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Evaluation of the Neurophysiologic Effects of 1,2-Propylene Glycol Dinitrate by Quantitative Ataxia and Oculomotor Function Tests

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1,2-Propylene glycol dinitrate (PGDN), a nitrated ester found in the torpedo propellant Otto Fuel II, has been suspected of causing neurologic and cardiovascular effects. This study evaluated the possible acute and chronic neurophysiologic toxicity of PGDN in U.S. Navy torpedo facilities. The test procedures included a medical and occupational history, neuro-opthalmologic examination, and quantitative tests of both oculomotor function and ataxia. A study population of 87 workers chronically exposed (CE) to PGDN during torpedo maintenance procedures was compared to a group of 21 controls (CON). Although workers often complained of vascular effects (headaches, nasal congestion), no evidence of chronic neurotoxicity was found, even among a subgroup of workers (CE_{SUB}) with the longest total duration of exposure.

To detect possible acute effects, 29 subjects from the study group were tested before and immediately after PGDN exposure during a torpedo maintenance procedure or turnaround (TA). These personnel had a statistically significant decline in saccade velocity and a prolongation of saccade delay time, even though most peak airborne concentrations of PGDN were well below 0.2 ppm.

Key words: propylene glycol dinitrate, nitrated esters, oculomotor function tests, neurotoxicity, behavioral toxicology, saccades, eye tracking tests, quantitative ataxia tests

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INTRODUCTION

1,2-Propylene glycol dinitrate (PGDN) is a pharmacologically active, nitrated ester found in the torpedo propellant, Otto Fuel II. Its chief toxicologic effects in laboratory animals have been well documented and include: renal and hepatic hemosiderin deposits and necrosis, hypotension, and methemoglobinemia [Jones et al., 1972; Clark and Litchield, 1969]. Behavorial studies in specially-trained monkeys failed to demonstrate any changes in avoidance behavior patterns [Mattson and Jenkins, 1975]. Less information is available concerning the effects of PGDN on human performance and physiology. Volunteers continuously exposed to 0.2 ppm for eight hours daily developed headaches and progressive disruption of the evoked visual response (EVR) [Stewart et al., 1974]. Tolerance developed to headache; however, the alteration in EVR was cumulative during exposure on successive days and was consistent with changes produced by central nervous system depressants. Marked disequilibrium as measured by heel-to-toe and modified Romberg tests became manifest in subjects exposed to 0.5 ppm for 6.5 hours. Some normotensive individuals exposed to 0.5 ppm for 8.0 hours exhibited elevation of diastolic pressure unaccompanied by alterations in pulse or cardiac rhythm disturbances. There was no biochemical, hematological, or spirometric evidence of other toxic effects.

Based on headache and the central nervous system effects (disruption of EVR and disequilibrium) noted in the aforementioned human exposure study, the American Conference of Governmental Industrial Hygienists (ACGIH) in 1975 proposed the establishment of a ceiling threshold limit value (TLV) for PGDN at 0.05 ppm [TLV Documentation, 1975]. Since the United States Navy is the principle user of PGDN and had established a ceiling value of 0.2 ppm with the assistance of the National Academy of Sciences' Committee on Toxicology, the ACGIH granted a temporary delay in implementation of its proposed standard pending further studies on the health effects of Otto Fuel II.

The primary purpose of our study was to obtain valid neurophysiologic data on the response of humans exposed to PGDN under actual working conditions. Continuous inhalation exposure to a constant concentration of PGDN in the experimental laboratory is dissimilar from that encountered in the usual work environment. In the latter situation, considerable variability may exist in both the duration (briefer) and nature (intermittent) of the exposure and in the peak airborne levels of PGDN. Furthermore, there is a possibility of dermal absorption under working conditions. It was anticipated that data from this study would facilitate the establishment of a TLV capable of simultaneously protecting the worker while avoiding the imposition of serious operational constraints on this weapons system.

The secondary purpose was to assess the utility of quantitative oculomotor function tests (saccade and smooth pursuit) as investigative tools in behavorial toxicology. Also known as quantitative eye tracking tests, these parameters have been used to evaluate the clinical aspects of neurologic disease and the central nervous system effects of certain pharmacologic agents [Baloh et al., 1975, 1976; Wilkinson et al., 1974; Frecher and Llewellyn-Thomas, 1974]. They have been included in an ongoing study of the potential subclinical effects of chronic increased lead absorption [Baloh et al., 1979; Spivey et al., 1980].

MATERIALS AND METHODS

Subject Selection

As of January, 1977, approximately 370 military and civilian personnel were regularly exposed to PGDN at 11 shore-based torpedo facilities. An indeterminate number also had contact with PGDN during its manufacturing process, while aboard US ships or as members of allied navies. Administrative and logistic constraints prevented evaluation of these populations. Routine shipboard torpedo maintenance involving PGDN exposure was completely phased out by 1980.

The study population itself consisted of 87 active duty and civilian personnel from the following U.S. Navy torpedo facilities: Naval Weapons Stations, Charleston, SC; Naval Weapons Station, Yorktown, VA; Naval Submarine Support Facility, New London, CT; and Naval Torpedo Station, Keyport, WA. These sites, where PGDN exposure was regarded as representative of other shore-based facilities, also had the greatest concentration of torpedo personnel. Furthermore, workers at one location (Keyport) had experienced regular contact with PGDN since its introduction into the fleet in 1967. They were therefore regarded as most likely to exhibit any chronic toxicologic effects.

The 87 subjects who volunteered for evaluation as part of a cross-sectional study had regular contact with PGDN during MK-46 or MK-48 torpedo maintenance procedures and were designated as "chronically exposed" (CE). From the same population, a subgroup of 28 workers (CE_{SUB}) with 60 or more months of total exposure to PGDN was identified. In addition, a cohort of 29 workers was selected from the study group for short-term prospective evaluation. They were tested before and immediately after PGDN exposure during a routine torpedo maintenance procedure or "turnaround" and were therefore designated as "turnarounds" (TA). The control group (CON) consisted of 21 nonexposed clerical and technical personnel from the same facilities who were comparable to the study group in age, sex distribution, and race.

Although all study and control subjects were volunteers, cooperation among exposed personnel at all four torpedo facilities was greater than 95%.

Test Procedures

All test procedures were conducted on-site by Navy Environmental Health Center physicians, hospital corpsmen and industrial hygienists. Study and control group workers were intermixed to minimize their identification by examiners. The study protocol was reviewed for scientific validity by the National Academy of Sciences' Committee on Toxicology and approved by the Naval Medical Research Institute's Committee for the Protection of Human Subjects.

Medical and Occupational History

After the study was thoroughly explained and informed consent obtained, a pertinent medical and occupational history was taken on each subject. The medical history was designed to identify those individuals with preexisting, nonoccupational neurologic disease that could affect test parameters. Identification and quantification of other potentially confounding variables such as medication and alcohol were undertaken. The presence and frequency of certain symptoms (headache, dizziness, etc.) pos-

sibly related to PGDN were also recorded. For the study group, the total duration of exposure was determined and expressed in months. The average number of turnarounds or similar maintenance procedures engaged in monthly was also obtained. The total duration of exposure multiplied by turnarounds per month produced the exposure index expressed in turnaround-months.

Physical Examination

A limited physical examination, consisting of a neuro-opthalomologic evaluation (visual acuity, visual fields, pupillary reactions, nystagmus, extraocular muscle movement), was conducted by a physician or trained hospital corpsman. Four exposed subjects with a past history of preexisting neuro-opthalomologic disease or concurrent use of medications with possible central nervous systems effects were excluded from the study. These were for conditions (severe head trauma, cerebral vascular accident, meningitis) or medication (pilocarpine for glaucoma) not thought to be causally related to PGDN exposure.

Quantitative Oculomotor Function Tests

Measurement of the parameters of human eye motion was selected as the principle investigative tool. Each eye uses synchronized jumps called saccades to move from one stationary object in the visual field to another [Westheimer, 1954; Bahill and Stark, 1979]. For any given saccade amplitude, there is a characteristic maximum velocity that cannot be voluntarily altered. Maximum velocities as high as 700° per second have been recorded. Each saccadic eye movement has a latency period (approximately 200 msec) before eye motion begins and an acceleration to maximum velocity followed by deceleration to the final position. For saccades greater than 15°, the normal strategy is to undershoot the target slightly, then produce a small corrective saccade, bringing the target to the fovea. Three parameters can be measured from each saccadic eye movement: maximum velocity, accuracy (ratio of saccade amplitude/target amplitude), and delay time (latency).

The central nervous system control of saccadic eye movements is a complex process requiring the interaction of several brain centers including: the frontal and occipital cortex, superior colliculus, cerebellum, basal ganglia, medial longitudinal fasciculus, and the parapontine reticular formation. Lesions in these areas, either structurally as occurs in Huntington's chorea, brain stem degeneration, and multiple sclerosis [Baloh et al., 1975] or chemically from tranquilizers and alcohol [Wilkinson et al., 1974; Frecher and Llewellyn-Thomas, 1974; Franck and Kublo, 1970; Gentles and Llewellyn-Thomas, 1971], can alter visual saccades. Determination of the various parameters of eye movement has therefore been regarded as a sensitive functional test of the oculomotor system and its brain control centers.

Quantitative oculomotor function tests were conducted using published electronystagmographic techniques [Baloh et al., 1975]. Small Beckman skin electrodes (Kit No. 650944, Beckman Instruments, Inc., Schiller Park, Illinois) were taped lateral to both outer canthi and to the subject's forehead, the latter being a reference ground. The subject was then seated in a chair with his head fixed in a stationary position. Horizontal saccadic eye movements were induced by having the subject follow a target moving in a standardized, random sequence both left and right at amplitudes varying from 2 to 34° (Saccade Velocity Test Display, Integrated Systems Engineering, Logan, Utah). The electrical potentials produced by these movements were detected, amplified, and

simultaneously recorded on a Beckman R-511A polygraph (strip chart) for quick visual verification and stored on a magnetic tape by a Tandberg TIR 115 recorder (Sangamo Weston Inc., Springfield, Illinois).

The maximum velocity, reaction time and accuracy of recorded saccades were then determined by a MODCOMP computer. The program for this analysis was developed by the Southwest Ohio Regional Computer Center (SWORCC) of Cincinnati under a NIOSH contract (GS-05S-1045A) according to the specifications of Dr. R.W. Baloh, University of California at Los Angeles (UCLA). The package consists of four main programs and numerous subroutines that digitalize analog signals, analyze the data to identify eye saccades, plot saccade statistics, and maintain data files. The entire program was validated by a test tape of artificially prepared saccadic signals of fixed velocity. A more detailed description is available on request.

Horizontal smooth pursuit was induced by following a moving pendulum. The resultant sinusoidal curves were recorded on the polygraph and graded visually by a technician according to the method described by Wilkinson et al. [1974]. A smooth pursuit eye movement containing no definite saccadic element was scored as zero. One that contained any definite saccade was given a score of one, unless the saccadic element was greater than 15% of the entire amplitude of eye movement, in which case it was scored as two. Ten consecutive side-to-side smooth pursuit eye excursions were evaluated in this manner.

Abnormalities in smooth pursuit have been detected in patients with brain stem disease [Baloh et al., 1976], schizophrenia [Halzman et al., 1974], cerebellar dysfunction [Corvera et al., 1973], acute labyrinthine disorders [Benitez, 1980], and certain drug intoxications including alcohol [Wilkinson et al., 1974] and barbiturates [Halzman et al., 1974].

Quantitative Ataxia Tests

Quantitative ataxia tests were used to grade inability to coordinate voluntary muscular movements while walking or standing. Also known as tests of postural equilibrium-disequilibrium, they have been described by Fregly and normative standards published [Fregly et al., 1972; Fregly, 1974]. Abnormalities from both spontaneous and vestibular ataxia can be detected by such tests, even when less sensitive indices of postural disequilibrium remain unaffected. The quantitative ataxia test battery and scoring system utilized in this study are summarized in Table I.

A baseline set of oculomotor and ataxia tests was obtained on all subjects. A single set of data was obtained on all 87 chronically exposed workers and the 21 controls. In addition, for those 29 workers further designated as turnarounds, studies were then repeated after an actual torpedo turnaround or a similar maintenance operation. In the MK-48 torpedo, maximum PGDN exposure occurs during removal of the fuel pump, which often contains residual Otto Fuel (Fig. 1). In the MK-46 torpedo, the most intense exposure results from cleaning the fuel tank. Approximately two-thirds of the 29 turnaround procedures involved the MK-48 model. Both these work operations were conducted with a local exhaust ventilation system operating at slot velocities equal to or exceeding 2000 feet per minute (fpm). All workers wore disposable protective clothing, rubber gloves and eye goggles (Fig. 1).

During these maintenance procedures, which usually lasted 30–60 minutes, several ambient air samples were obtained in the subject's breathing zone using 1 ml gas-tight syringes. The concentration of PGDN in each was determined on site by means of direct-

TABLE I. Quantitative Ataxia Test Battery

1.	Sharpened Romberg (SR): standing on floor with eyes closed, arms folded against the chest and feet aligned heel-to-toe for 60 seconds.
	Maximum trials: 4
	Maximum score: 240 seconds
2.	Stand on one leg, eyes closed (SOLEC-R and SOLEC-L): standing on each leg for 30 seconds with arms folded against chest and eyes closed.
	Maximum trials: 5
	Maximum score: 150 seconds on each leg
3.	Walk on floor, eyes closed (WOFEC): walking with eyes closed and arms folded against the chest for a maximum of 10 steps per trial.
	Scoring: Best 3 out of 5 trials
	Maximum score: 30 steps

on-column injection, electron capture gas chromatography. In this procedure 0.5 ml aliquots were injected directly into a 3-ft × 0.125-in. glass column containing 3% SE-30 on Chromosorb W, 60/80 mesh operating at 100°C. The injector temperature was 170°C, while the detector temperature was 150°C. The mean number and range of grab samples per turnaround, the range of PGDN levels (including the peak concentrations) and the number of samples exceeding the TLV were then determined. Alveolar breath samples for PGDN analysis were collected from two workers 5 and 15 minutes postexposure.

In the analysis of neurotoxicologic data, the authors compared group means of test parameters and examined correlations between these parameters and PGDN exposure indices. Multiple statistical tests were performed and therefore a number of statistically significant correlation coefficients were expected by chance alone. In the presentation and interpretation of such findings, the authors have considered consistency and biologic plausibility in inferring causal relationships.

RESULTS

Subject Profile

The control and chronically exposed groups were comparable in race and sex distribution being predominantly white males. The study population tended to be somewhat older than controls (mean age 34 years versus 30 years). Workers consumed over twice as much alcohol as did the controls (191 ml equivalent of 100% alcohol weekly versus 94 ml).

The subgroup of 28 workers with 60 or more months of total exposure to PGDN was also compared to the controls. In addition to the increased alcohol consumption already noted, this group was also substantially older (mean age 41 versus 30 years).

Exposure Data

The mean total duration of exposure for the study group was 47.4 months with a range of 1–132 months. However, two-thirds had less than 5 years total exposure. For the subgroup with 60 or more months of total exposure, the mean was 91.8 months with a range of 60–132 months. The average number of turnarounds or equivalent pro-

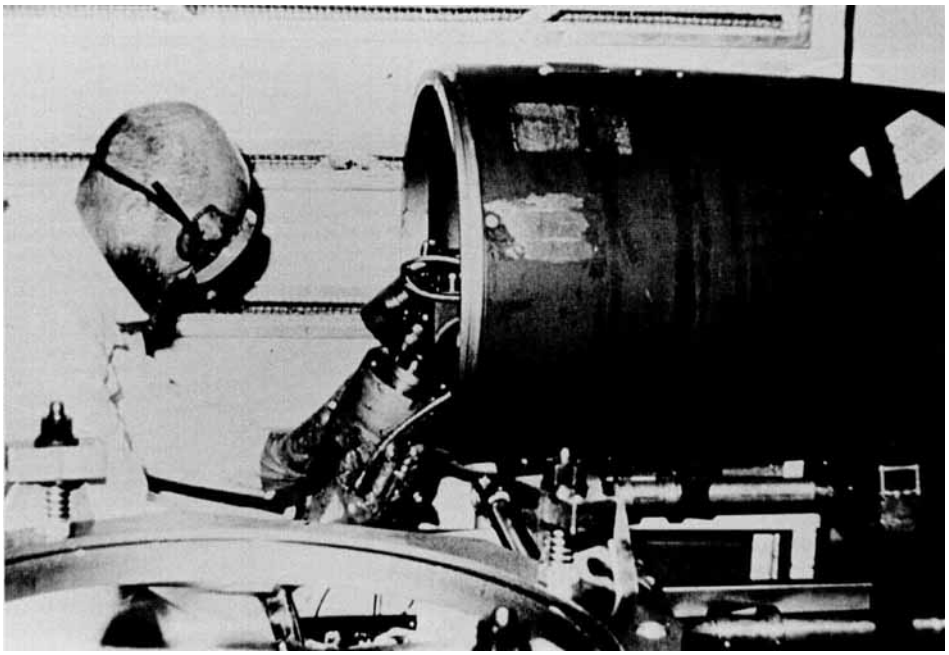

Fig. 1. Removal of fuel pump. An Otto Fuel worker removes a fuel pump from a MK-48 torpedo, a procedure resulting in PGDN exposure. The worker is wearing protective clothing, rubber gloves, and eye goggles. Slot velocity for the local exhaust ventilation system noted in the background must equal or exceed 2000 feet per minute (fpm).

cedures per month was 20.6 for all workers and 22.0 for the subgroup, with a range of 1-60 turnarounds per month or an average of approximately one or less per work day. Only 15% of workers performed 30 or more turnarounds or equivalent maintenance procedures per month. The mean total exposure index was 718.8 turnaround-months for the study group as a whole and 2017.4 for the subgroup.

Environmental Data

A mean of 14 grab samples (range 6-21) was obtained during each turnaround procedure. The concentration of PGDN in these ranged from 0.00-0.22 ppm with only a single sample being in excess of the ceiling TLV of 0.2 ppm. Regarding peak airborne concentrations for each turnaround, 88% were equal to or less than 0.1 ppm while 50% were equal to or less than 0.05 ppm.

Alveolar breath analysis for PGDN was conducted in two workers. Five minutes postexposure only trace quantities (1.0 and 0.8 ppb, respectively) were detected in the expired breath. After 15 minutes, no PGDN was present in the first worker while a trace amount (0.4 ppb) persisted in the second. For the first worker airborne PGDN levels ranged from 0.01-0.026 ppm. For the second worker the range was 0.015-0.222 ppm.

Symptoms

Headache was by far the most common symptom reported by workers during past exposure to PGDN. It was listed as a "frequent" or "occasional" occurrence by

TABLE II. Results of Oculomotor and Quantitative Ataxia Tests: Chronically Exposed (CE) Versus Controls (CON)

	Chronically exposed (N = 87)[a]	Controls (N = 21)[a]	Probability[b]
Saccade maximum velocity (degrees/sec)	494.7 ± 86.9	504.0 ± 89.9	NS[c]
Saccade accuracy (%)	83.9 ± 11.6	83.7 ± 9.1	NS
Saccade delay time (msec)	208.9 ± 22.6	208.8 ± 24.7	NS
Smooth pursuit index	6.5 ± 4.5	6.9 ± 3.5	NS
SR (sec)	212.8 ± 54.0	220.3 ± 36.8	NS
SOLEC-R (sec)	99.5 ± 49.9	109.8 ± 47.9	NS
SOLEC-L (sec)	104.6 ± 50.2	117.8 ± 46.2	NS
WOFEC (steps)	27.2 ± 5.1	28.8 ± 2.4	NS

[a] Mean ± standard deviation.
[b] Nonpaired t-test, two-tailed.
[c] Not significant at $p > 0.05$.

65% of respondents. Nasal congestion, eye irritation, and dizziness were also relatively common, being reported by 31%, 26% and 13%, respectively. The following complaints were noted less frequently: palpitations (10%), dyspnea (6%), chest pain (4%), and loss of balance (1%). None of the personnel who participated in the 29 monitored turnaround procedures experienced symptoms, although one individual exposed during an accidental spill did develop a headache.

Chronically Exposed Versus Controls – Test Parameters

Table II compares the mean and standard deviation of the test parameters between the chronically exposed workers and controls. No statistically significant differences were found. Table III is a similar analysis comparing the subgroup of workers with 60 or more months of total exposure to the controls. Again there were no statistically significant differences in the mean scores of the oculomotor and ataxia tests.

Among workers, saccade maximum velocity correlated with total duration of exposure ($r = 0.190$, $p < 0.05$) and exposure index as measured in turnaround-months ($r = 0.211$, $p < 0.05$). Scatter plots failed to identify outlying data points as an explanation for these findings. To further clarify the possible interrelationship of confounding variables in this group, partial correlation coefficients were calculated. After controlling for age and alcohol, the relationships of saccade maximum velocity to total duration of exposure and exposure index persisted. Saccade delay time correlated significantly with age in workers ($r = 0.234$, $p < 0.05$) but not in controls.

Turnarounds

Test results for the 29 workers who were evaluated before and after PGDN exposure in a turnaround procedure are summarized in Table IV. Mean saccade velocity declined from 516.6° per second to 479.3° per second ($p < 0.05$) and mean saccade delay time was prolonged from 202.5 msec to 208.9 msec ($p < 0.05$). Statistically significant changes in the other oculomotor tests (saccade accuracy and smooth pursuit) did not occur.

Significant decrement in performance of the quantitative ataxia tests was not observed although a postexposure increase in the mean score of one test (SOLEC-L, $p < 0.05$) was noted.

TABLE III. Results of Oculomotor and Quantitative Ataxia Tests, Chronically Exposed Subgroup(CE_{SUB})[a] Versus Controls (CON)

	Chronically exposed subgroup (N = 28)[b]	Controls (N = 21)[b]	Probability[c]
Saccade maximum velocity (degrees/sec)	518.7 ± 97.5	504.0 ± 89.9	NS[d]
Saccade accuracy (%)	86.4 ± 12.6	83.7 ± 9.1	NS
Saccade delay time (msec)	214.1 ± 23.5	208.8 ± 24.7	NS
Smooth pursuit index	7.0 ± 4.3	6.9 ± 3.5	NS
SR (sec)	220.0 ± 46.9	220.3 ± 36.8	NS
SOLEC-R (sec)	95.3 ± 51.5	109.8 ± 47.9	NS
SOLEC-L (sec)	95.6 ± 52.9	117.8 ± 46.2	NS
WOFEC (steps)	27.0 ± 5.0	28.8 ± 2.4	NS

[a]Otto fuel workers with 60 or more months of total exposure.
[b]Mean ± standard deviation.
[c]Nonpaired t-test, two tailed.
[d]Not significant at $p > 0.05$.

TABLE IV. Results of Oculomotor and Quantitative Ataxia Tests Turnarounds (TA)

	Before TA[a] (N = 29)	After TA[a] (N = 29)	Difference	Probability[b]
Saccade maximum velocity (degrees/sec)	516.6 ± 92.1	479.3 ± 99.6	37.3	$p < 0.05$
Saccade accuracy (%)	87.9 ± 10.0	85.2 ± 9.3	2.7	NS[c]
Saccade delay time (msec)	202.5 ± 22.7	208.9 ± 23.7	− 6.4	$p < 0.05$
Smooth pursuit index	7.2 ± 4.5	7.6 ± 4.2	− 0.4	NS
SR (sec)	210.9 ± 59.6	225.9 ± 43.7	− 15.0	NS
SOLEC-R (sec)	107.1 ± 49.2	113.9 ± 48.5	− 6.8	NS
SOLEC-L (sec)	108.3 ± 49.7	117.7 ± 45.2	− 9.4	$p < 0.05$
WOFEC (steps)	28.1 ± 4.1	26.3 ± 7.0	1.8	NS

[a]Mean ± standard deviation and difference.
[b]Paired t-test, two-tailed.
[c]Not significant at $p > 0.05$.

In the turnaround group, correlation coefficients were calculated between the changes in test parameters and the peak airborne concentrations of PGDN. Observed differences in oculomotor function tests did not correlate with peak PGDN levels as measured during the turnaround procedures. The change in SOLEC-L correlated with peak PGDN concentrations ($r = 0.466$, $p < 0.05$). However, this relationship did not persist after removal of outlying data points from a scatter plot.

DISCUSSION

1,2-Propylene glycol dinitrate (PGDN) is structurally related to other nitrated esters and has similar physiologic properties (Fig. 2). Its principal action is vasodilation, which is thought to explain the headache and nasal congestion often experienced by workers. In 1976, Anderson and his co-workers [1976] discovered that a structurally similar nitrated ester, triethylene glycol dinitrate (TEGDN), exhibited biologic activity in both the central and peripheral nervous system of rats. Central nervous system ef-

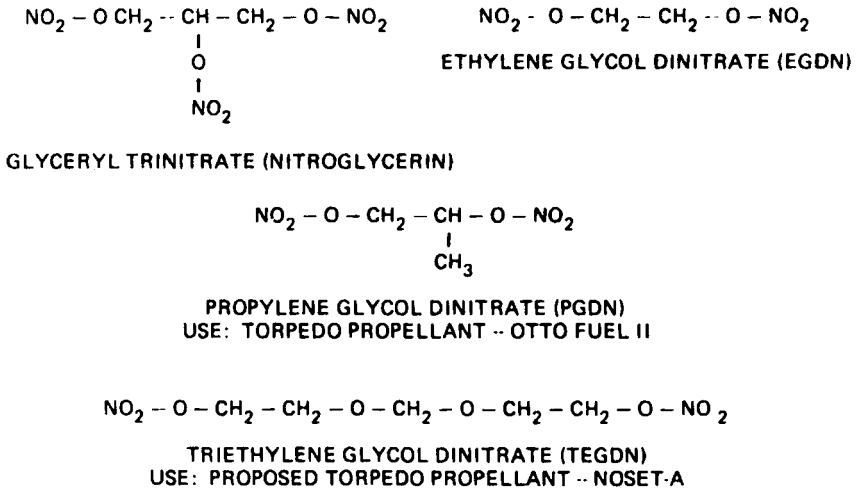

Fig. 2. Chemical structures of nitrated esters.

fects were characterized by enhancement of the depressant action of zoxazolamine and pentobarbital and amelioration of the analeptic effects of pentylenetetrazol. In the peripheral nervous system, TEGDN appeared to interfere with normal cholinergic transmission resulting in convulsions, tremors, hyperactivity, and respiratory arrest.

The reported neurophysiologic effects of PGDN in humans have been less striking. The disruption of the evoked visual response noted in Stewart and coworkers' [1974] volunteers was unaccompanied by gross neurologic manifestations at levels of PGDN controlled at 0.2 ppm. Continuous exposure to concentrations of 0.5 ppm, well above the TLV, was required to induce disequilibrium. Furthermore, there have been no cases of confirmed acute or chronic neurologic disease reported to the Otto Fuel II Incident Registry in over 10 years of field use.

Statistically significant changes in oculomotor function test scores were observed after acute exposure to PGDN during turnarounds. The decrease in saccade maximum velocity and prolongation of delay time were effects one would expect from a central nervous system depressant [Frecher and Llewellyn-Thomas, 1974; Gentles and Llewellyn-Thomas, 1971]. Further, they are consistent with available human and animal data regarding the neurotoxicty of PGDN or similar compounds [Stewart et al., 1974; Anderson et al., 1976], and may therefore represent subclinical disruption of the extraocular motor system. However, because subjects with low initial oculomotor test scores tended to increase and those with high values tended to decrease, regression towards the mean cannot be excluded as a possible explanation of these findings. The lack of correlation between exposure (peak PGDN levels) and biologic effects (changes in test parameters) is not unusual in toxicologic studies and by itself, does not preclude a causal relationship. Variations in sampling technique, laboratory analytic error, or undetected dermal absorption of PGDN could have obscured a dose-response relationship.

While the authors believe their findings support the hypothesis that PGDN can exert acute neurophysiologic effects, it is improbable that such a slight decrease in saccade maximum velocity and prolongation in delay time are functionally significant.

If one assumes the aforementioned alterations in oculomotor function tests were

induced by PGDN exposure, the question naturally arises as to whether these were transient or permanent. Unfortunately, logistic considerations prevented longitudinal testing of workers after the single, monitored turnaround exposure described above. To determine if repeated, acute episodes could lead to permanent neurologic dysfunction, the investigators compared 87 chronically exposed workers with 21 control subjects. As indicated in Table II, mean values for the oculomotor function and quantitative ataxia tests did not differ significantly between these two groups.

However, the mean duration of exposure among the workers was only 47.4 months and in two-thirds it had been less than 60 months. Because of the concern that inclusion of a large number of subjects with relatively brief working histories may have masked a chronic effect, a subgroup of workers with 60 or more months of exposure was compared to the controls. The subgroup had a mean duration of exposure of 91.8 months, almost twice that of the worker group as a whole, with a range of 5–11 years. This comparison revealed no evidence of a chronic neurotoxicologic effect in the subgroup (Table III).

The positive correlations of saccade maximum velocity to exposure duration and exposure index were puzzling because they implied that increased contact with PGDN actually improved saccade performance. These relationships were not particularly strong from a statistical standpoint ($r = 0.19$, $p < 0.05$ and $r = 0.211$, $p < 0.05$). Furthermore, they were inconsistent with both the decline in saccade maximum velocity observed during the turnaround procedure and the absence of any difference in this test parameter between the exposed group and the controls (Tables II and III). These results were therefore regarded as spurious or chance correlations.

The vasodilitation induced by nitrated esters results in rapid lowering of systolic and to a lesser extent, diastolic pressure with a compensatory tachycardia [Nickerson, 1968]. A throbbing headache from distension of dural arteries and nasal congestion, also probably due to vasodilatation, are relatively common among PGDN-exposed workers. However, none of the 29 well-controlled turnaround procedures reported in this study resulted in any complaints of headache or nasal congestion. This suggests these vascular effects tend to occur primarily from excessive airborne exposure or with dermal absorption associated with poor work procedure and accidental spills.

Although headache and nasal congestion are admittedly uncomfortable, greatest concern has been appropriately focused on more serious nitrate-induced cardiovascular problems including diastolic hypertension, enhanced atherogenesis, angina, and sudden death [Lange et al., 1972; Einert et al., 1963; Forssman et al., 1957; Carmichael and Lieben, 1963; Tund et al., 1968]. The last syndrome characteristically occurs in relatively young workers, 24–48 hours after their last exposure to nitrated compounds in the workplace. Although a retrospective study of torpedo workers has not been conducted, no cases of cardiac disease attributable to PGDN have come to the attention of the Otto Fuel Incident Registry. While an occasional case of hypertension may have gone unnoticed, it is unlikely sudden death in a young worker would have gone unreported, particularly in view of the attention focused on the health hazards of Otto Fuel II since 1967.

CONCLUSIONS AND RECOMMENDATIONS

Our study suggests PGDN exposure during routine torpedo maintenance procedures can produce acute, subclinical neurologic alterations as measured by oculomotor function tests. Furthermore, these changes can occur at peak airborne concentrations of PGDN equal to or less than 0.1 ppm. However, there was no evidence that repeated

PGDN exposure for up to 11 years causes any permanent impairment in the oculomotor system or its brain control centers. If a probably transient, subclinical neurologic alteration is regarded as an unacceptable physiologic response, then the data presented here support lowering of the TLV. On the other hand, if avoidance of "physiologically significant" [Stokinger, 1974] changes is the prime concern, the results would not seem to justify a decrease in the 0.2-ppm exposure limit.

Finally, while PGDN exposure under certain circumstances can result in vascular effects (headache, nasal stuffiness), it has not been implicated as a cause of sudden cardiac death.

The present study is only the second systematic attempt to assess the human health effects of PGDN reported in the medical literature [Stewart et al., 1974]. Cognizant of this problem, the ACGIH Chemical Agent TLV Committee is especially interested in obtaining further toxicologic information on this compound. A controlled-environment (exposure chamber) study of PGDN's effects on oculomotor function could validate the findings of our field investigation as well as provide more meaningful data regarding dose-response relationships. The latent period for any chronic neurologic effects of PGDN is not known but could conceivably be greater than the maximum exposure duration reported in this study (11 years). Repeat neurophysiologic evaluations on a periodic basis should be done on all Otto Fuel workers with long-term exposure. The cardiovascular effects of PGDN remain largely uninvestigated. Consideration should be given to a retrospective study of torpedo workers and a cross-sectional evaluation using ambulatory electrocardiographic monitoring.

Our study is one of the few reported where oculomotor function tests have been used to evaluate the potential toxic effects of a workplace chemical [Baloh et al., 1979; Spivey et al., 1980]. Their technical feasibility for field use has been enhanced by the recent development of simple-to-operate, on-line digital computer systems for quantitative analysis of test results [Baloh et al., 1980]. However, the ultimate role of oculomotor function and other neurophysiologic tests awaits further experience with other chemical exposures and resolution of the philosophic issues complicating application of such data to the standard setting process.

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