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COMBINED EFFECTS OF SHIFTWORK AND ENVIRONMENTAL HAZARDS (HEAT, NOISE, TOXIC AGENTS)

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The paper deals with the results of studies or discussions concerning the problem of nightwork combined with other adverse working conditions. Special emphasis is laid on the untoward effect of high temperature during nightwork, as well as on noise and exposure to chemicals. It is shown that there is no substantial influence of heat stress on the circadian rhythm of adrenaline excretion under sitting working conditions with the subject performing a difficult mental task at warm climates up to 30 °C BET. Shiftwork and noise induce independent different effects which can be explained in terms of activation for shiftwork and in terms of tension for noise. The combination of both adverse exposures is therefore partly subtractive but partly additive as night work and noise negatively affect daysleep. Practical experience in the field of combined effects of shiftwork and chemical agents is lacking, but theoretical speculations lead to the conclusion that there may exist a time of day dependence of some chemicals, used at workplaces.

Shiftwork is nowadays generally recognized as a particular complex phenomenon. This is not only true of the interaction between the re-entrainment problems of the circadian rhythms and psychosocial problems but also of the working conditions. This further implicates that it is not possible to discuss shift systems on a highly abstract level without considering the work performed by the shiftworkers.

In the past a few self-administered questionnaire studies (1, 2, 3) came to the conclusion that the negative effects of shiftwork may not have been caused only by the phase difference between circadian rhythms and living conditions but also by adverse negative working conditions combined with shiftwork. To structure these conclusions *Knauth* (4) has recently used standardized job descriptions, collected by the Institute of Ergonomics, University of Darmstadt, and this Institute for about 2500 workplaces. The job description was carried out by trained personnel from both institutions, using a German extended version (5) of the »Position Analysis Questionnaire« (PAQ) of

McCormick and co-workers (6). The results of that study allow to conclude that unfavourable climatic conditions are more frequent in shiftwork systems which include nightwork, that noise frequently accompanies all types of shiftwork, that unfavourable lighting conditions are very seldom present during daywork, and that the same is true of vibration. When *Knauth* (4) used the frequency of unfavourable working conditions for ranking the working organization, he came to the conclusion that the worst shift system was the three-shift system, followed by irregular and night shift systems. However, in this first step each adverse environmental factor was only analysed separately. As several factors may occur together a second analysis of the data of about 2500 workplaces was carried out. Table 1 shows that the combination of two factors with nightwork is likely to be the most frequent one; the combination of three and more factors occurs less often.

Table 1

Relative frequency of combined unfavourable environmental conditions at 2429 workplaces dependent on the organization of working time

Shift system	N and C (%)	N and L (%)	C and L (%)	N and C and L (%)	N and C and L and V (%)	average rank* (%)
daywork	3.2	0.7	0.4	0.4	–	1.4
two-shift system	3.0	2.8	1.2	0.2	–	1.4
continuous system	11.3	5.6	5.4	3.9	1.1	3.0
nightshift system	13.5	6.5	6.2	4.5	1.6	4.8
irregular system	11.5	8.4	10.1	7.5	1.3	5.0
three-shift system	15.4	6.2	5.1	4.1	1.8	4.4

* rank 6 = highest frequency of unfavourable conditions compared with other types of organization of working time

N = Noise, C = unfavourable climate, L = unfavourable lighting, V = Vibration

Generally, combined effects can be additive, subtractive or multiplicative (7, 8, 9). For example, noise and vibration should produce, based on theoretical considerations, additive effects. However, little is known if people working under shiftwork conditions, including nightwork, have a higher incidence of hearing loss than dayworkers, or if the 85 dB(A) level is similarly safe for both working conditions (10, 11, 12). Nearly nothing is known about the combined effects of long-lasting exposure to nightwork and of adverse, in particular warm working conditions. This is not only true of workplaces in mid-European countries but also of working conditions in the tropics and subtropics where the climatic conditions are bad not only during work but also during the daysleep. The same is true of the combination of nightwork with the exposure to toxic agents (13, 14). For this reason we want to present the results of studies and discussions on combined effects of nightwork and other adverse working conditions.

I. COMBINED EFFECTS OF SHIFTWORK AND HEAT STRESS

This chapter discusses the question of whether or not circadian rhythms of certain physiological functions are influenced by the combination of nightwork and heat stress in respect to their chronobiological characteristics and whether their re-entrainment under such conditions may be influenced, positively or negatively.

SUBJECTS AND METHODS

The study consisted of two sets of experiments with healthy male young subjects. The first set of experiments included four groups of two subjects each (age 22–31), who agreed to participate in the study after having been informed about possible risks. Each person worked in a climatic chamber (15) under one of four experimental conditions, which resulted from combining two heat stress conditions with two shiftwork conditions. The climatic conditions were 23.4 °C BET (»normal climate«) and 27.7 °C BET (»hot climate«). Under daywork conditions the subjects had to work from 8 a.m. to 6 p.m. for five consecutive days. Nightwork conditions demanded work from 8 p.m. to 6 a.m. during five consecutive nights. After two days of rest the subjects changed to the opposite experimental conditions for another five days. The two experiments were performed in two runs each with four subjects in two groups during weeks of extremely warm weather. These weeks were selected in order to take advantage of the natural summer acclimatization.

All subjects worked in a sitting position for 10 hours continuously, changing after each hour between two types of task. The first task was an inspection task (Gallwey) (16, 17), the second task (DORN test, a version of the BAKAN-task modified by A.P. Smith) involved to a higher degree short-term memory and showed a clear circadian rhythm in respect of the mean response time under both conditions (18). Before the experiment all subjects had standardized training sessions for at least four hours under normal climatic conditions. It must be noted that all subjects after having worked in hot climatic conditions slept under elevated room temperature in a noise- and temperature-controlled sleeping room. The sleeping time was in accordance with the mean sleeping time of shiftworkers (19), fixed at eight hours nightsleep for daywork and at six hours daysleep for nightwork. Napping was not allowed. In the second set of experiments the different shifwork conditions, combined with different heat stress and acclimatization procedures were applied in uncombined series of six different groups of two subjects. As acclimatization problems were expected to be involved in this series the experiments were carried out during fall and winter. In the two series of experiments the subjects were motivated by both intrinsic motivation (»benefits for developing countries«) and extrinsic motivation (»incentive payment«). All experiments were supervised by experienced medical staff.

Throughout the study heart rate and rectal temperature were continuously recorded using valid ambulatory monitoring instruments (20, 21). Urine samples were collected at four-hour intervals during the whole series of the observed 24-hour-periods, in order to determine the circadian rhythms of adrenaline (A), noradrenaline (NA), sodium and potassium excretion. The analysis of catecholamines was performed by cleaning up the samples with Al_2O_3 followed by RP-HPLC separation and the fluorimetric detection of trihydroxyindoles with a chemical reaction detector. Each sample was analysed twice using the standard additions' methods for the correction of chemical recoveries (22, 23, 24). The sodium and potassium analyses were performed by flame photometry.

RESULTS

From our experiments we could expect three effects, which should be partly different for the three functions in question (25):

– Modification of circadian rhythms by emotional stress »during the first days of each experiment«: »Emotional stress«, not yet fully defined (26), was operationally described as the »psychological phase of habituation to a new task and/or a new situation«. Emotional stress should depend on individual differences in recognizing tasks and situations. Based on theoretical conclusions emotional stress should lead to strain reactions resulting only in an increase of adrenaline excretion but not in potassium excretion or temperature changes. As expected, there were individual differences in the adrenaline excretion rate at the beginning of the experiments. Some subjects did not have elevated excretion rates either under normal or hot climate in contrast to some others who showed this effect especially during the day; the same phenomenon was true also during night for higher BET (30.5) (Figure 1). Those individuals who started with high excretion rates of adrenaline showed in their individual data of the two first days normal circadian fluctuations superimposed by emotional effects. Their circadian rhythm was fully entrained mostly after 4–8 hours, at the latest after 12–16 hours. For the potassium excretion rate and for body temperature a similar behaviour could not be demonstrated.

– Modification of circadian rhythms by hot climatic conditions during day and nightwork: If the hot climatic conditions, used in our experiments, had been stressful for the subjects, an elevated adrenaline excretion rate could have been expected. However, this happened only to an insignificant extent (Figure 2). This means that in general the circadian rhythm of adrenaline excretion was not altered by the climatic conditions, except by the 30 °C BET condition at the beginning of the nightshift. In all other cases a reduced adrenaline excretion rate could be demonstrated. The same result was confirmed for the potassium excretion rate for all climatic conditions without any exception (Figure 3). Rectal temperature showed a marked elevation during the working hours at day and night clearly depending on the climatic conditions (Figure 4).

– Modification of circadian rhythms by nightwork: For adrenaline the modification of circadian rhythms by nightwork is clearly demonstrated in Figure 2, which allows a comparison of the results from dayshifts, »days off«, and nightshifts under the different climatic conditions. The lower part of the figure shows there is a quick partial re-entrainment of adrenaline excretion for the sleeping phase during daysleep after the nightshift and a small elevation of the excretion rate during the working hours at night compared to the sleeping level during nightsleep phases. This means that the adrenaline excretion rate approaches zero during sleeping periods –

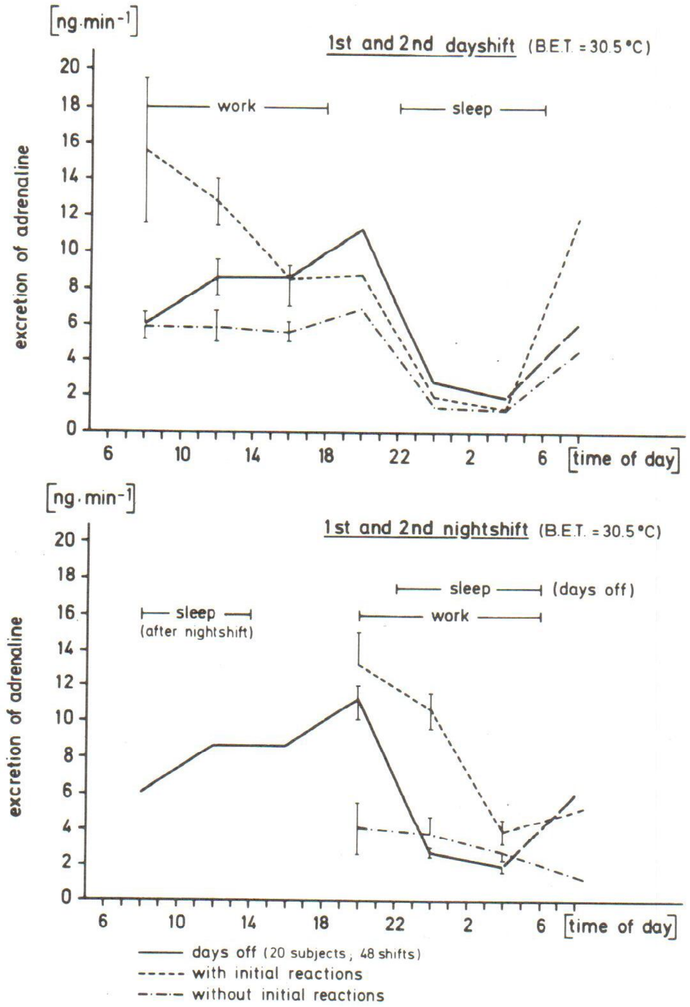

Figure 1: *Urinary excretion rate of adrenaline during the initial period of an experimental shiftwork study using a mentally loading task (25).*

either at night or day – and is for the same work lower during working hours at night than at day. Therefore, sleep seems to have the most important influence on the modification of adrenaline excretion for the situational and working conditions under study. In contrast to these findings, there was no effect of nightwork on the circadian rhythm of potassium excretion (Figure 3). The circadian rhythm, however, of rectal temperature by nightwork was only modified by the climatic conditions during the

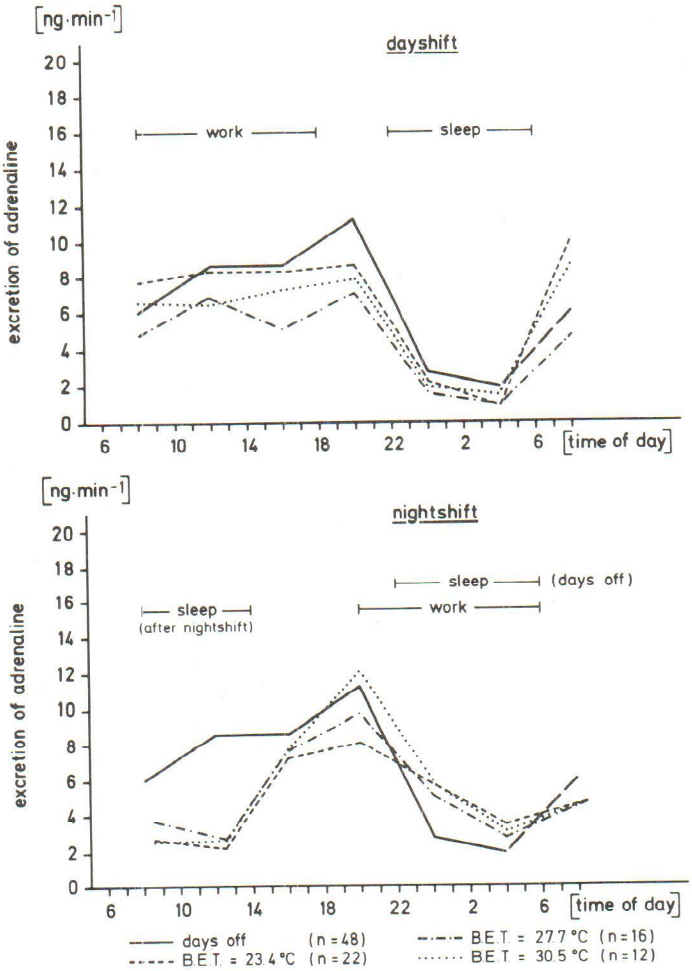

Figure 2: *Circadian rhythm of urinary adrenaline excretion rate during an experimental shiftwork study combined with different heat stresses using a mentally loading task (25).*

night phase but not during the sleeping time at day. During day only an additional minimum of body temperature occurs, which may be explained as masking phenomenon (Figure 4).

DISCUSSION

In many field studies (27) and controlled experiments (26, 28) it has been demonstrated that adrenaline excretion is temporarily elevated by stressful situations or

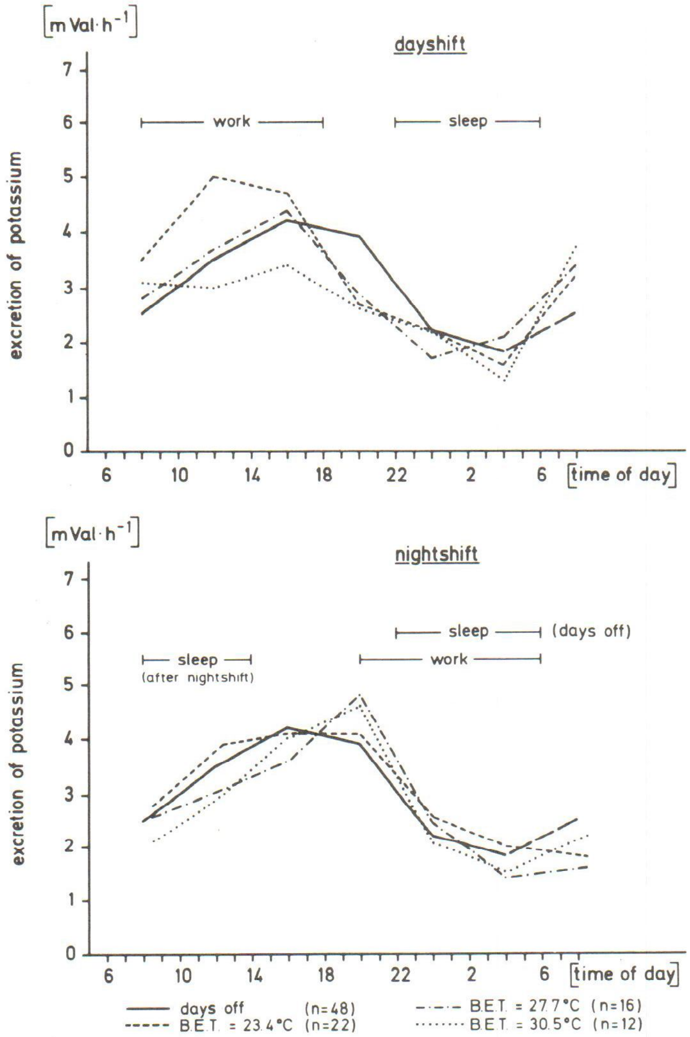

Figure 3: *Circadian rhythm of urinary potassium excretion rate during an experimental shiftwork study combined with different heat stresses using a mentally loading task (25).*

working conditions. Long-term effects on the circadian rhythms, caused by stressful situations including nightwork could be demonstrated only in a few studies (29, 30). In our experiments we could show that emotional stress tends to increase adrenaline excretion, if a new situation is subjectively of great importance for the individual. The experiments also indicate that sleep/wakefulness is the leading influence for the

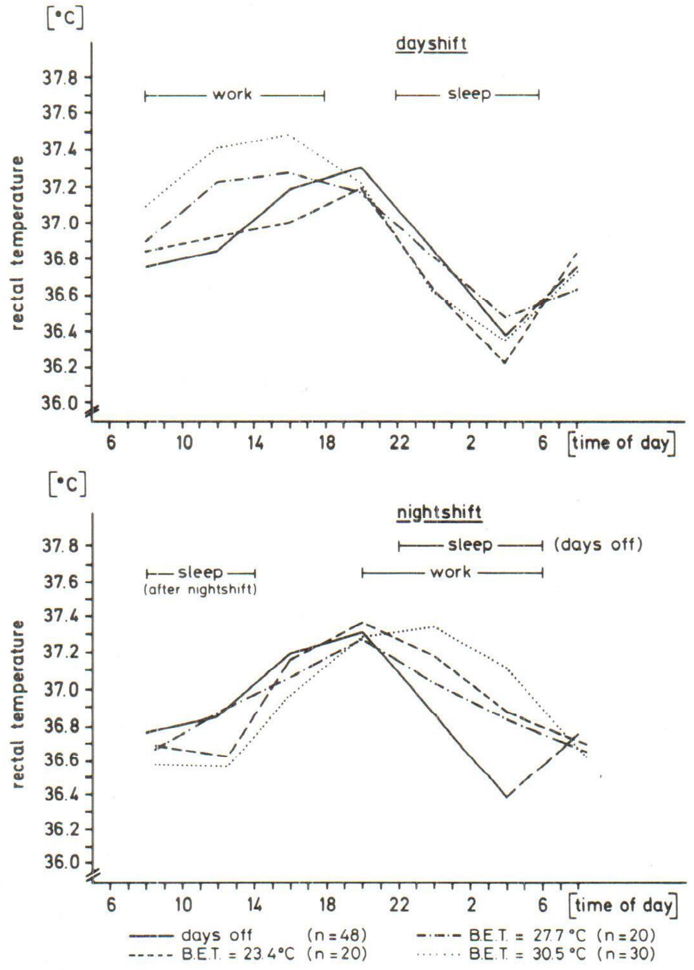

Figure 4: *Circadian rhythm of rectal temperature during an experimental shiftwork study combined with different heat stresses using a mentally loading task (25).*

circadian rhythm of adrenaline excretion (31, 32, 33). However, a substantial influence of heat stress on the adrenaline excretion under sitting working conditions with the subject performing a difficult mental task at warm climates up to 30 °C BET could not be found. We could, however, demonstrate the expected increase of rectal temperature in relation to the climatic conditions during day and nightwork, but this effect was modified during the night by chronobiological influences. This raises the question of whether border limits for the body temperature can be the same during day and night.

Therefore the question if people working in shifts tolerate heat stress during night better than during day, or if we need different limitations for heat stress during day and night remains unanswered.

II. COMBINED EFFECTS OF SHIFTWORK AND NOISE

Shiftwork and noise are well known as stress inducing factors with influence on performance, physiological functions and wellbeing. As a rule shiftwork effects are explained in terms of activation. In contrast to shiftwork, different concepts are in competition for the explanation of noise effects. Beside the activation model, the concept of tension is used. Therefore it is not possible to predict the consequences of a combination of shiftwork and noise with a simple model, although both stress types occur together often under occupational conditions.

SUBJECTS AND METHODS

Four groups of six subjects each worked under one of four experimental conditions, which resulted from combining two noise conditions with two shiftwork conditions. The noise conditions were 50 dB(A) and 80 dB(A) (noise) of a white noise (presented by earphone). In the daywork condition the subjects worked from 8 a.m. to 6 p.m. and slept from 10 p.m. to 6 a.m. Night work demanded work from 8 p.m. to 6 a.m. and sleep from 8 a.m. to 2 p.m. The experiment was carried out on five consecutive days followed by resting days. The subjects worked on a visual display unit using in principle the same task described before (34). The main task was a test, known as detection of repeated numbers. To vary task demands this type of task was sometimes combined with a second test, a reaction time task or an adding task.

RESULTS

Different and separate patterns of effects were observed depending on shiftwork and noise (35). One pattern of results summed up the effects induced by shiftwork. This pattern showed differences in activation between dayworkers and nightworkers which grew up with progress in time. On the performance level, differences in activation were documented by the reduced number of correct responses and by the decelerated reaction times of the nightworkers (Figure 5). Shiftwork effects on the physiological level could also be explained as activation alterations. Nightworkers showed reduced adrenaline excretion and lower heart rates during working time. Further evidence for reduced activation for nightworkers was given by the ratings of alertness and activation. These effects occurred independently of noise conditions.

Noise during working times induced tension effects, which could not only be documented during exposure but also during subsequent sleep. Noise exposure compensated the time-related reduction of performance, which was observed in the

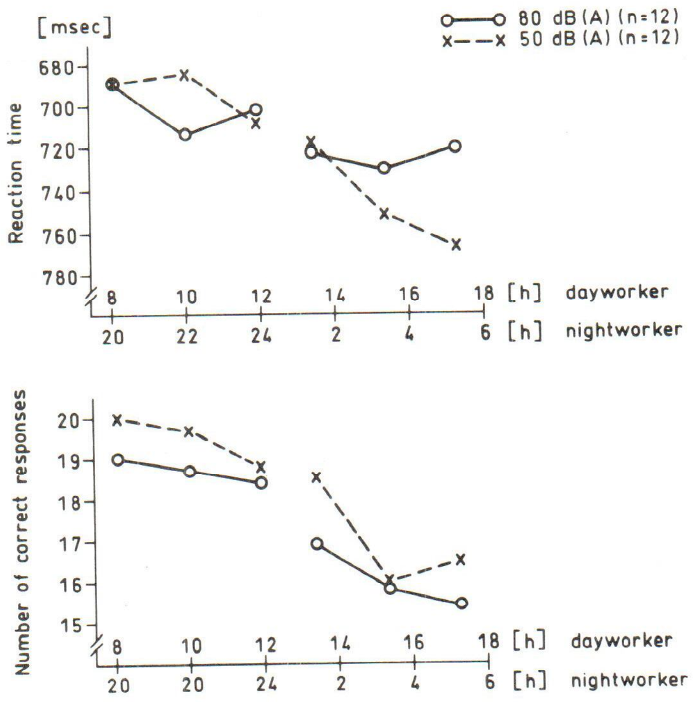

Figure 5: *Mean reaction time and number of correct responses during experimental shiftwork in combination with different noise levels (35).*

quiet condition. This effect was in accordance with the concept of reactive increase of psychic tension and was accompanied by a reduction of heart rate variability. During the first sleep period the subjects of the noise condition showed a higher adrenaline excretion rate than the subjects of the quiet condition. This pattern was independent of the shiftwork condition (Figure 6). Shiftwork and noise differed further in the duration of adaptative processes. While partial adaptation to noise was over at the end of two days, adaptation to shiftwork was not completely terminated after five days.

DISCUSSION

Our study proves that shiftwork and noise induce independent different effects, which can be explained in terms of activation for shiftwork and in terms of tension for noise. The combination of both adverse exposures is therefore partly subtractive (performance level) but partly additive since nightwork and noise affect the subsequent daysleep negatively.

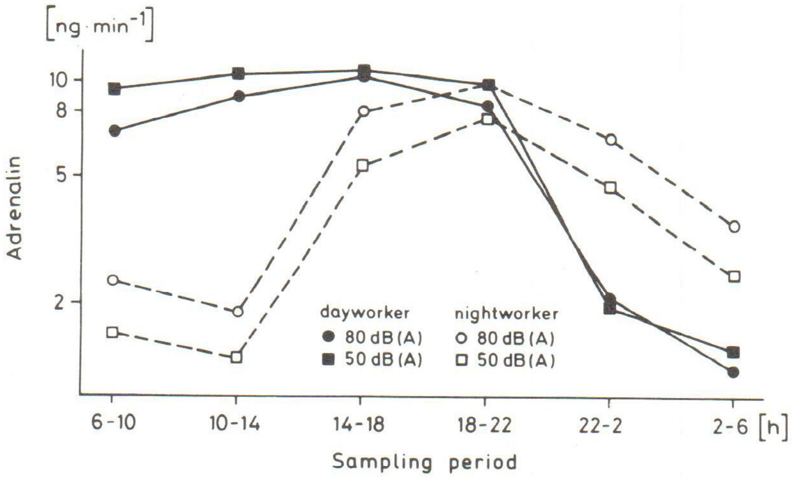

Figure 6: *Excretion rates of adrenaline during experimental shiftwork in combination with different noise levels (35).*

III. COMBINED EFFECTS OF SHIFTWORK AND CHEMICAL AGENTS

Shiftwork is very common in most chemical industries; one should therefore expect that all protective measures, like MAC values, would have a time-related structure. The policy for defining MAC values for specific substances is, however, different in different countries (36). In most countries MAC values are set for eight working hours per day and 40 hours per week. Often, however, this does not correspond to reality since the organization of working hours, including shiftwork, implies substantial variations, depending on national regulations and social contracts in certain or even in the same industries; different shift systems are involved (37). The regular working hours in the German chemical industry vary between 8 and 12 hours, the weekly working hours in special parts of shift systems between 36 and 60 hours. It is obvious from several reviews (38, 39) that shift systems should not be constructed arbitrarily, but should meet special physiological and psychological criteria. Resuming the mostly accepted criteria for continuous systems with four crews, a shift system should be rapidly rotated, should include shifts of either 8 or 12 hours depending on the load of the task, and include two free days on weekends (at least one weekend per month); compressed weekly working hours should be avoided (40). Partly in contrast to these proposals in the most important chemical plants in West Germany it is current practice (Fig. 7) to use rapidly rotated 12-hour-shift systems with 48 hours free after nightshifts, shift systems with 5–7 identical shifts (morning, afternoon, night) in succession, or shift systems in which the working hours of four weeks are compressed in three weeks with weekly working hours up to 60 hours.

Day		Mo	Tu	We	Th	Fr	Sa	Su
Crew	1	▨	N	N	N	N	N	N
	2	N	▨	▨	▨	M	M	M
	3	M	M	M	M	▨	▨	▨
	4	A	A	A	A	A	A	A

Day		Mo	Tu	We	Th	Fr	Sa	Su
Crew	1	D̄	N̄	▨	▨	D̄	N̄	▨
	2	▨	D̄	N̄	▨	▨	D̄	N̄
	3	▨	▨	D̄	N̄	▨	▨	D̄
	4	N̄	▨	▨	D̄	N̄	▨	▨

Day		Mo	Tu	We	Th	Fr	Sa	Su
Crew	1	M	M	M	M	M	M	M̄
	2	A	A	A	A	A	A	▨
	3	N	N	N	N	N	N	N̄
	4	▨	▨	▨	▨	▨	▨	▨

D̄ = day shift (12 hours)
M = morning shift
M̄ = morning shift (12 hours)
A = afternoon shift
N = night shift
N̄ = night shift (12 hours)
▨ = day off

Figure 7: *Shift systems for continuous production used in different plants in the chemical industry (41).*

These variations in working hours and shift systems reflect a great variation of time, duration and sequence of exposure, which may lead, under special conditions, not only to problems of accumulation of toxic agents but also to changes in toxicokinetics and toxicodynamics. There exists therefore the problem as to whether MACs/TLVs should be adapted to different work schedules; furthermore the limitations of present MACs/TLVs have to be discussed on the basis of new concepts developed by the subdiscipline of »chronopharmacology«. Our discussions (41) consider practical as well as theoretical aspects of this topic. The practical considerations will be based on the current regulations in the Federal Republic of Germany (42) concerning environmental monitoring (MAC values) and biological monitoring (BAT values).

Environmental monitoring (MAC)

The maximal concentration value in the workplace (MAC) is defined as the maximum permissible concentration of a chemical compound present in the air within a working area (as gas, vapour, particulate matter) which, according to current knowledge, generally does not impair the health of the employee nor causes undue annoyance (42). This means, that »under these conditions, exposure can be repeated and of long duration over a daily period of eight hours, constituting an average work week of 40 hours (42 hours per week as averaged over four successive weeks) for firms having four work shifts«. The main reasons for this fixation are matters of legislation, and the question arises how far it is based on scientific knowledge. In fact, this precondition of MAC values was changed in 1979 as average working time had been fixed to 45 hours per week. This nominal change was, however, introduced without changing the MAC values. The question of theoretical dependence of MAC values upon time of exposure and work schedules cannot uniformly be answered for all the compounds listed. A necessary differentiation may be based on the categories already established for limitation of peak exposures. This concept of regulating short-term exposure limits has been explained in detail elsewhere (43). Most of the compounds mentioned in the MAC list are separated into »peak limitation categories«, according to their toxicological and pharmacokinetic properties. No problems with different work schedules may arise with local irritants (category I) where the MAC is set with the intention to avoid irritation. The same holds true for »substances having intensive odour« (category V), comprising mostly thiols and aliphatic amines. Also, »substances eliciting very weak effects« (category IV; $\mathrm{MAC} \geq 500$ ppm) are not problematic at all. The remainder of »substances with systemic effects« are separated according to their pharmacokinetic behaviour (categories II and III). Highly cumulating compounds, such as many heavy metals and organochlorine pesticides, are grouped under category III. In practice, the long period in which cumulation of these compounds occurs renders MAC independent of a distinct exposure profile; after long periods of exposure cumulation in the body reaches a plateau where the average effective intake per unit time is equivalent to the eliminated dose. The possible intake, under a given MAC, therefore is theoretically determined by the average weekly exposure hours.

Compounds from category II (also exhibiting systemic effects, but with short half-lives) are more difficult to assess. The MAC list distinguishes between two subcategories: II, 1 (compounds of short half-life, up to 2 hours) and II, 2 (compounds of longer half-life, between 2 hours and shift length). The MAC of such compounds may be considered dependent on the maximal daily exposure time (shift length). However, this may not hold true for some of the short-lived compounds (falling into category II, 1) which are eliminated very rapidly. In this context, the importance of elimination from the organism for the setting of occupational standards must be stressed (44). The practice of standard setting is characterized by the necessity of a variety of compromises, e.g. lack of knowledge of basic data, lack of long-term experience, lack of human data (44). This, along with the considerable interindividual variations in response to, and in metabolism of, toxicants, leads to uncertainty in standard setting. A careful review of some 150 occupational chemicals in the German list of MAC values has revealed that less than 10% of their exposure limits was based on appropriate and sufficient animal testing and/or human field experience (44). Accordingly, MAC values of volatile chemicals are usually fixed at graduations of 1, 2, 5, 10 etc. ppm (ml/m^3). A noteworthy exception is carbon monoxide (MAC = 30 ppm), where sufficient knowledge was available to set the MAC to this particular level. This also implies that, in general, the minute influences exerted by possible alterations of work schedules are not or cannot be taken into account.

Biological monitoring (BAT)

The biological tolerance value for a working material (BAT value) is defined as the maximum permissible quantity of a chemical compound, its metabolites, or any deviation from the norm of biological parameters induced by these substances in exposed humans (42). It is explicitly stated: »As with MAC values, the maximum period of exposure to a working material is generally given as eight hours daily and 40 hours weekly« (42). The result of a short compilation published elsewhere (41) is that the Biological Acceptable Thresholds of nearly all compounds included in the BAT list are independent of the exposure schedule, as far as different times of exposure and different shift systems are concerned (Table 2). However, these considerations did not take into account possible »chronopharmacological« differences in individual susceptibility towards chemical toxicants. As practical experience in this field is lacking, such a question can at present only be approached from a very theoretical point of view.

Table 2

Alphabetical list of substances on the 1985 BAT list

Substance	BAT parameter and commentary
Acetylcholine esterase inhibitors	30% inhibition (see text). This parameter is generally valid.
Aluminium	Al in urine. The justification of this BAT value is very provisional because only limited data are available. Because of a presumably long half-life a dependence on exposure schedules, at first glance, is not likely.
Aniline	The analysis on aniline released from its haemoglobin conjugate renders the monitoring of this compound independent of exposure schedules.
Cadmium	Cd in whole blood and urine. Because of the long biological half-life no dependence of BAT on exposure schedules.
Carbon monoxide	The toxic effect (binding to haemoglobin) can be directly monitored. The BAT of 5 % CO-Hb is therefore a true ceiling value, which is independent of exposure schedules.

Carbon tetrachloride	CCl_4 in expired alveolar air. Because of the only fragmentary data on human exposure and kinetics, no evaluation of different exposure schedules is possible.
Dichloromethane	The toxic effect (binding of CO to haemoglobin) can be directly monitored (see above, carbon monoxide). This BAT is independent of exposure schedules. When the concentration of dichloromethane itself in biological media is monitored, dependence of the biological limit on shift length is predictable.
Fluorine: HF and fluorides	Two BAT values for F^- in urine (pre- and postshift). Upon application of both parameters, the biological monitoring can be applied to any shift regime.
Halothane	Trifluoroacetic acid in whole blood. Evaluation is only provisional. Because of the long half-life of this metabolite, a significant dependence on exposure schedules is not likely.
Hexachlorobenzene	Compound in plasma. Because of the long biological half-life, the BAT is independent of exposure schedules.
Lead	Pb in blood; ALA in urine. Long biological half-life and persistence in the organism. Therefore, no dependence of BAT on exposure schedules.
Mercury, inorganic	Hg in blood and urine. Long biological half-life. Therefore, no dependence of BAT on exposure schedules.
Mercury, organic	Hg in blood. Long biological half-life. Therefore, no dependence of BAT on exposure schedules.
Styrene	Metabolites in urine. The biological half-life (2 compartments; $t_{1/2}$ = 2.2 to 4 days) suggests a potential cumulation, which might be dependent on exposure schedules. However, it is presently thought that BAT (determination at end of the shift) will generally protect against health hazards.
Tetrachloroethene	Compound in blood and exhaled air. Because the compound is active by itself (CNS) the BAT refers to determination of the active principle. Therefore, the BAT is valid for any exposure schedule.
Toluene	Compound in blood and exhaled air. The same applies as for tetrachloroethene.
Trichloroethene	Trichloroethanol in blood. As this is the biologically active metabolite, BAT is independent of exposure schedule.
Xylene	Xylene in blood, metabolite (toluric acid) in urine. Determinations should be done at the end of exposure. For interpretation of results, the justification (45) must be consulted.

Aspects of chronopharmacology

The toxicity of many foreign compounds is known to be dependent on the time point of application, and chronopharmacological influences have been described (46). This refers to many drugs acting on the CNS, such as barbiturates, benzodiazepines, lithium and anaesthetic drugs. Similar effects have been seen with poisons acting on the autonomous nervous system (e.g. paraoxon, nicotin), and with other compounds (antimycin A, cardiac glycosides). As an example, the mortality rate of a single dose of 190 mg/kg phenobarbital in light-dark synchronized rats varies between 0% (in the phase of maximal motor activity) and 100% (at the end of the resting phase) (47). Such diurnal variations in sensitivity may be triggered directly by the light-dark cycle (which may be likely for compounds acting on the central or autonomous nervous system), or may be indirectly due to diurnal variations in metabolism of foreign compounds. The occurrence of diurnal rhythms of hepatic metabolism of drugs has been classically demonstrated in humans by Versell's group (48), using aminopyrine. In animal experiments, similar observations have been made using aminopyrine, p-nitroasinol, hexobarbital, 4-dimethylaminoazobenzene, and other xenobiotics (46). However, in further investigations by Versell's group (49) it turned out that the diurnal variations of (oxidative aminopyrine) metabolism were triggered by food intake. Changes in eating times influenced the diurnal cycle of aminopyrine half-life, but not that of plasma 11-hydroxycorticoids. The importance of the time of food intake for hepatic function and for toxicity towards the liver has been highlighted in a series of animal experiments (50, 51, 52). It is well known that alphahexachlorocyclohexane (HCH) induces liver growth and cell replication in rats. This process requires stimuli by food intake (amino acids, and a carbohydrate, e.g. glucose). Food consumption is needed (a) before or at the time of HCH administration (G_0), and (b) 12–15 hours later, i.e. 5–8 hours before initiating DNA synthesis (»R-point«). Thus, it is experimentally well established that »hepatic rhythms« are likely to be a consequence of the daily distribution of food intake. The importance of such phenomena for action of chemical toxicants in man at the workplace is very difficult to evaluate but may be of greater importance in the future.

Finally, an interesting observation (the only one dealing with a particulate matter) should be discussed. In experimental studies on the pulmonary clearance of asbestos fibres, *Bolton et co-workers* (53) have compared rats with a normal light-dark-cycle with those under »reverse daylight« conditions where the activity phase was shifted towards daytime. It turned out that inhaled amosite, at two different concentration levels, was cleared much better than normal when »reverse daylight« conditions were applied. An explanation of this phenomenon could not be given so far, but the example demonstrates that diurnal rhythms may in fact be of some importance in occupational toxicology.

Conclusions

The presented examples for the combination of nightwork with other adverse working conditions led to the following practical consequences:

Work under hot climatic conditions during night should be performed under lower threshold limits (<38,3 °C) for the rectal temperature. Epidemiological studies, however, are needed to decide if the prevalence of heat strokes occurs during night under lower environmental climatic conditions or/and lower rectal temperature than during daytime.

Noise below 85 dB(A) has no positive effects on physiological activation but involves a reactive increase of psychic tension. This affects the noradrenaline excretion during the first sleep periods, independently of the sleeping time. Noise of this level may therefore influence performance processes positively during nightshifts but seems to have unwanted aftereffects during the recuperation time.

Theoretical speculations led to the consequence that there may exist a time of day dependence of some chemicals, used at the workplaces. MAC values for such groups of chemicals should in future be proposed for the different working hours per day (8 or 12 hours) and for day or nightshifts. The experience gained from chronopharmacological studies should be considered in such proposals. The influence of eating habits on chronopharmacological effects may, in future, require more strict regulations for meal breaks of shiftworkers.

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Sažetak

KOMBINIRANI UČINCI SMJENSKOG RADA I FAKTORA OKOLINE (VRUĆINA, BUKA, TOKSIČNI AGENSI)

U radu su prikazani rezultati istraživanja i iznesena je teorijska rasprava o problemu smjenskog rada povezanim s drugim nepovoljnim uvjetima rada. Naročito je naglašeno moguće negativno djelovanje visoke temperature za vrijeme smjenskog rada, kao i utjecaj buke i izloženost kemikalijama. Nađeno je da nema značajnog utjecaja toplinskog stresa na dnevni ritam izlučivanja adrenalina pri sjedećem teškom mentalnom radu sve dok temperatura ne pređe 30 °BET. Smjenski rad i buka imaju neovisno djelovanje koje se može razjasniti aktivnošću u smjenskom radu i napetošću uzrokovanom bukom. Stoga je djelovanje ovih dvaju negativnih utjecaja djelomično suprotno, a djelomično aditivno, budući da noćni rad i buka negativno utiču na san slijedećeg dana. Nedostaju iskustva o kombiniranoom djelovanjuu smjenskog rada i kemijskih spojeva u radnoj okolini, no teorijske pretpostavke dovode do zaključka da bi mogle postojati razlike u toksičnosti pojedinih kemikalija s obzirom na doba dana.

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