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Jet fuel and liver function

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DØSSING M, LOFT S, SCHROEDER E. Jet fuel and liver function. *Scand J Work Environ Health* 11 (1985) 433–437. The impact of occupational exposure to jet fuel on antipyrine elimination was studied in 91 fuel-filling attendants. The mean antipyrine clearance was enhanced to 68.4 (SD 19.5) ml/min during exposure to jet fuel compared to 57.9 (SD 18.1) ml/min after an exposure-free period of two to four weeks. The corresponding values for 47 office workers (referents) were 62.7 (SD 22.2) ml/min and 56.4 (SD 22.3) ml/min. The median jet fuel concentration in the breathing zone of the fuel-filling attendants was 31 (range 1–1 020) mg/m³. No known inducing factor could be identified in the work environment of the office workers. No difference in the concentration of aspartate aminotransferase and alkaline phosphatase in serum was found either within or between the groups. Our study indicates that jet fuel, which is a mixture of aliphatic and aromatic organic solvents resembling gasoline and white spirit, is an inducer of hepatic drug metabolism in man.

Key terms: antipyrine, drug metabolism, induction, liver enzymes, microsomal enzyme function, organic solvents.

A recent study on man and rats has shown that gasoline, which is a mixture of aliphatic and aromatic hydrocarbons, is an inducer of microsomal enzyme activity as assessed by the widely used antipyrine test (9). Animal studies indicate that microsomal enzyme activity is changed by organic solvents in concentrations not high enough to cause elevations in conventional liver enzyme tests but nevertheless high enough to lead to alterations in the hepatic ultrastructure (7), a phenomenon which may be potentially harmful.

Jet fuel is another widely used mixture of aliphatic and aromatic hydrocarbons which is more volatile and lipophilic than gasoline.

Our purpose was to study microsomal enzyme activity and conventional liver enzymes in a large group of workers with daily exposure to jet fuel. The study included a reference group and was designed so that every person served as his own referent in order to enhance the sensitivity of the applied liver test (22).

Subjects and methods

All fuel-filling attendants (N = 94) from the seven military air force bases of Denmark participated in the study. Office workers employed in two offices of the Danish Air Force served as referents (N = 48). None of the subjects took drugs containing phenacetine or

phenazone (antipyrine) or drugs with known impact on antipyrine clearance. Four subjects (three fuel-filling attendants and one referent) were excluded because they had an average daily alcohol consumption of more than five drinks. One of the four had a biopsy-proved moderate steatosis. None of the included subjects suffered from known liver disease. The median duration of employment in the air force was 6.4 (range 0.2–31.0) years and 7.6 (range 0.5–36.9) years for the 91 tank operators and 47 office workers, respectively.

Age, body weight, body height, and information on the average daily consumption of tobacco, alcohol, coffee, and tea were recorded. The subjects were also asked about their alcohol consumption the day before each investigation and about daily physical activity. No attempt was made to control the life-styles of the subjects. The subjects were questioned about mucous membrane irritation, headache, excessive tiredness, and feelings of drunkenness without alcohol intake. Relief or disappearance of symptoms during weekends and vacations were recorded.

The 91 fuel-filling attendants controlled jet fuel by spot samples and visual inspection of the outlet from the bottom of the tanks. They filled up tank trucks, jet planes, and helicopters with jet fuel. No gloves or protective respirators or protective clothing was used. The median daily duration of exposure to jet fuel was 4 (range 0.5–8) h.

The employed jet fuel is a complex mixture of various hydrocarbons, physically characterized by a vapor pressure of 12–21 kPa, a distillation point of 170–350°C (most distilled at 270°C), and a freezing point of –58°C. Chemically, the jet fuel contains about 17–20 vol% aromatics (maximum 25 %) and 1–5 % oleofines, and it has a total sulfur content of 0.4 %.

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Sixty-nine samples from the breathing zone of 12 randomly chosen fuel-filling attendants were collected on charcoal tubes for two to four workdays during the period when the first liver test was performed. The tubes were desorbed with dimethylformamide and analyzed by gas-liquid chromatography with a Hewlett-Packard HP 5831 A equipped with a flame ionization detector (7671 A) and with 2-ethoxyethanol as the internal standard (15). Spot samples collected during the exposure and samples collected during several hours of work were obtained in order to determine the variation in exposure and the average daily exposure level. The median air concentration of jet fuel was 31 (quartiles 9–82, range 1–1 020) mg/m³. Four samples were above 700 mg/m³, two of which were collected during 3 h of work indoors. The other two measurements were collected in open air during 10–20 min of exposure.

On the fourth or the fifth workday of one of the last weeks before summer vacation antipyrine clearance

was measured and a venous blood sample was drawn for the estimation of serum aspartate aminotransferase and serum alkaline phosphatase by routine laboratory methods (autoanalyses). The procedure was repeated on one of the last days of a two- to four-week summer vacation. For antipyrine clearance determination antipyrine (1 g) dissolved in water was taken orally and saliva was collected 24 h later by the subjects according to written instructions. Saliva was stored at –20°C until analyzed by high-pressure liquid chromatography (20) within three months after the sampling. The simplified antipyrine clearance (Cl_{AP}) was calculated as $Cl_{AP} = \{[\ln(D/V_d) - \ln c_i]/t\} \cdot V_d$, where D is dose; V_d is the volume of distribution assumed based on the recorded age, sex, body weight, and height of each person; and c_i is the concentration of antipyrine at sampling time t (4).

Differences within and between the groups were compared by a Wilcoxon's rank sum test for paired and nonpaired data, respectively. For the evaluation of the antipyrine data a t-test was used. A p-value of <0.05 was considered statistically significant.

Figure 1. Salivary clearance of antipyrine in workers occupationally exposed to jet fuel and in referents measured during work and after two to four weeks of vacation. The bars are means with standard deviations.

Results

The salivary clearance of antipyrine was 18 % higher in the fuel-filling attendants ($p < 0.001$) during exposure to jet fuel as compared to the measurement made after two to four weeks free from exposure (figure 1). The enhanced clearance in the group of office workers, amounting to 11 %, was also statistically significant ($p < 0.02$) (figure 1). The referents were employed at two different air force bases, and the mean antipyrine clearance was only increased in one of the groups [72.4 (SD 21.8) ml/min versus 57.4 (SD 12.1) ml/min, $N = 24$ ($p < 0.001$), and 54.8 (SD 20.6) versus 55.1 (SD 31.1) ml/min, $N = 23$ ($p > 0.3$)]. Although the antipyrine clearance was 9 % higher in the fuel-filling attendants than in the office workers in the first measurement, this difference between the groups did not reach statistical significance ($p < 0.1$). The duration of daily exposure to jet fuel and the duration of employment with jet fuel did not correlate significantly either with antipyrine clearance or with the relative change in antipyrine clearance from the first to the second measurement. In both measurements the smokers had a significantly (on the average 31 %) higher antipyrine clearance than the nonsmokers in both groups ($p > 0.01$) (figure 2).

No difference in serum aspartate aminotransferase and serum alkaline phosphatase was found either between or within the groups ($p > 0.2$) (table 1). The fuel-filling attendants were younger (median 34 years, range 21–59 years) than the office workers (median 44 years, range 19–66 years) ($p < 0.01$), but there was no difference in duration of employment in the air force ($p > 0.3$). No significant difference between the groups was found between the average daily consump-

Figure 2. Salivary clearance of antipyrine in 48 smoking and 43 nonsmoking tank operators occupationally exposed to jet fuel and in 18 smoking and 23 nonsmoking referents investigated before and after two to four weeks of vacation. The bars are means with standard deviations.

Table 1. Results of the serum aspartate aminotransferase and alkaline phosphatase measurements during a period of work (measurement 1) and after two to four weeks free from work (measurement 2) for workers exposed to jet fuel and for their referents.

Group	Serum aspartate aminotransferase (U/l; normal <40) ^a				Serum alkaline phosphatase (U/l; normal <275) ^a			
	Measurement 1		Measurement 2		Measurement 1		Measurement 2	
	Median	Range	Median	Range	Median	Range	Median	Range
Exposed (N = 91)	19	5–54	14	6–100	135	10–385	145	25–560
Reference (N = 47)	19	7–84	16	3–58	125	10–550	140	10–535

^a 1U/l = 16.66 nkat/l.

tion of ethanol, cigarettes, or coffee/tea, ethanol consumption the day before each investigation, or in the amount of physical activity, and no significant difference was recorded for these host factors from the first to the second investigation. The fuel-filling attendants reported a significantly higher frequency of mucous membrane symptoms [29 versus 16 % ($p < 0.05$)], headache [44 versus 19 % ($p < 0.01$)], and excessive tiredness [31 versus 13 % ($p < 0.05$)] than the office workers.

Discussion

Our study shows that the fuel-filling attendants with daily exposure to jet fuel had a higher antipyrine clear-

ance before two to four weeks of vacation than after. No changes in the host factors with known impact on antipyrine clearance were recorded within the groups between the two measurements. We did not record or control dietary factors. However, it is difficult to imagine that the fuel-filling attendants would reduce their intake of food with inducing properties during vacation. Intuitively, it is more likely that they would increase their consumption of inducing food items, such as charcoal broiled meat, during a summer vacation. Accordingly, our data indicate that jet fuel is an inducer of microsomal enzyme activity in man.

Jet fuel is a mixture of aliphatic and aromatic hydrocarbons closely related to white spirit and gasoline, both of which are inducers of microsomal enzyme ac-

tivity in rats (9, 11). In 19 gas station attendants exposed to gasoline during conditions of work resembling those of our fuel-filling attendants, a significantly lower antipyrine half-time was found in comparison to that of 19 referents from a university staff and students. The study was weakened by its cross-sectional design and lack of information about host factors with known impact on antipyrine clearance (9).

While experiments with rats indicate that exposure by inhalation to the aromatic hydrocarbons toluene, styrene, and xylene are inducers of microsomal enzyme activity (8, 17, 21), this occurrence has not been confirmed in man (3). However, polyaromatic hydrocarbons such as polychlorinated biphenyls and various pesticides are well established inducers of antipyrine (1, 13) and phenylbutazone metabolism (19). Also the anesthetic agent halothane may be an inducer of antipyrine metabolism (5, 6).

Surprisingly, antipyrine clearance was also significantly increased in our office workers during work in comparison to the measurement made at the end of their summer vacation. The office workers were equally distributed between two air force bases. At one base (air base I) ($N = 24$) the antipyrine clearance was greater by 26 % ($p < 0.001$), while it was almost unchanged (-1 %) in the other group (air base II) ($N = 23$). Since our previous studies with a similar design and methods of analyses have shown an unchanged antipyrine clearance in reference groups (2, 3, 5), the results of the present study strongly indicate a possible inducing factor in the work environment of air base I. One of these may be photoprinting, which carries a risk of exposure to chemicals such as carbon black consisting of polyaromatic hydrocarbons with potential inducing properties (14). However, an inquiry among the two groups of office workers showed that at air base I 15 of the 25 employees were daily employed in photoprinting in contrast to 18 of 23 employees at air base II. Accordingly, the result of the inquiry does not lend support to the hypothesis of photoprinting as the inducing factor in the office work environment. Despite a careful investigation of both air base offices it was not possible to reveal any differences in the work environment.

The well-established strong inducing capacity of cigarette smoke (10, 23) was confirmed in our study. The antipyrine clearance of both the smokers and non-smokers was induced to about the same extent during exposure to jet fuel (figure 2), a result which indicates that one inducing factor is added to the other by simple addition. This simple rule does not always apply, however. During concomitant exposure to inducing drugs the result may be potentiating (16), additive (2), or less than additive (18).

We did not find any change in the conventional clinical chemistry indices of toxic liver injury (serum transaminase and alkaline phosphatase). Our results are in agreement with most previous studies in which occu-

pational chemicals alter antipyrine clearance but leave the transaminase and alkaline phosphatase unchanged (1, 3). Hence, the recorded change in microsomal enzyme activity is hardly an expression of a harmful toxic effect on the liver, but it may lead to altered metabolism of other microsomally metabolized drugs carrying a risk of therapeutic failure or toxicity. Clinically important therapeutic failure or toxicity of drugs associated with occupational exposure to chemicals has hitherto only been reported in a few case histories (12, 24). However, the possible impact of microsomal enzyme induction on health on a long-term scale is not known.

We conclude that occupational exposure to jet fuel at concentrations high enough to cause mucous membrane irritation enhances the clearance of antipyrine. Our study also indicated an unknown inducing factor in the work environment of one of the reference groups of office workers.

Acknowledgments

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