Neurologic Dysfunction From Exposure to 2-t-Butylazo-2-Hydroxy-5-Methylhexane (BHMH): A New Occupational Neuropathy

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Abstract: Seven cases of subacute central and peripheral neurologic dysfunction developed in 18 workers employed in the manufacture of reinforced plastic bathtubs. Cases were characterized by weight loss, dizziness, paresthesias, muscle weakness, incontinence, memory loss, and loss of peripheral, color, and night vision. Neuropathies began distally, involved both sensory and motor function, and were associated with prolonged sensory latency, muscle fibrillation, and reduced numbers of functioning motor units. One patient developed posterior lenticular cataracts. Slow improvement occurred on removal from exposure, but residual neuropathies persisted for as long as two years. Epidemiologic investigation disclosed that the first case developed approximately two weeks after introduction of a new plastic foaming agent, 2-t-butylazo-2-hydroxy-5-methylhexane (BHMH). All cases occurred in workers exposed directly to BHMH. No new cases developed after use of BHMH was discontinued. A survey of the firm which produced BHMH and of 68 user firms found two additional clusters of mild neuropathy which may have been caused by BHMH. BHMH was withdrawn from distribution following discovery of these cases. Subsequently, BHMH has been shown in rats to be a potent neurotoxin. Adequate premarket testing could have averted this outbreak. (*Am J Public Health* 1985; 75:513–517.)

Introduction

For centuries neuropathy and encephalopathy have been recognized consequences of overexposure to heavy metals such as lead,[1–3] arsenic,[4] and mercury.[5] Since the advent of the chemical revolution,[6] a number of synthetic chemicals have also been found to exhibit neurotoxic properties and have been responsible for outbreaks of neurologic disease,[7] the majority of them in industrial workers. Among these newer neurotoxins are acrylamide[8]; carbon disulfide[9–10]; dimethylaminopropionitrile (DMAPN)[11]; chlordecone (Kepone)[12]; n-hexane[13]; methyl n-butyl ketone (MBK)[14]; organophosphates such as parathion,[15] leptophos,[16] and tri-ortho cresyl phosphate (TOCP)[17]; styrene[18]; and 2,4-dichlorophenoxyacetic acid (2,4-D).[19]

We describe here an outbreak of encephalopathy and peripheral neuropathy which occurred among workers at a small plastics manufacturing plant. The affected workers had all been previously healthy, but developed central and peripheral neurologic dysfunction shortly after the introduction to the plant of a new foaming agent, 2-t-butylazo-2-hydroxy-5-methylhexane (BHMH). Although this compound has subsequently been shown in rats to be neurotoxic,[20,21] information describing its neurotoxicity was not available at the time of its commercial introduction.

Background

BHMH is an azo-substituted aliphatic hydrocarbon used in the manufacture of polyester-based plastics (Figure 1). It decomposes in the presence of polyester resin to produce free radicals which cross-link the resin, and it also releases bubbles of nitrogen which cause the resin to foam.[22–24]

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Limited premarket evaluation of BHMH in rats and rabbits demonstrated acute dermal, conjunctival, and pulmonary toxicity.[25] In addition, tremors, subconvulsive jerking, and ataxia were noted in rats exposed by inhalation for one hour at a concentration of 20 mg/liter.[26] Ataxia was noted in rats exposed for one hour at 2.55 mg/liter.[26] Chronic tests were not performed. Nevertheless, information on BHMH distributed by its manufacturer did not warn of possible neurotoxicity.[27]

In September 1979, BHMH was introduced to the manufacture of reinforced plastic bathtubs in a newly designed plant in Lancaster, Texas near Dallas.[24] In the manufacturing process, layers of chopped fibrous glass, polyester resin, t-butyl perbenzoate, styrene, ethyl acetate, and either methyl ethyl ketone peroxide (MEKP) or BHMH were applied to a mold with a spray gun. Application took place in a ventilated booth. Ventilation was designed to maintain airborne concentrations of styrene vapor below 100 parts per million (ppm).

Between October and December 1979, three workers from the plant sought medical care for neurological symptoms and loss of weight. They did so through different physicians, and the possibility of a common-source outbreak was not immediately recognized. However, in September 1980, more than six months after last exposure to BHMH, the first three affected workers were referred for evaluation to one of the authors (TLK). Examination confirmed the presence of residual neurologic impairment in all three and prompted the subsequent investigation. Case histories of the first three affected workers are presented in the Appendix.

Methods

To determine the etiology of these cases of neurologic illness, we attempted to interview and examine all current and former workers at the Texas plant. Because plant management refused initially to provide a list of personnel, we began with interviews of the three previously identified workers; from them we compiled the names of other employees. We obtained information from each worker on job history, on extra-occupational exposures, and on use of personal protective equipment. Examinations were per-

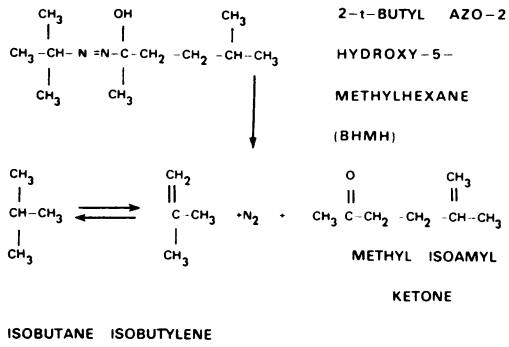

FIGURE 1—Structural Formulae and Spontaneous Decomposition Products of BHMH

formed by one of us (TLK) during and subsequent to September 1980 (five to six months after use of BHMH was discontinued). Patients who had objective evidence of motor or sensory deficits were evaluated electromyographically and ophthalmologically. A case was defined as a previously healthy person, exposed to BHMH, who developed all of the following abnormalities: 1) peripheral neuropathy, 2) impaired memory or concentration, and 3) visual disturbances (either impaired color vision, decreased peripheral vision, diplopia, or blurring).

Shortly after initiation of this study, the National Institute for Occupational Safety and Health (NIOSH) informed the manufacturer of BHMH of the preliminary findings. The manufacturer, in turn, notified all customers of the presumed hazard, subsequently withdrew BHMH from production, and provided NIOSH a list of all customers for the chemical.

To evaluate the possible occurrence of illness at other plants, NIOSH investigators mailed a questionnaire to the management of each company which had received BHMH seeking information on the volume and dates of BHMH use, and on the occurrence of any neurologic or other symptoms in exposed employees. Follow-up telephone interviews were conducted with managers of firms which reported symptoms. In addition, we conducted site visits and interviewed workers at the plant where BHMH had been produced and at the plant which (after the Texas plant) had used the largest volume of BHMH.

Results

Texas Plant

Workers at the Texas plant were able to recall the names of 20 current and former employees who had been exposed to BHMH. Eighteen agreed to be interviewed.

We found that seven of these workers had histories of illness which fulfilled our case definition (Table 1). All seven had evidence of residual neurologic impairment at the time of our investigation, six months or more after last exposure to BHMH. Three had abnormal electromyograms, and four had abnormal nerve conduction studies. One worker had decreased visual acuity, a posterior subscapsular cataract in the left lens, and subtle superior arcuate defects in the visual fields of both eyes.

Epidemiologic evaluation indicated that onset of symptoms in all seven cases occurred during the six months in which the plant had used BHMH.[28] No cases developed before or after that period (Figure 2). Onset of symptoms in the first case occurred approximately two weeks after introduction of BHMH. Five of the seven cases had onset during October and November 1979.

From September until mid-November 1979, workers in the spray booths were provided no protective gear (Figure 2). Second-hand clothing was worn at work and would be discarded after a few days' use due to accumulation of plastic accretions. Because BHMH did not produce severe skin irritation as did MEKP, the compound which it replaced, workers reported that they were unlikely to wash sprayed plastic containing BHMH off their skin. On at least two occasions a helper was reported to have been accidentally sprayed in the mouth with BHMH. No showering facilities were provided.

In November 1979, after appearance of disease in the index case, management issued a memorandum of caution to workers. Later in the same month, workers were provided for the first time with plastic coveralls (Figure 2). Beginning in January 1980, the use of organic vapor respirators was required. After March 1980, full protective gear was required in the spray booths and only supervisors were allowed to spray. Finally, in April 1980, use of BHMH was discontinued. The incidence of new cases was observed to decline as

TABLE 1—Clinical Findings in Workers Exposed to 2-t-Butylazo-2-Hydroxy-5-Methylhexane (BHMH) Lancaster, Texas

		Abnormalities (Physical Examination)			Dysfunction (Reported by Workers)			
Case #	Age/Sex	Sensory	Motor	Nerve Conduction	Visual	Ataxia	Bladder/ Bowel	Memory Loss
1	27 M	4+	4+	Abnormal	C/P/B	+	+	+
2	33 F	3+	4+	Abnormal	C/P/B	+	+	+
3	25 M	3+	4+	Abnormal	D/P/B	–	–	+
4	27 M	1½+	1+	Abnormal	P	–	–	+
5	20 M	1+	1+	Normal	B	–	–	+
6	28 F	1+	—	Normal	D/B	–	–	+
7	21 M	1+	1+	Not Done	D/B	–	–	+

Visual Changes
B—Blurring
C—Loss of Color Vision
D—Diplopia
P—Loss of Peripheral Vision

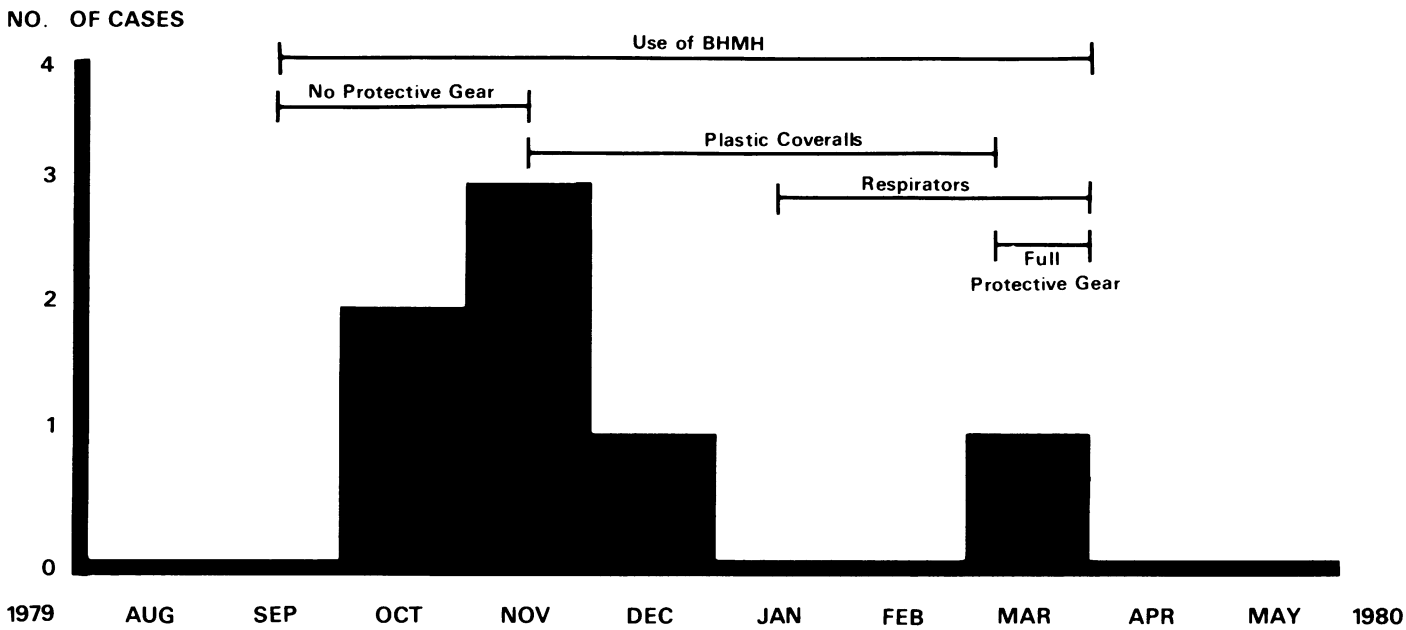

FIGURE 2—Cases of Neuropathy by Month of Onset—Plastics Plant, Texas, 1979–80

increasingly effective protective equipment was employed. The process consumed approximately 200 gallons of BHMH per month, or a total of 1,300 gallons. Thorough review revealed no use in the plant of other known neurotoxins, with the exception of styrene.

Six (86 per cent) of the seven cases occurred in spray gun operators or their assistants, and all seven patients had worked directly with BHMH for at least one month. By contrast, only three of 11 non-cases were spray-gun operators, and only six of the 11 non-cases had at least one month of direct exposure to BHMH.

With regard to protective equipment, five (71 per cent) of the seven cases reported that they sometimes or always worked without a respirator while using BHMH; by contrast, only four of the 11 non-cases worked without a respirator. Six of the seven cases reported that they sometimes or always failed to wear gloves while using BHMH; only five of the 11 non-cases failed occasionally or always to wear gloves.

The mean age of the seven cases was 26 years; and of the 11 non-cases, 27 years. Average duration of employment was nine months for cases compared to seven months for non-cases. Two of the seven cases and one of the 11 non-cases were female. None of the cases reported excessive use of alcohol, and there were no significant differences between cases and non-cases in consumption of alcohol or tobacco. No cases reported serious drug abuse; two reported occasional use of marijuana. None reported glue- or solvent-sniffing. No unusual extra-occupational exposures or significant exposures in prior employment to heavy metals, solvents, herbicides, or pesticides were reported.

Other Plants

The manufacturer of BHMH indicated that 86 plants had received the chemical. We were able to obtain information from 68 (79 per cent) of these firms. Most were small-volume customers.

Only one plant reported the occurrence of symptoms compatible with neuropathy. Two workers, both laboratory technicians, had noted transient paresthesias of the right hand after working with BHMH. Each had extensive prior experience with polyester resins and had not previously experienced similar symptoms.

We conducted a field survey at a plant which had used 370 gallons of BHMH in the manufacture of plastic swimming pools. This plant had used BHMH for only three hours per day, as contrasted with eight hours daily at the Texas plant. Partial protective gear, including organic vapor masks, was reported to have been provided to all exposed workers. Although management was aware of no problem, five workers—all members of spray teams—reported having experienced subtle sensory or motor symptoms after starting work with BHMH. Three of these five consented to physical examination; one had diminished deep tendon reflexes, but no other demonstrable abnormalities. Four additional workers, all of them spray gun operators, also underwent physical examination. Although none reported neurological symptoms, all four exhibited diminished deep tendon reflexes.

We also conducted a survey of workers at the plant where BHMH had been produced. This investigation revealed no manifestations of neurotoxicity. Production had taken place in an enclosed system operated by remote control, and opportunity for exposure appeared to be virtually non-existent.

Discussion

The data from this investigation indicate that BHMH was the agent responsible for the outbreak of neurologic disease in workers at the Texas plant. The first case occurred shortly after introduction of BHMH; symptoms were most severe in persons most heavily exposed; and the outbreak ended abruptly after use of the chemical was discontinued. Further, BHMH was the only new chemical in use in the spray process. Three other plants operated by the same manufacturer used the same materials as the Texas plant, except that they used methyl ethyl ketone peroxide (MEKP) rather than BHMH; workers in none of those other

plants developed neurological disease. Finally, experimental animal studies conducted after this outbreak have demonstrated unequivocally the neurotoxic potential of BHMH.[20] Pathological findings in the exposed animals included: 1) loss of nerve fibers in the peripheral nerves and spinal cord; 2) degeneration of nerve fibers in the optic tracts; and 3) the development of lenticular cataracts.[20] These findings provide a rational explanation for the pattern of neurological dysfunction observed in the affected workers.

We considered the possibility that the neuropathy might have been due to styrene, a reported neurotoxin [18] which was in use at the Texas plant before, during, and after this episode. However, styrene neurotoxicity does not typically involve motor nerves.[29] Further, no neuropathies were reported in any of the three sister plants, each of which also used styrene.

Our data suggest that BHMH may have been responsible for episodes of neurologic dysfunction in workers exposed to the compound in two other plants. In each of those instances, symptoms developed after exposure to BHMH and occurred only in those workers most directly exposed; the relative mildness of these cases may reflect a shorter duration and lower intensity of exposure. An additional aggravating factor in the Texas plant may have been the concomitant exposure of workers there to other lipophilic compounds such as ethyl acetate; previous studies of the hexacarbon neuropathies have suggested that simultaneous exposure to methyl ethyl ketone (MEK) can potentiate the neurotoxicity of n-hexane and of MBK.[30,31]

BHMH appears to be the prototype of a new family of neurotoxic aliphatic hydrocarbon compounds. Although initial examination of its 6-carbon straight-chain structure might suggest that it is simply a congener of n-hexane with similar neurotoxic action, the decomposition products of BHMH (Figure 1) do not appear to include 2,5-hexanedione, the metabolic derivative of both n-hexane and of MBK which is the actual mediator of the neurotoxicity of those compounds.[32] Also, several features of the neurotoxic syndrome induced by BHMH, in particular the disturbances of vision and the formation of cataracts,[20] are not found in the usual hexacarbon neuropathies. The mechanism by which BHMH exerts its neurotoxicity is not yet known and will require further investigation.

The tragic lesson of this epidemic is that it could have been prevented by adequate premarket evaluation of BHMH. Premarket testing is the most effective means of assessing the toxicity of new chemicals compounds. However, until passage of the Toxic Substances Control Act (TSCA) in 1976,[33] there was no legal mechanism in the United States for prospective evaluation of the neurotoxicity of new industrial compounds. Even since passage of TSCA, inadequacies in testing requirements remain. Many thousands of potentially neurotoxic compounds whose introduction to commerce antedated passage of the Act remain untested,[34] and there are no requirements at present for testing such compounds; these compounds, BHMH among them, were simply registered with the US Environmental Protection Agency (EPA) and were added by EPA to the TSCA Inventory. Also testing procedures for new industrial compounds have not been standardized; responsibility for deciding whether or not to test a new chemical and for development of testing protocols is left almost entirely to the discretion of chemical manufacturers. Governmental review of the toxic potential of new chemicals consists typically only of examination of their structural formulae.

Although testing of BHMH for acute toxicity demonstrated ataxia, tremors, and possible convulsions in exposed rats,[25,26] the manufacturer apparently did not consider the compound to be neurotoxic on the basis of those results and did not warn users of potential neurotoxicity.[27] Also no chronic testing of the compound was performed. The severe neurologic damage incurred by the workers who were exposed to BHMH provides an object lesson of the inadequacies of our present premarket testing procedures.

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APPENDIX

Case Histories

Case #1

This 27-year-old Black male was the first employee to use BHMH. He wore no protective clothing, and his forearms and feet were usually covered with accretions of foam spray. Neurological illness began in October 1979, two weeks after the beginning of work with BHMH. He complained of pain in his palms and soles, extremity weakness, ataxia, diminished night and color vision, and shooting pains and muscular spasms in his back. He also experienced a weak and dribbling urinary stream, decreased sexual interest, flatulence, diarrhea, and unintentional weight loss of 40 pounds.

Sensory examination in September 1980 revealed selective, symmetrical distal extremity dysfunction: fingers and toes were dysesthetic; there was decreased sensation to pinprick; patellar, biceps, and ankle jerks were absent; and there was loss of proprioception. Vibration sensation was unimpaired. Babinski and Hoffman signs were absent. Heel-to-shin ataxia was evident. Motor weakness was marked, more severe distally than proximally, and most pronounced in the lower extremities. There was euphoria and decreased learning ability. Electrodiagnostic studies were performed 11 months after last exposure to BHMH. Sensory nerve conduction was unobtainable in left ulnar and sural nerves. Motor nerve conduction velocity was 47.2 m/sec in the ulnar nerve and 35.8 m/sec in the peroneal nerve; motor latency was 3.3 msec in the ulnar nerve and 4.7 msec in the peroneal nerve. Positive waves were absent from the electromyogram.

Follow-up examinations over a two-year period demonstrated slow recovery of body weight, partial return of motor strength proximally and then distally, and resolution of sexual dysfunction. Residual problems were mild-to-moderate weakness in lower extremities, worse at the end of the day, aching pains and spasms in the lower back, reduced strength in the hands and slight ataxia.

Case #2

This 33-year-old White female was supervisor of the BHMH production line. She had no known prior exposure to neurotoxins, except for brief exposure to BHMH during a pilot run conducted four months before formal introduction of BHMH to the process. In October 1979, after approximately two weeks of work on the production line, she experienced dizziness and subsequently reported sensations of feeling as though she were in a roller-coaster when traveling in a car. Over the ensuing weeks and months, she developed numbness of fingertips and then toes, which subsequently traveled up the extremities. After two months, there was difficulty with color and lateral vision. She continued working with BHMH for approximately eight months. During this period, she lost 10 pounds, had decreased and irregular menses, severe stress incontinence, and nasal drainage, in addition to sensorimotor polyneuropathy, ataxia and short-term memory loss. Limb weakness was more evident on the left and in the upper extremities. Cataracts developed in both eyes; there was no history of diabetes, use of corticosteroids or birth control pills.

Her neuropathy improved after cessation of exposure to BHMH, and seven months later she complained only of numbness in the tips of fingers and toes, and aching pains in the hands. Sensory examination at that time revealed decreased perception of light touch and pinprick in the distal extremities, sluggish reflexes on the left side, especially the upper extremity, and normal vibration and position sense. Babinski and Hoffman reflexes were absent. Motor weakness was moderate to severe and most prominent in the left upper extremity.

Case #3

This 25 year-old White male began working at the plant in summer 1979. Within several months he was transferred to spray gun work in the BHMH spray booth, replacing another employee (Case #2) who had become ill while working there. After a few weeks he began to notice numbness of his feet and dizziness. He requested a transfer back to his previous work, and his symptoms gradually resolved. In January 1980, the plant began using BHMH foam spray in two spray booths, and he was again assigned to spraying. Within several weeks he had developed a 25-pound weight loss and was experiencing weakness and numbness of his hands and arms, difficulty in remembering and concentrating, impaired color vision (mainly difficulty in distinguishing blues and reds), and loss of peripheral vision. He was referred to a neurologist who diagnosed a severe and possibly irreversible peripheral neuropathy, probably related to chemical exposures at work. The neurologist sent copies of his reports to the plant management, and shortly thereafter they discontinued use of BHMH.

In September 1980 the patient was referred to a medical toxicologist. Physical examination revealed weakness of the wrist extensors bilaterally and severe wasting and weakness of the intrinsic muscles of both hands. Deep tendon reflexes were absent in both upper limbs and were diminished symmetrically in both lower limbs. Sensory examination revealed diminution of pinprick sensation in both hands. Ophthalmologic evaluation, including color vision testing with HRR plates and Goldmann visual field testing, was normal.

Electromyographic evaluation of involved limb muscles revealed decreased numbers of motor units and polyphasicity. Nerve conduction studies showed modestly increased latencies (3.7 msec, 6.0 msec, 4.1 msec) for the left median, left peroneal, and right sural nerves respectively, and mildly slowed conduction velocity for the left peroneal nerve (42.5 m/sec). Follow-up examination, conducted five months later, showed some improvement; latencies in the same three nerves were 3.4 msec, 6.0 msec, and 3.8 msec, respectively, and conduction velocity for the left peroneal nerve was 45.1 m/sec.