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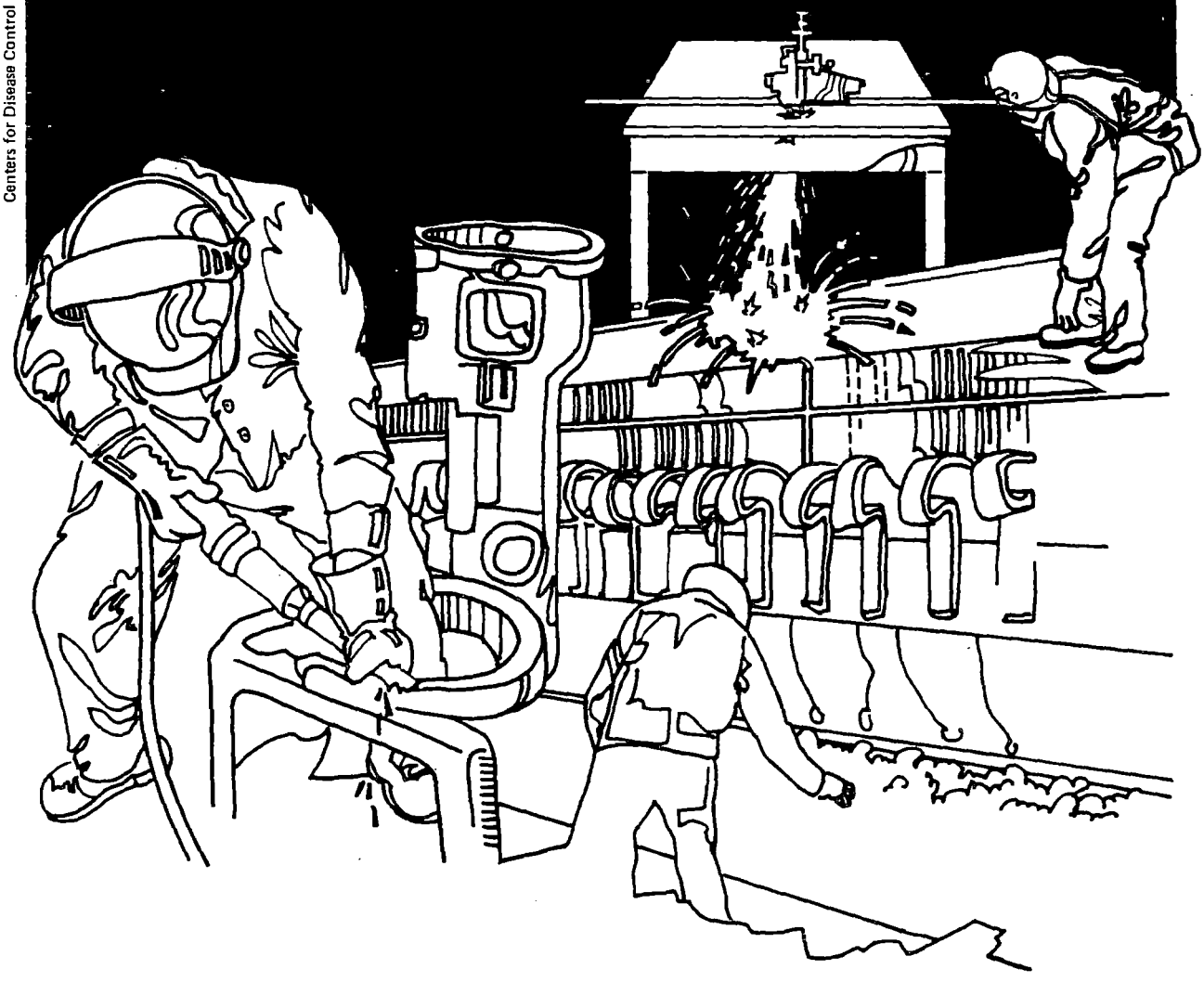

Health Hazard Evaluation Report

HETA 80-111-861
LEAR-SEIGLER COMPANY
MARBLEHEAD, MASSACHUSETTS

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to Federal, state, and local agencies; labor; industry and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

HETA 80-111-861
April, 1981
Lear-Seigler Company
Marblehead, Massachusetts

NIOSH INVESTIGATORS:
Edward Baker, M.D.
James Melius, M.D.

I. SUMMARY

In April, 1980 the United Auto Workers International Union requested that the National Insititute for Occupational Safety and Health do a follow-up medical study of workers previously found to have bladder neuropathy as a result of occupational exposure to NIAX^R catalyst ESN at Lear-Seigler Co., Marblehead, Massachusetts. The workers had been exposed to the catalyst in 1977 and 1978 during the manufacture of polyurethane foam at the plant. The catalyst was withdrawn from the market in March, 1978, and the plant closed in January, 1980.

The medical study included 13 workers who were found (in July 1978, i.e., three months after exposure was discontinued) to have persistent symptoms. This evaluation included standard questionnaire evaluation of urinary symptoms and sexual history; complete neurological examination; urological evaluation including cystmetrography; electromyography of the anal sphincter and measurement of sacral latency time; nerve conduction studies of the right peroneal and right sural nerves; and visual and auditory evoked responses. Results were compared when possible with those of the 1978 studies.

Although the overall prevalence of urological and other symptoms were considerably less than in 1978, a considerable proportion continued to report abnormal symptoms, and the proportion reporting sexual difficulties had increased . Seven (67%) of the workers still reported urinary hesitancy and six (55%) reported difficulty with incomplete bladder emptying. Five (45%) reported sexual difficulties (loss of libido or impaired sexual function) compared to three (27%) in 1978. Three of the ten symptomatic individuals had neurological abnormalities - one with lower extremity sensorimotor neuropathy; one with hyper-reflexic knee jerks and ankle clonus; and one with a right lower extremity radiocalopathy. Three of four workers examined in both years had objective neurological findings in 1978 which were not present now. EMG abnormalities were present in three of ten workers. Visual and auditory evoked responses, sacral latency, and sphincter electromyograms were normal in all ten workers. Two individuals were found on cystmetrography to have the first sensation of bladder filling at abnormally large volumes. The results indicate that those most severely affected in 1978 were most likely to have persistent neurological abnormalities.

Based on the results of this medical evaluation, NIOSH concludes that some workers previously found in 1978 to have a bladder neuropathy as a result of exposure to NIAX^R catalyst ESN continue to have persistent neurological abnormalities.

KEYWORDS: SIC 2822, NIAX^R catalyst ESN, neurological symptoms, bladder neuropathy, sexual impotence, dimethylaminoproprionitrile.

II. INTRODUCTION

In April, 1980 the United Auto Workers requested that NIOSH do a follow-up study of workers previously found to have developed a bladder neuropathy as a result of occupational exposure to NIAX^R catalyst ESN at a Lear-Seigler polyurethane foam plant in Marblehead, Massachusetts. The plant had recently closed, and no assessment had been made of any long term effects in those workers already affected by this exposure. NIOSH contracted the evaluation to the Occupational Health Program at the Harvard School of Public Health. Thirteen workers from this plant were medically evaluated over the summer of 1980. All were individually notified of their test results.

III. BACKGROUND

In March, 1978, a local board of health notified the Occupational Hygiene Physician for Massachusetts that 11 employees of the Lear-Seigler polyurethane foam plant, Marblehead, Massachusetts, had come to a hospital emergency room complaining of urinary problems. A NIOSH Health Hazard Evaluation conducted in April, 1978 found that workers exposed to NIAX^R catalyst ESN had developed a bladder neuropathy as a result of occupational exposure to and systemic absorption of this substance (8). The suspected chemical responsible for the neuropathy was dimethlaminopropionitrile, (DMAPN), the principal ingredient in NIAX^R catalyst ESN. A similar outbreak of bladder neuropathy was investigated by NIOSH at a plant in Baltimore, Maryland, which used the same chemical process (7). In addition to bladder symptoms, workers reported an increased prevalence of peripheral neuropathies and memory disturbances. The catalyst was withdrawn from the plant on March 29, 1978. The Lear-Seigler Co. plant in Marblehead, Massachusetts was closed for economic reasons in January, 1980.

Symptoms of urinary tract dysfunction resolved rapidly after removal of the catalyst from production. Only 14 of the 104 workers who were originally diagnosed as having DMAPN toxicity at the Marblehead plant were found to have persistent symptoms when interviewed in July, 1978. These "delayed improvers" are the subject of the current follow-up investigation. In addition, the evaluation included two other workers subsequently identified as having persistent symptoms.

IV. DESIGN and METHODS

The fourteen employees who reported two or more urinary syptoms at the three-month follow-up interview in July, 1978, were defined as "delayed improvers," and were re-contacted in 1980. One individual initially classified as a "delayed improver" was found on interview in 1980 not to meet the criteria for that classification and therefore 13 "delayed improvers" were available for follow-up evaluation.

Ten of the 11 "delayed improvers" interviewed (91%) had persistent symptoms two years after cessation of exposure to DMAPN. Two additional patients, who were not recognized as delayed improvers in 1978, now complained of symptoms. Three of the original group of eight patients evaluated early in 1978 (within 3 weeks of exposure) became "delayed improvers". Two of these continued to have symptoms and were re-evaluated in 1980; one was not contacted in 1980.

Thus the cohort evaluation included eleven "delayed improvers" and two workers not previously identified as "delayed improvers".

After obtaining informed consent from each worker, physicians administered a standardized questionnaire covering interim medical history (1978-1980), job history (e.g., current job, reason for leaving Lear-Seigler), urinary symptoms, alcohol consumption, medication, and sexual history. A complete neurological examination was performed with postural blood pressure measurement. Urologic evaluation included cystometrography using CO_2 according to standard techniques (3,9), in which bladder volume was recorded at the point of first urge to void and at the point of bladder emptying. Electrophysiologic evaluations included electromyography of the anal sphincter and measurement of sacral latency time using ring electrodes around the penis (11). Standard nerve conduction studies (1,5,12) of the right peroneal and right sural nerves were performed. F-wave latencies in the peroneal were also determined. Finally, visual and auditory evoked responses were performed to assess central nervous system function.

V. TOXIC SUBSTANCE MEDICAL DATA

NIAX^R catalyst ESN has been associated with epidemics of urinary dysfunction in at least six polyurethane foam plants in the United States (8). ESN consists of 95% DMAPN (Dimethylaminopropionitrile), 5% of bis (2-dimethylaminoethyl) ether, and less than 1% of acrylonitrile and dimethylamine, the materials from which it is formulated.

ESN and its components have been evaluated by a variety of short-term tests for neurologic activity, in vivo (rat and mouse) and in vitro (isolated tissue) (4). Results revealed that both ESN and DMAPN at equal doses, administered intraperitoneally, produced tremors, convulsions, and cardiovascular effects in rats and mice. At low doses (.01 ml/kg) both also induced a loss of micturition reflex in rats. Bis (2-demethylaminoethyl) ether, though more acutely lethal, caused no neurologic or reflex effects at doses up to 1.0 ml/kg. Hence, DMAPN was considered to be the neuropathic agent.

The extent of toxicity of the catalyst to other systems and organs including kidney, liver, eye, and skin are unknown. In the animal studies, (in both rats and mice), all signs of toxicity from ESN or DMAPN intoxication disappeared within a week after discontinuation of dosing. This was observed in both rats and mice.

In vitro assays on isolated nerve tissues revealed initial stimulation by ESN in the ileum and bladder preparations, followed by a depression (4). Depression was reversible and was overcome by higher doses of carbachol or by washing of tissue.

DMAPN also gave an initial tissue stimulation in both ileum and bladder, followed by lack of response to lower doses of carbachol. Neither agent had any additional action on the ganglionic preparation.

VI. RESULTS

1. History - The "delayed improvers" surveyed were mostly male (82%), white, English speaking, and relatively young (median age 36 years). Three had chronic problems (2 persons on medication - 1 Lithium Carbonate, 1 antibiotics). There were no diabetics; only one of eleven drank more than 20 oz. of ethanol per week.

Although the overall prevalence of urologic and other symptoms was less than in 1978, a considerable proportion of the workers continued to report abnormal symptoms (Table 1). In fact, the proportion reporting sexual difficulties (loss of libido or impaired sexual function) had increased over the two year period (Table 1).

In the original evaluation, the highest rate of bladder dysfunction occurred among production line workers. However, no clear associations with job category, age, or demographic characteristics and disease were seen in the "delayed improvers".

2. Physical Examination - Three of the ten individuals complaining of symptoms were noted to have neurologic abnormalities on physical exam. One, a 29 year old white male had a sensorimotor neuropathy characterized by decreased pinprick sensation in the lower extremities, and hyper-reflexic ankle jerks. A 43 year old male had hyper-reflexic knee jerks and ankle clonus. A third individual had signs consistent with a right lower extremity radiculopathy. The remaining seven had normal neurological exams (Table 2).

Neurologic examinations of the four individuals examined in both years (1978 and 1980) showed that three of the four had objective abnormalities in 1978 (sensory or sensorimotor neuropathy), which were not detected on follow-up exam in 1980. One individual had a persistent sensorimotor neuropathy by physical exam.

3. Neurologic Testing - Three of ten had EMG abnormalities affecting the lower limbs (Tables 3 and 4). Two of the three were "delayed improvers". The third individual who had abnormal findings in 1978 did not go on to become a "delayed improver"; but then complained of a reappearance of symptoms in 1980.

Visual and auditory evoked responses were normal in all ten individuals tested.

4. Urologic Testing (Table 5) - On urologic testing, sacral latency time was normal in all ten individuals. Three workers who had prolonged sacral latencies in 1978 had reverted to normal in 1980. Sphincter electromyograms (EMG) were abnormal in two workers in 1978, but returned to normal in 1980. The first sensation of bladder filling occurred at abnormally large volumes in two patients in 1980 who had had normal values on initial exam. The Detrusor reflex, which was absent in two of these patients in 1978, were present, but occurred at unusually large bladder volumes in 1980.

VII. DISCUSSION

This investigation has documented the persistence of abnormal symptoms of urinary tract dysfunction along with objective evidence of neurologic damage in a small group of workers exposed to the industrial catalyst, dimethylaminopropionitrile, over two years ago. Their symptoms improved considerably after removal from exposure to the substance, but continued improvement ceased approximately one year prior to our investigations. As was the case in the original investigation (8), we were unable to identify any individual factors that would account for the persistence of symptoms in this group as opposed to the vast majority of workers at the plant who recovered without residual effects. The only distinguishing factor which separated those with persistent symptoms from those recovering completely was the severity of their initial illness. Those most severely affected during the initial outbreak in 1978 were those whom we found most likely to have persistent symptoms and abnormal results on standardized testing two years later.

The course of the illness in this population differed somewhat from that described in a similar plant in Maryland (10), in which workers employed in a similar process experienced similar symptoms. In our experience, symptoms of sexual dysfunction became considerably more prominent in the "delayed improver" group over the two years following the initial illness outbreak. Since different interview techniques were used between 1978 and 1980, some of the differences in symptom prevalence noted (Table 1) could be attributed to differences in evaluation technique. However, several individuals noted that their

symptoms of sexual impairment had actually become more prominent over the months following the initial episode. In our experience, improvement in the objective parameters of urologic and neurologic function paralleled the improvement in symptoms (Tables 3-5). Individuals with abnormal function as measured by standardized testing consistently had reports of persistent symptom referable to the affected organ system. We did not observe the bi-phasic course of DMAPN toxicity noted in Maryland: initial bladder symptomatology which resolved and was followed by the appearance of sign and symptoms of lower extremity peripheral nerve disorders. Only one individual seen in our follow-up examinations was asymptomatic on initial examination and developed neurologic symptoms thereafter.

Experimental studies of animals exposed to DMAPN and chemically related substances have attempted to elucidate the pathophysioloy of this disorder. Rats and mice dosed with 0.25 ml/kg experienced convulsions, tremors, and loss of the micturition response. Within a week of discontinuance of dosing, these abnormalities disappeared. The maximum duration of exposure for these animals was two weeks (4).

A chemically similar substance (B, B -iminopropionitrile) (Figure 1) has been demonstrated to have potent neurotoxic properties. Animals chronically exposed to this substance develop proximal axonal swellings associated with intra-axonal neurofilament accumulations (2). This histologic abnormality has been attributed to impairment in slow axonal transport. (6). In fact, this experimental neuropathy produced by IDPN is felt to represent the best experimental model of inhibition of slow axonal transport leading to a peripheral neuropathy.

The only pathological evaluation of humans exposed to DMAPN showed a mild degree of axonal degeneration with axonal swellings containing disordered neurofilaments (10). Similar histologic abnormalities have been reported in other axonal neuropathies such as those caused by acrylamide and hexane (6). Thus, the primary site of action for DMAPN appears to be on the axon itself rather than on the other portions of the neuron.

The syndrome associated with DMAPN exposure differs significantly from previously reported occupational neuropathies in the predominance of genito-urinary dysfuction. Presumably, this difference is related to the metabolism of DMAPN, but no specific data exists to confirm this hypothesis. Additional animal studies would be of particular value in clarifying the pathogenesis of this unique disorder.

Although the initial three month follow-up of workers at this plant showed encouraging results in the high rate of recovery of function in these individuals, the current evaluation illustrates the importance of long-term follow-up of individuals exposed to environmental neurotoxins with potentially irreversible effects. Additional follow-up studies of workers affected by other industrial neurotoxins, such as methyl-n-butylketone, chlordecone, and the recently-studied (13)2-t-butylazo-2-hydroxy-5-methyl hexane require continued follow-up to assess the rate of permanent disability in these individuals.

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IX. AUTHORSHIP AND ACKNOWLEDGEMENTS

Report Prepared By:

Edward Baker, M.D.
Occupational Physician
Harvard School of Public Health

James M. Melius, M.D.
Chief, Hazard Evaluations and Technical Assistance Branch
Division of Surveillance, Hazard Evaluations, and Field Studies
NIOSH
Cincinnati, Ohio

Originating Office:

Hazard Evaluations and Technical Assistance Branch
Division of Surveillance, Hazard Evaluations, and Field Studies
NIOSH
Cincinnati, Ohio

Report Typed By:

Carol Goetz
Secretary
Hazard Evaluations and Technical Assistance Branch

X. DISTRIBUTION AND AVAILABILITY OF REPORT

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Copies of this report have been sent to:

1. United Auto Workers International Union
2. Lear-Seigler Company
3. NIOSH, Region I
4. OSHA, Region I

For the purposes of informing the affected employees, copies of the report shall be posted by the employer in a prominent place accessible to the employees, for a period of 30 calendar days.

TABLE 1

Symptom Prevalence in Late Improvers - 1978, 1980

SYMPTOM	% CASES 1978 (n=11)	% CASES 1980 (n=11)
Urinary hesitancy	100	64
Need to	100	45
Incomplete bladder emptying	82	55
Sexual difficulties (Loss of libido or impaired sexual function)	27	45
Parasthesia	27	55
Dry mouth	45	9
Weakness in arms/legs	45	45

TABLE 2

NEUROLOGICAL EXAMINATION

FOLLOW-UP

CLINICAL FINDINGS

(n = 10) 1980

Age Yr/Sex	Sensory	Motor	Clinical Impression
29M	Decreased Pinprick Right Leg	Hyperreflexic Ankle Jerks	Sensorimotor Neuropathy
43M	None	Hyperreflexic Knee Jerks Clonus - Ankle Jerks	Motor Neuropathy
36M	Decrased Pinprick Right Leg	Decreased Strength Rt. Leg, Hyper-reflexic Knee Jerks	Radiculopathy
25 M			
47 M			
46 F			
47 F	None	None	Normal

TABLE 3

ELECTRODIAGNOSTIC PREIPHERAL NERVE TESTING

	Peroneal Nerve			
Age	Distal Latency, MS		Velocity m/s	
Yr/Sex	1978	1980	1978	1980
47 M	4.3	8.5*	47.3	46.0
29 M	6.8	6.4	43.4	45.0
32 M	5.5	5.0	46.0	44.2
34 M	4.0	4.2	49.5	50.8
Median	4.9	5.7	44.7	44.6
Normal	3 - 6.5		38 - 59	

* = abnormal

ELECTRODIAGNOSTIC PERIPHERAL NERVE TESTING

	Peroneal Nerve Amplitude, MV			
Age	Ankle		Knee	
Yr/Sex	1978	1980	1978	1980
47 M	4.0	4.0	4.0	3.0
29 M.	.65*	.35*	.65*	.45*
32 M	5.6	6.0	5.0	6.0
44 M	3.0	2.0*	3.0	2.0*
Median	3.5	3.0	3.5	2.5
Normal		2.2 - 14.8		

* = abnormal

TABLE 4

Electrodiagnostic Peripheral Nerve Testing - 1980

Sural Nerve

Age Yr/Sex	Velocity, M/S		Amplitude, MV	
	1978	1980	1979	1980
47 M	35*	Absent	3.5*	Absent
29 M	32.5*	46	21	11
32 M	38.8*	38	6.0	12
44 M	43.5	44.8	-	25
Normal	40 - 54.7		6 - 42	

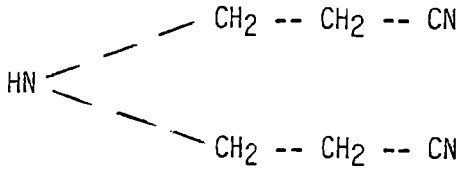
TABLE 5

Urologic Studies of DMAPN Workers

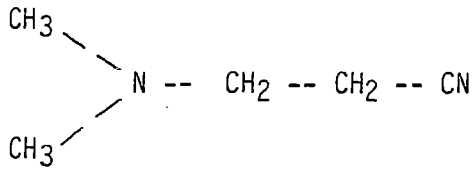
	Electrodiagnostic Testing				Cystometrogram			
	Sacral Latency, MS. Normal 42		Sphincter Electromyogram		First Sensation Filling, ML Normal 125 ml		Detrusor Reflex ML	
Age Yr/Sex	1978	1980	1978	1980	1978	1980	1978	1980
47 M	120*	38	Increased Polyphasia	Normal	175*	Not Done	Absent-Not Done	
29M	43*	33	Increased Polyphasia	Normal	100	200*	Absent	700
32 M	38	28	Normal	Normal	50	250*	Absent	450
44 M	50*	35.2	Normal	Normal	80	100	275	325
MEAN	62.75	33.55			101.25	183.33	Absent	491.67

FIGURE 1

STRUCTURES OF TWO NEUROTOXIC NITRILES



B,B' - iminodipropionitrile (IDPN)



dimethylaminopropionitrile (DMAPN)

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