



PR 54367
8EHQ-0402-13646

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April 18, 2002

TSCA Document Control Officer (7408)
Office of Pollution Prevention and Toxics
US Environmental Protection Agency
1200 Pennsylvania Ave NW
Washington, DC 20460

Attn: TSCA Section 8(e) Coordinator

RE: Methyl-tert-butyl ether (MTBE), CASRN 1634-04-4
Central Nervous System Effects of the Gasoline Additive Methyl-tert-butyl ether
8EHQ Number: 8EHQ-0596-13646

Dear Sir or Madam:

Enclosed, on behalf of Lyondell Chemical Company, please find a final report entitled **Central Nervous System Effects of the Gasoline Additive Methyl-tert-butyl ether (MTBE)**. Lyondell is submitting this report as follow-up to a TSCA Section 8(e) notification (8EHQ Number: 8EHQ-0596-13646) based on preliminary data from the study.

A recent inquiry prompted review of the original notification at which time we realized that the submission was based on preliminary data. Our records do not indicate whether the final report for this study was ever transmitted to EPA, thus prompting today's submission.

Should you have any questions or require additional details, please do not hesitate to call me at 713/309-2136. I may also be reached by facsimile at 713/951-1574 or by e-mail at patrick.gibson@lyondell.com.

Sincerely,

Patrick L. Gibson
Product Safety Specialist - Regulatory
Corporate TSCA Coordinator
Lyondell Chemical Company/Equistar Chemicals, LP



8EHQ-96-13646



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Central nervous system effects of the gasoline additive methyl-*tert*-butylether (MTBE)

Finnish Institute of Occupational Health
Neste Oy, Espoo, Finland
ARCO Chemical Europe, Inc.

Final report

14.6.1996

Introduction

In order to decrease environmental pollution, oxygen-containing chemicals such as methyl-*tert*-butylether (MTBE) have recently been added to gasoline. Because of the wide-spread use of gasoline, the number of people exposed to these chemicals is very large - in addition, their use is rapidly increasing. Exposed people have claimed that exposure to this chemical with a foul smell may cause symptoms of nervous system and ill health at levels encountered in the general environment. Clinical and epidemiological studies, however, failed to corroborate these claims^{1,5,8}. Experimental data on the effects of MTBE on humans are very scanty, and mainly concentrate on irritation of mucous membranes^{6,7}. The purpose of this study was to elucidate the acute neurological effects of MTBE on humans, as assessed by objective measurements, and symptom questionnaire.

Subjects and Methods

SUBJECTS

Thirteen healthy male volunteers, age 23.2 ± 2.2 (mean \pm sd), were studied using a protocol approved by the Ethics Committee of the Finnish Institute of Occupational Health. Routine health examination was performed before and after the exposure period.

EXPOSURE

The exposures were conducted at weekly intervals and they were designed to be run in a balanced order. However, since the volunteers were exposed in groups of three, and because of dropout of some individuals, 6 subjects started with 75 ppm of MTBE, 4 subjects with 25 ppm and 3 subjects with 0 ppm. One volunteer among the thirteen was exposed to 0 ppm and 75 ppm, but not to 25 ppm, because of a transient elevation of serum transaminases subsequent to exposure at 75 ppm. The study supervisors were not aware that the subject had started medication with isotretinoin which may be associated with the finding.

Exposure was conducted in a dynamic exposure chamber where ventilation was adjusted to approximately 10 air changes per hour. Atmosphere containing 0, 25 and 75 cm³/m³ of MTBE was generated by mixing saturated MTBE-vapour with laboratory room air drawn into the chamber. The content of MTBE in the chamber air was monitored by an infrared spectrophotometer and it was automatically controlled with the aid of an industrial processor by varying the feed rate of saturated MTBE-vapour⁹. The observed average MTBE concentrations in different experiments were 24.9 ± 0.4 cm³/m³ (mean \pm SD) (N=5) and 74.9 ± 0.9 cm³/m³ (N=5).

REPORTED SYMPTOMS

The subjects reported with a questionnaire on 15 statements concerning symptoms and mood with a rating "not at all", "slightly" or "clearly". The statements of the questionnaire were as follows:

- | | |
|----------------------------------|-------------------------------------|
| 1. I feel tired | 9. My head feels heavy |
| 2. I feel tense | 10. My mouth feels dry |
| 3. I feel alert | 11. I feel cheerful |
| 4. My eyes are smarting | 12. I feel slightly dizzy |
| 5. I have palpitation | 13. I am nervous |
| 6. I feel low-spirited | 14. I have headache |
| 7. My throat or nose is smarting | 15. I have difficulty concentrating |
| 8. I feel nauseated | |

The questionnaires were filled at one and three hours during exposure as well as at one hour post exposure. Each of the symptom statements and four aggregated symptom complexes: (1) "irritation", composed of questions 4, 7 and 10, (2) "feelings in the head", composed of questions 9, 12 and 14, (3) "tension-nervousness", composed of questions 2, 13 and 15, and "moods", composed of questions 6 and 11 were used as effect parameters. The dose dependence of the effect was analysed with the linear association/trend test and statistical differences between the different exposures were tested with the sign-test and the paired T-test. Limited number of data points precluded use of multiparametric statistical testing.

SIMPLE REACTION TIME

Simple reaction time was measured with the computer-aided Swedish Performance Evaluation System (SPES) ^{2, 4, 10}. The test measures psychomotor speed and sustained attention in a monotonous situation. The subject reacted to a visual stimulus given at variable intervals; the total test duration was 6 minutes. The programme registers individual reaction times and calculates the mean reaction time as well as the variability (SD) of the individual reaction times. The tests were performed in the morning prior to exposure, at one hour and 3.5 hours of exposure, and at one hour post exposure. The results of the mean reaction time and variability are expressed as *changes from the morning pre-exposure value*. The results were analysed with a paired T-test.

POSTUROGRAPHY

The posturography instrument is a stable platform of 40x40 cm in size on which the subject stands. The ground reaction forces are recorded by strain gauges placed in each corner, and the movement of the centre of gravity is measured. Altogether five measurements were performed on each experimental day: before the exposure, at one hour, 2.5 hours and 3.5 hours during exposure, and at one hour after the cessation of exposure. Each time the examination was performed twice: first with eyes open, then with eyes closed. The duration of each measurement was 60 seconds. Length of the movement (total path) of the centre of gravity and the maximal deviation in antero-posterior and side-to-side direction were calculated ³.

BIOMONITORING

Biological samples from blood and urine were used to verify the levels of exposure. MTBE and its metabolite *tert*-butyl alcohol (TBA) were determined in blood and urine by head space gas chromatography using photoionization detector. Blood samples were collected before the end of exposure and urine spot samples about 2-3 hours after the exposure. The determination limit of MTBE was 5 nmol/l and of TBA, 20 nmol/l, respectively. Coefficient of variation for the analysis of MTBE was 2.7 % in the concentration area 13-77 nmol/l and for TBA, 3.8 % in the concentration area 45-261 nmol/l.

Results and Discussion

REPORTED SYMPTOMS

On the symptom scale "not at all", "slightly", and "clearly", almost all reported symptoms were in the class "slight"; the only exception was the question of feeling tired. To this question, several responded feeling "clearly" tired; however, this had no relationship with exposure to MTBE. The results of the statistical analyses of symptom data are shown in Tables 1 and 2.

Analysis of dose response. Some of the exposed subjects but none in the control situation reported feeling "heavy in the head": at one hour of exposure 2/12 subjects at 25 ppm, 4/13 at 75 ppm, reaching a statistically significant trend at three hours (2/12 at 25 ppm, 5/13 at 75 ppm). In the post exposure phase, 1/12 subjects at 25 ppm and 2/13 at 75 ppm still reported feeling heavy in the head. There was also a statistically significant trend in impairment of mood (feeling less cheerful) at three hours of exposure and one hour post exposure.

Although not a statistically significant finding, 1-3 individuals per group reported slight smarting in the throat and nose, or dryness in the mouth, during exposure versus none in the control situation. Additionally, at one hour of exposure 2 subjects of 13 reported slight dizziness at 25 ppm and 2/13 at 75 ppm. In the post exposure phase 1/12 at 25 ppm and 3/13 at 75 ppm reported slight dizziness versus none in the control situation. There were similar reports of slight headache: at one hour of exposure 1 subject of 13 reported slight headache at 75 ppm, at three hours 1/12 at 25 ppm and 2/13 at 75 ppm reported slight headache. In the post exposure phase, 1/12 at 25 ppm and 3/13 at 75 ppm reported slight headache. None of the subjects reported headache in the control situation.

Concerning the aggregated symptom complexes there was a statistically significant trend of increasing "feelings in the head", and decreasing "moods" with increasing exposure. The effect on "moods" related to reported cheerfulness only, because the other variable (feeling low-spirited) received no positive responses.

Analysis of concentration threshold for effect. For specific symptoms, "heavy feeling" in the head occurred significantly more frequently during exposure to 75 ppm of MTBE as compared to the control day. Similarly, the subjects reported less cheerfulness at three hours of exposure to 75 ppm of MTBE than at 0 ppm, and the effect was still found at one hour after the cessation of exposure.

Positive responses in the aggregated symptom complexes "feelings in the head" and "moods" all occurred significantly more frequently at three hours of exposure to 75 ppm of MTBE than at corresponding time of the control day. For "irritation" the

statistical significance was borderline. The effect on mood persisted at the post exposure enquiry.

Distribution of symptoms among individuals. An analysis of the individual reporting of the leading symptoms, i.e. head feelings and irritation, revealed that among the 13 volunteer subjects 6 had been symptom free throughout the series of exposures. By contrast, altogether 7 individuals had experienced MTBE-related head feelings (feeling "heavy in the head", headache or dizziness in different combinations), and among the seven, four had also felt irritation (notably smarting of the nose and throat). Thus, it cannot be concluded that the MTBE-induced symptomatology at the studied levels of exposure is limited to a special subset of highly sensitive individuals only.

SIMPLE REACTION TIME

There were no statistically significant differences of performance between the exposures. The behaviour of the mean reaction time during the course of the experiments is shown in figure 1, and that of the variability of the reaction time is shown in figure 2. There is an obvious daytime rhythm of the reaction time performance: first impairment up until after lunch time, then improvement. Interestingly, no such improvement (in the post exposure measurement) can be discerned at exposure to 75 ppm of MTBE, although the difference is not statistically significant.

POSTUROGRAPHY

Exposure to MTBE had no significant effect on the body sway in either of the studied concentrations. Figure 3 shows the effect on the total path length of movement of the centre of gravity, figure 4 on maximal deviation in the antero-posterior axis and figure 5 on maximal deviation in the lateral axis.

LEVELS OF MTBE AND TBA IN BIOLOGICAL SAMPLES

During the 4 hour-exposures to 25 cm³/m³ of MTBE, the concentration of MTBE and TBA in the blood increased up to 8000 ± 2500 nmol/l (mean ± SD) (N=12) while the corresponding TBA concentration was 11100 ± 2900 nmol/l (N=12). The corresponding values in blood during exposures to 75 cm³/m³ were: 22600 ± 6500 nmol/l (N=13) for MTBE and 32200 ± 7300 nmol/l for TBA. The mean concentrations of MTBE and TBA in urine 2-3 hours after exposure to 25 cm³/m³ of MTBE were 2700 ± 900 nmol/L and 8300 ± 3200 nmol/l (N=13) and after exposure to 75 cm³/m³ 10100 ± 4300 nmol/L and 26500 ± 8500 nmol/l.

CHANGES IN SERUM TRANSAMINASE ACTIVITIES

An slightly elevated activity of serum glutamate oxalate transaminase (60), glutamate pyruvate transaminase (126), and glutamyltransferase (54) was observed in one of the volunteers in the specimen collected 2 hours after the cessation of the 4-h exposure to 25 ppm MTBE. These levels had been 23, 19, and 16 before starting the experiment, and were 32, 26 and 19 six days after the observed elevated values. One week before this exposure, he had been in the control exposure (0 ppm). and still one week earlier, in exposure to 75 ppm. In view of the rapid return of the serum enzyme activities to normal levels, it was considered unlikely that the exposure to 75 ppm 2 weeks before could have induced these effects. Further, it was also considered unlikely that the rather low exposure (25 ppm) immediately before the enzyme activity determination could have caused this

effect, especially in the absence of previous information on hepatotoxicity of MTBE. Thus it was concluded that MTBE had not been the cause of these enzyme changes, although no other apparent causative agent or event for them could be identified.

Another individual was observed to have elevated activities of SGOT (233), and SGPT (92) but not of GT (21) 2 h after the cessation of exposure to 75 ppm MTBE. In the medical examination at the beginning of the study these values had been 45, 15, and 22, and 8 days after the elevated values were observed, they were 55, 37, and 21. It was found in questioning him that he had been using isotretinoin as treatment for acne at a dose of 20 mg x 2/d for six weeks, and had increased to 30 mg x2/d 10 days before the elevated enzyme activities were observed. He then returned to the original lower dosage two days before the third (control) blood specimen was collected. The elevated transaminase levels thus coincided with the high-dose isotretinoin treatment. Isotretinoin is a potentially hepatotoxic drug: elevated transaminase levels, and even hepatitis has been described during isotretinoin treatment. It is recommended that transaminase levels are monitored during isotretinoin treatment. It was considered possible but not demonstrated that in this person who simultaneously was treated with a hepatotoxic drug at a rather high dose level, MTBE exposure had contributed to the observed transient elevation of serum GOT and GPT activities.

After this incident, transaminase levels were studied before and after all MTBE exposures, and after the 75 ppm exposure, also a week after the exposure. Among the eleven other (in addition to those two described above) individuals exposed in the experimental series, no elevated transaminase activities were observed.

Conclusions

Mild symptoms, mainly feeling of heaviness in the head, and to a smaller extent, of mild mucous membrane irritation, were reported by volunteers exposed to MTBE. The frequency of symptoms reported was related to the level of exposure to MTBE and reached statistical significance at 75 ppm exposure after 3 hours of exposure. For the most part, a recovery was reported by 1 hour after the exposure. Altogether 6 persons of the 13 studied reported some MTBE-related symptoms.

No effect related to MTBE was observed in reaction times, their variability or in body sway as observed in posturography.

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Table 1 Statistical testing for a linear association trend between the frequency of symptoms and MTBE exposure level (0, 25, 75 ppm). Symptoms, for which at least one p value < 0.1 was observed, have been indicated. The time points for questioning were at 1 (T1) and 3 h (T2) during the exposure, and 1 h after the cessation of the exposure (T3).

	Time T1	Time T2	Time T3
Individual symptoms			
My head feels heavy	0.07	0.01	0.29
I feel cheerful (negative association)	0.58	0.05	0.03
I feel slightly dizzy	0.11	0.29	0.07
I have headache	0.34	0.29	0.07
Symptom aggregates*			
Irritation	0.18	0.09	1.0
Feelings in the head	0.06	0.01	0.03
Moods	0.56	0.05	0.03

*) Symptoms included in the aggregates: **Irritation**: My eyes are smarting; My throat or nose is smarting; My mouth feels dry; **Feelings in the head**: My head feels heavy; I feel slightly dizzy; I have headache; **Moods**: I feel low-spirited; I feel cheerful (negative association).

Table 2. Statistical testing for the significance of symptom frequency at different exposure levels and at different time points. T1 = at one hour, T2 = at three hours during the exposure, T3 = one hour after the exposure. The frequencies observed at 25 ppm and 75 ppm were tested against those observed at 0 ppm using sign test (S) and paired T-test (T). All symptoms, for which at least one p value was lower than 0.1 have been indicated.

Individual symptoms	T1		T2		T3	
	25 ppm	75 ppm	25 ppm	75 ppm	25 ppm	75 ppm
My throat or nose is smarting	S	0.50	0.50	0.25	-	-
	T	0.17	0.17	0.08	-	-
My head feels heavy	S	0.25	0.12	0.06	1.0	0.50
	T	0.10	0.04	0.02	0.34	0.17
I feel cheerful (negative association)	S	1.0	0.69	0.06	1.0	0.06
	T	0.55	0.44	0.02	0.67	0.03
I feel slightly dizzy	S	-	0.50	0.50	1.0	0.25
	T	-	0.17	0.17	0.34	0.08
I have headache	S	-	1.0	0.50	1.0	0.25
	T	-	0.34	0.17	0.34	0.08
Symptom aggregates*						
Irritation	S	0.25	0.12	0.50	0.12	1.0
	T	0.10	0.04	0.19	0.05	0.34
Feelings in the head	S	0.25	0.12	0.25	0.03	0.50
	T	0.10	0.07	0.10	0.02	0.19
Tension-nervousness	S	0.25	0.69	0.50	0.62	1.0
	T	0.10	0.44	0.19	0.27	0.34
Moods	S	1.0	0.69	0.62	0.06	0.06
	T	0.55	0.44	0.02	0.02	0.03

*) Symptoms included in the aggregates: **Irritation:** My eyes are smarting; My throat or nose is smarting; My mouth feels dry; **Feelings in the head:** My head feels heavy; I feel slightly dizzy; I have headache; **Tension-nervousness:** I feel tense; I am nervous; I have difficulty in concentrating; **Moods:** I feel low-spirited; I feel cheerful (negative association).

Figure 1. Changes of the mean simple reaction time in milliseconds (the morning pre-exposure value is used as a reference) over the course of the experimental day. At MTBE level 25 ppm the number of subjects is 12, in other exposures 13.

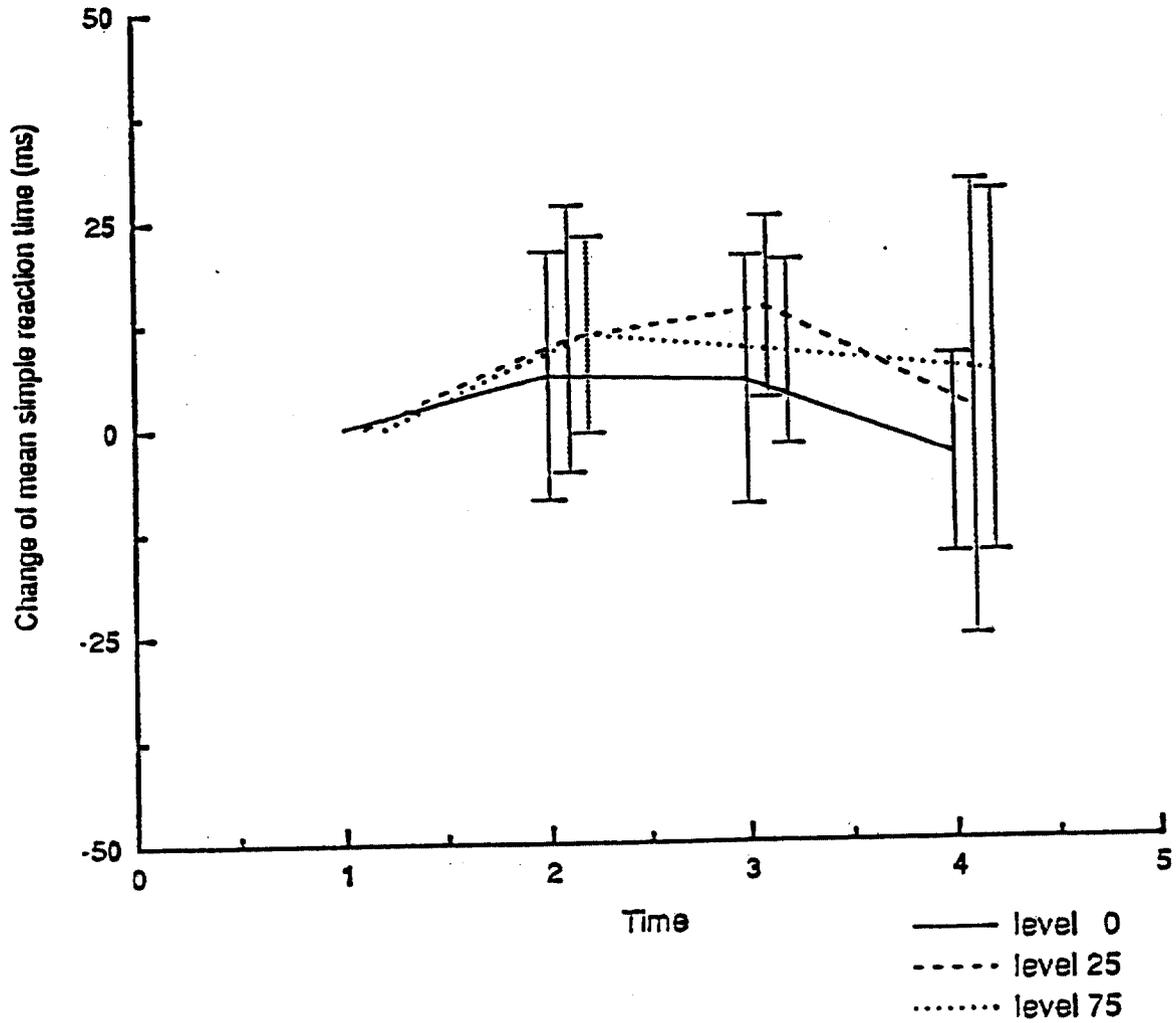


Figure 2. Changes of the variability (SD) of simple reaction time in milliseconds (the morning pre-exposure value is used as a reference) over the course of the experimental day. At MTBE level 25 ppm the number of subjects is 12, in other exposures 13.

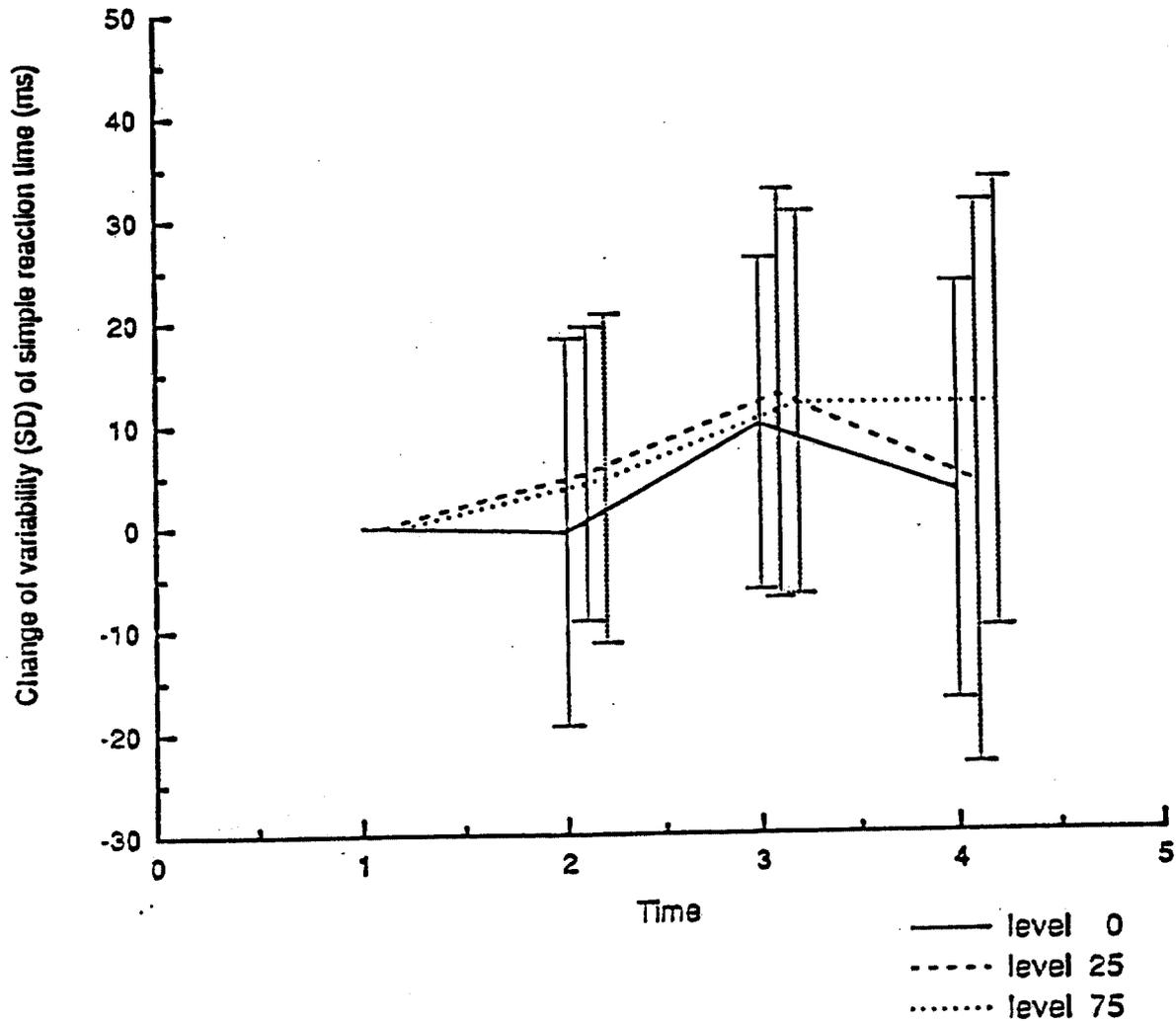


Figure 3. Total path length of the centre of gravity during a 60 s body sway recording with eyes open (A) and closed (B). The standard deviations are indicated. The number of subjects are as in previous figures.

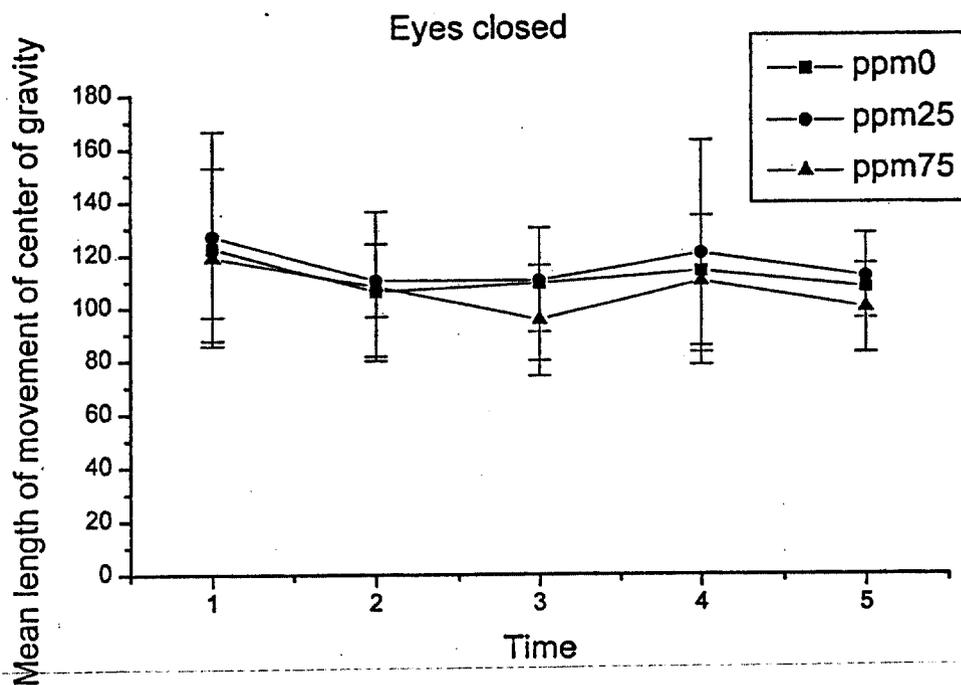
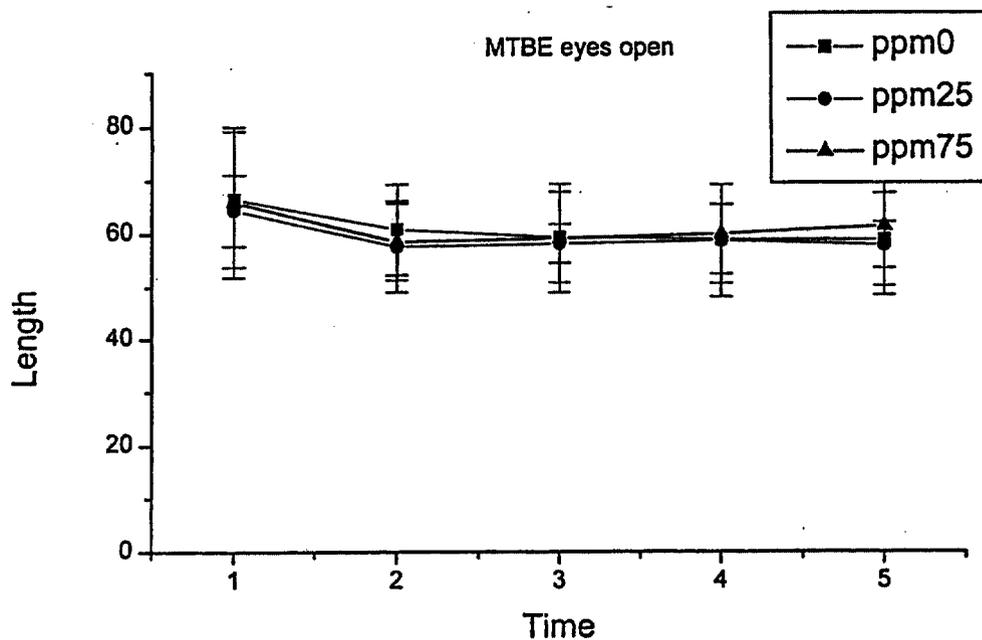


Figure 4. Maximal deviation in the antero-posterior direction during a 60 s body sway recording with eyes open (A) and closed (B).

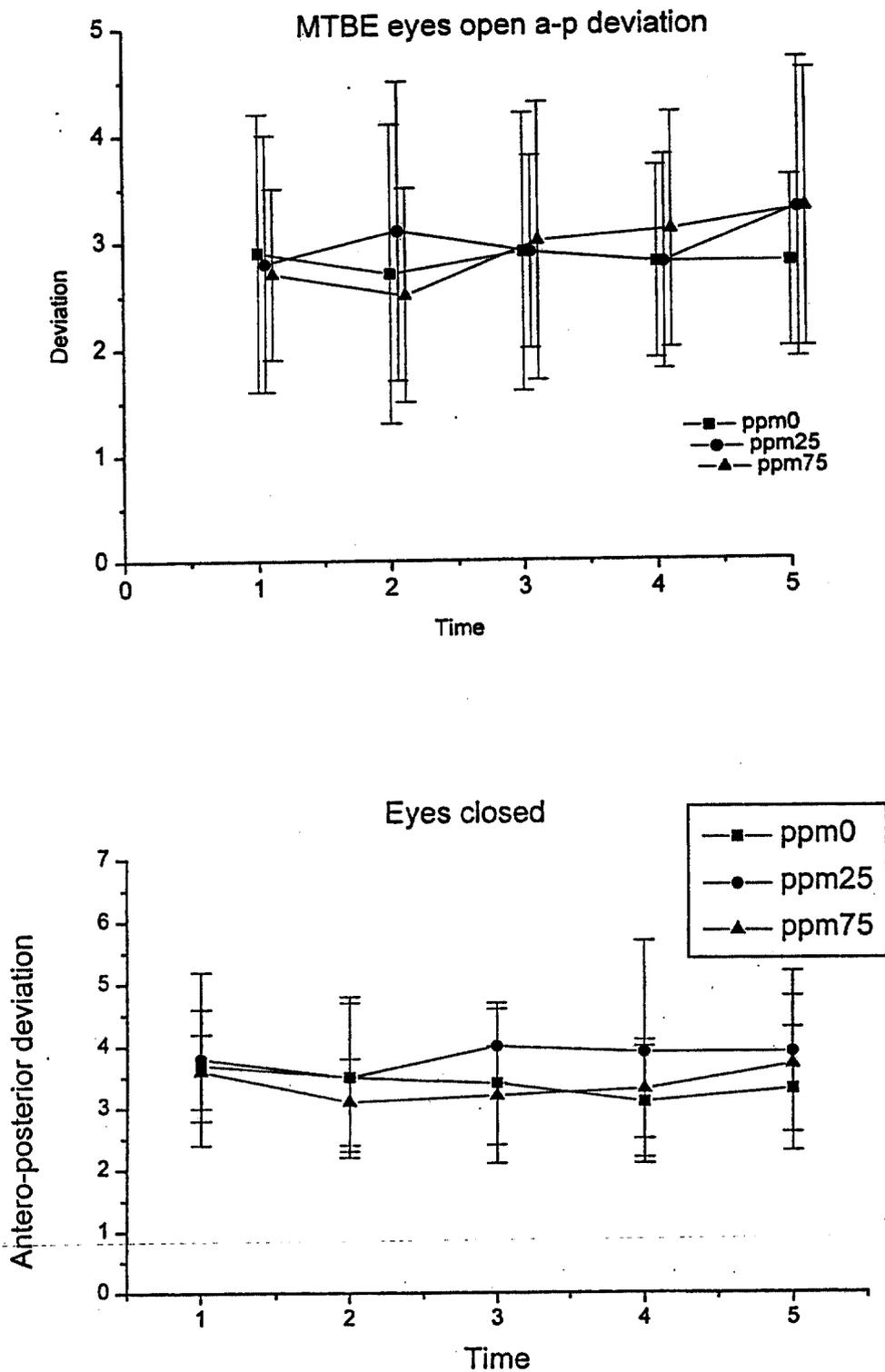


Figure 5. Maximal deviation in the lateral direction during a 60 s body sway recording with eyes open (A) and eyes closed (B).

