 3)

3.2. Long term exposure

Annoyance

Fig. 7 shows the mean values of the responses to two questions regarding annoyance during the exposure time of 60 min at 0.3 ppm acrolein. K corresponds to the control measurement in "clean" air before the metering-in of the acrolein and 0 to the measurement immediately after the metering-in, which lasted 1½ minutes.

It is apparent that at a constant acrolein concentration the annoyance increases during the first 20 to 30 minutes, depending on exposure time, and then remains approximately constant. This result shows that the annoyance caused depends not only on the concentration of the irritant present but also on the exposure time.

The increase in annoyance already increases significantly immediately after the acrolein is metered in (time 0 min). Compared to the other parameters (see Figs. 7, 8, 9), therefore, the annoyance is shown to be an especially sensitive measuring scale.

Eye, nose, and throat irritation: blink rate

In Figs. 8 and 9 the mean values of the irritation indices as well as the blink rate are plotted as functions of exposure time.

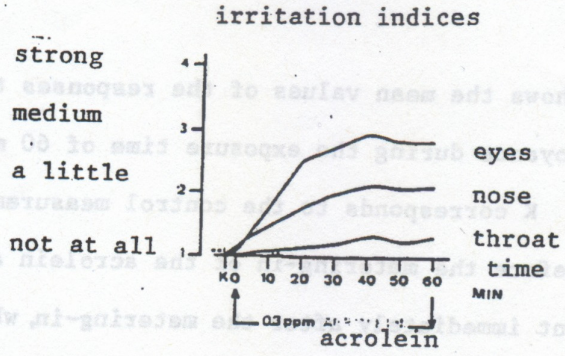


Fig. 8. Irritating effects of 1 hour acrolein exposure to 0.3 ppm on eyes, nose, and throat.

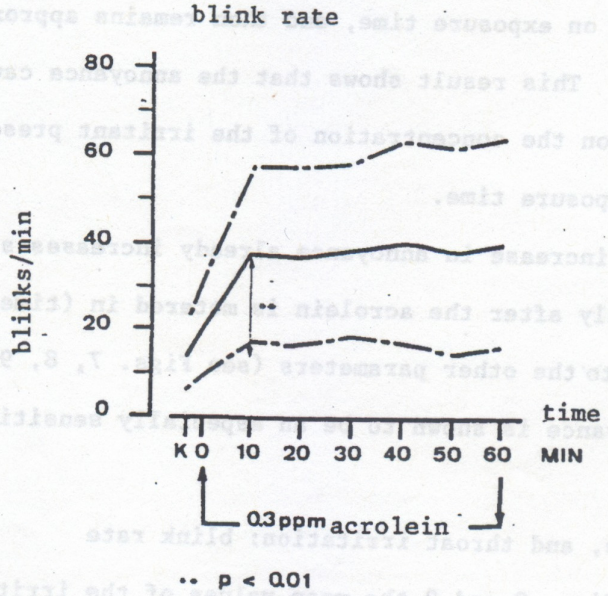


Fig. 9. Effect of a 1 hour acrolein exposure at 0.3 ppm on the blink rate.

All three indices as well as the blink rate increase with increasing exposure time. The subjective irritations reach

a constant intensity after ca. 40 min, while the blink rate has already reached its definitive value after 10 min. It is remarkable that the throat irritation, which varied only insignificantly in the two previous trials, increased significantly in this longer lasting exposure after only 10 min.

At each exposure time a significant individual correlation (τ between 0.33 and 0.43, p between <0.05 and <0.01) exists between the blink rate and the subjective eye irritation. This means that, for instance, the persons with a strong increase in the blink rate also reported a strong increase in eye irritation.

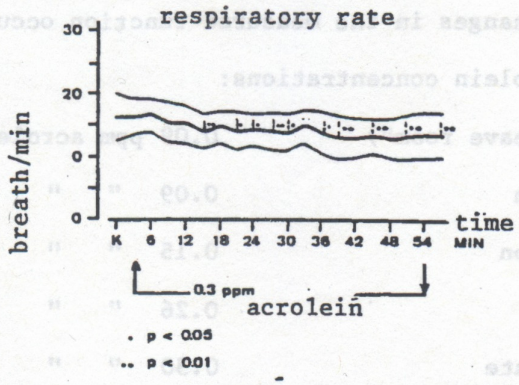


Fig. 10. Effect of 1 hour acrolein exposure on respiratory rate. The thin curves correspond to the standard deviation.

Respiratory rate

Fig. 10 shows the curve of the average respiratory rate of 16 subjects as a function of exposure time at 0.3 ppm acrolein.

On the average the respiratory rate decreases in the course of the exposure. The decrease is significant after 40 minutes of exposure ($p<0.01$) and moves between 2.9 and 3.2 breaths/min (ca. 20%).

As in the continuous trial, in 8 H of the subjects the irregularity of the breathing depth -- qualitatively considered -- increases, above all in the course of the second half of the exposure, at which time several of the subjects occasionally hold their breath (predominantly in the expiration cycle).

4. Discussion

On the average, with consideration of all our experiments, significant changes in the measured function occurred at the following acrolein concentrations:

Annoyance ("leave room")	0.09 ppm acrolein
eye irritation	0.09 " "
Nose irritation	0.15 " "
Blink rate	0.26 " "
Respiratory rate	0.30 " "
Throat irritation	0.30 " "

From this it follows that the average irritation threshold for pure acrolein in man lies in the range between 0.09 and 0.30 ppm.

A survey of the studies performed earlier with acrolein on man can be found (ref. 14). According to Smith (ref. 12),

an acrolein concentration of 0.25 ppm after 5 min causes moderate irritation of the eyes and nose. Other authors (ref. 11, 8) found an elevated tear flow both after 20 sec at 0.67 ppm acrolein and also after 5 sec at1.04 ppm. Our systematic studies show that the threshold value for irritation lies lower on the average, i.e. at least at 0.1 ppm.

The new US limits for acrolein in industry (TLV) were set in 1976 at 0.1 ppm for an 8 hour work day and at 0.3 ppm per day for four 15-minutes exposures (ref. 13). Our results confirm the 8 hour limit regarding all of the functions measured in our experiment.

To evaluate the limit of 15 min of exposure to 0.3 ppm in the light of our investigations, we have compared the percentage portion of the subjects displaying reactions at 0.3 ppm acrolein in Table 1.

Although results of one-time trials with college students are not directly extrapolable to industrial workers, nevertheless it appeared to us, on the basis of our results,that the US limits for 15 minutes exposures are too high.

Murphey et al., (ref. 10) observed a significant decrease in the respiratory rate and a significant increase in the total flow resistance and respiratory volume in guinea pigs after 2 hours of exposure at 0.4 to 1.0 ppm acrolein. The authors assume that acrolein primarily increase the flow resistance

and that secondarily, as a compensatory mechanism, the respiratory volume increases and the respiratory rate diminishes. The variation of the flow resistance is traced to a bronchoconstriction, since this variation vanishes after the addition of bronchodilatator substances such as atropine, epinephrine, aminophyline.

Davis et al., (ref. 5) also found an increase in the flow resistance and respiratory volume, a decrease in the respiratory rate and the minute volume, as well as a lengthening of the expiration cycle after 60 minutes of exposure to 17 ppm acrolein in guinea pigs. The authors assume that the receptors stimulated by the irritants trigger a reflex protective mechanism in the upper respiratory tract which reduces further inhalation of the irritant by holding the breath, reducing the respiratory rate and decreasing the volume. From the studies by Ulrich et al., (ref. 15) it emerges that these reflexes travel via the trigeminus nerve.

The reduction in the respiratory rate recorded by us and the qualitative observation of the holding of breathing show that acrolein triggers in man effects on the respiratory functions similar to those in guinea pigs. The assumption is obvious that acrolein also produces a bronchial constriction in man which already appears at 0.3 ppm.

The results of our long term trials of 60 min show that the subjective and objective irritaing effect of acrolein are

Table 1. Effects of 0.3 ppm acrolein.

effects	percentage of subjects after 10 min %	after 20 min %
"wish to leave room"	50	72
moderate eye irritation	18	35
strong/very strong eye irritation	3	18
moderate nose irritation	7	19
strong/very strong nose irritation	1	4
moderate throat irritation	1	2
strong/very strong throat irritation	0	1
doubling of blink rate	66	70
decrease in respiratory rate by10%	47	60

stronger in this time period than in the other two experimemts of shorter duration (continuous and discontinuous exposures). Within the 60 minutes, the irritations have an ascending rather than a descending character. From this it follows that within one hour, no adaptation mechanisms to the irritating effects of acrolein are manifested. Naturally, no conclusions can be drawn from this regarding exposure lasting for months or years. Actually, several authors (ref. 6, 9, 2) have observed a decrease in irritation phenomena in their test animals after exposures lasting for weeks.

Concerning the question of the relative involvement of acrolein in the irritating effects of the sidestream smoke of cigarettes, our results, in terms of annoyance, subjective irritations and blink rate show that at the same concentrations, acrolein alone is considerably less active than the sidestream

smoke. We obtained a similar result with respect to the relative involvement of formaldehyde in the irritating effect of the sidestream smoke (ref. 17).

In Table 2 we compare the frequency of the reactions (as % of the subjects) under the three above-mentioned conditions of exposure.

Table 2. Comparison of the effects of pure acrolein, pure formaldehyde and sidestream smoke at comparable concentrations. The percentages correspond to the proportion of subjects with the reactions stated. Sidestream smoke: 33 subjects = 100%. Pure acrolein: 53 subjects = 100%. Pure formaldehyde: 33 subjects = 100%. (a) 28 subjects = 100% (b) 48 subjects = 100% (c) 30 subjects = 100%. Since 5 subjects each in the sidestream smoke and acrolein trials and 3 subjects from the formaldehyde test already wanted to "leave the room" at the beginning, they were not considered.

condition	acrolein	HCHO	eye irritation moderate strong very strong		doubling of blink rate	"wish to leave room"
	ppm	ppm	%	%	%	%
side stream smoke	0.16	0.5	36	27	78	87 (a)
pure acrolein	0.16	–	2	0	15	8 (b)
pure HCHO	–	0.5	2	0	11	3 (c)

The comparison clearly shows that neither gaseous acrolein nor gaseous formaldehyde are substantially involved in the irritating effects of the sidestream smoke of cigarettes. The question therefore remains open as to what the primary causes of the irritating effects of side stream smoke are.

Here, for the sake of completeness, it should be mentioned once more that the concentrations of acrolein (0.16 ppm) and formaldehyde (0.5 ppm) listed as a thermometer of air pollution by sidestream smoke in Table 2 correspond to an unrealistically high smoke pollution of room air, i.e. to the smoking of 15 cigarettes per 15 min in an unventilated room with a volume of 30 m^3 (ref. 16). In other words, the effects reported in Table 2 cannot be expected on this scale under the real conditions of everyday life, since such high concentrations are never reached in rooms with smoking.

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