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Investigation of Reports of Sexual Dysfunction Among Male Chemical Workers Manufacturing Stilbene Derivatives

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A Health Hazard Evaluation was conducted by the National Institute for Occupational Safety and Health in an area of a large chemical plant that manufactured the stilbene derivative 4,4′-diaminostilbene-2,2′-disulfonic acid, an intermediate used for the production of optical brightening agents. Men employed in the area reported problems with impotence. The study population consisted of 44 men aged 20–57 years (mean age 37) employed in the area at the time of the evaluation. An industrial hygiene investigation, health and work history questionnaire survey, physical examinations, and blood chemistry and serum hormone evaluation were conducted. Fourteen percent of the men reported symptoms of impotence over the preceding 6 or more months, 7% had potency problems of shorter duration, and 7% were not currently impotent but had experienced impotence for 6 or more months in the past; 36% experienced decreased libido, all since beginning work in the production area. Low levels of serum testosterone (<350 ng/dl) were observed in 37% of the men. The low serum testosterone concentrations were not accounted for fully by diurnal variation or an effect of rotating shift work. It is suggested that exposures to chemicals possessing estrogenic activity may be related to the observed health effects in these workers.

Key words: impotence, serum testosterone, workplace exposures, stilbene manufacture

INTRODUCTION

A union local requested that the National Institute for Occupational Safety and Health (NIOSH) assess the work-relatedness of reports of male impotence among a group of chemical workers employed in part of a large chemical production facility [Landrigan et al., 1983; Quinn and Levenstein, 1985; Hammond et al., 1987]. The

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workers made 4,4′-diaminostilbene-2,2′disulfonic acid (DAS), an intermediate in the manufacture of a wide variety of optical brightening agents [Anliker and Muller, 1975].

Reports of reproductive health problems among men in the work environment are uncommon and have generally involved decreased fertility or adverse pregnancy outcomes in partners rather than decrements in sexual function [Manson and Simons, 1979; Rao and Schwetz, 1982]. A very few occupational studies have reported changes in sexual behavior such as loss of libido and impotence in workers manufacturing carbon disulfide, oral contraceptives, and diethylstilbestrol (DES) [Harrington et al., 1978; Manson and Simons, 1979; Zaebst et al., 1980]. A positive association between impotence and exposure to exogenous factors has been documented more frequently, however, in the clinical setting, as a side effect of some commonly used drugs including antihypertensive, antihypertensive with diuretic combination, antianxiety, antidepressant, antipsychotic, and anorexic drugs as well as androgens, estrogens, and progestogens [Story, 1974]. Comparisons among the workplace and clinical studies are difficult to make because they use different criteria to determine impotence. It is also difficult to determine whether reports of impotence in a given study are in excess, because there are very limited data on the prevalence of impotence derived from population-based surveys. These difficulties exist in part because the criteria for defining impotence and other sexual behavior such as loss of libido have a subjective component and because social restrictions limit discussions of inadequacies in male sexuality.

The toxicologic data on DAS are also limited. However, it seemed biologically plausible that DAS could be related to the reports of impotence because its chemical structure is similar to DES, a chemical reported to cause impotence among men who were occupationally exposed [Burton and Shumnes, 1973; Meyer et al., 1978] and among men who were given DES therapeutically [Leuprolide Study Group, 1984].

Under a contract to NIOSH, a prevalence survey was planned, which included a questionnaire-based survey of sexual and reproductive history and symptoms, a work history, an industrial hygiene investigation, physical examinations, and an evaluation of blood chemistry and serum hormone levels. Based on the results of the prevalence survey, a further study was planned to compare the population in the work area of interest to a similar group of workers employed at the same plant but not working in the area. The company would not permit further study, however, and so it was not possible to make this comparison. The results of the prevalence survey are reported here.

MATERIALS AND METHODS

Production Process

Details of the production of 4,4′-diaminostilbene-2,2′disulfonic acid are given elsewhere [Hammond et al., 1987]. The principal chemical processes involved sulfonation of para-nitrotoluene (PNT) to para-nitrotoluene sulfonic acid (PNTSA), dimerization of this to 4,4′-dinitrostilbene-2,2′-disulfonic acid (DNS), and then reduction to 4,4′-diaminostilbene-2,2′-disulfonic acid (DAS) (Fig. 1).

These processes took place in two multi-story, open structures holding reactor vessels, storage tanks, filters, pumps, and related equipment. Although the processes largely were automated, potential worker exposures to chemicals occurred at reactor

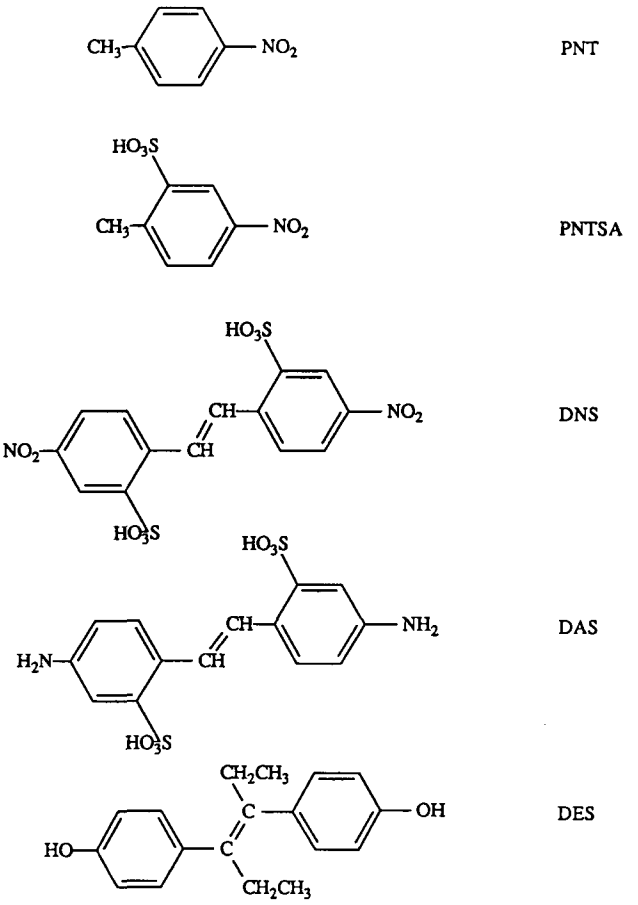

Fig. 1. Chemicals for the stilbene derivative manufacturing work area: PNT = para-nitrotoluene; PNTSA = para-nitrotoluene sulfonic acid; DNS = 4,4′-dinitrostilbene-2,2′-disulfonic acid; DAS = 4,4′-diaminostilbene-2,2′-disulfonic acid. The structure of the synthetic estrogen diethylstilbestrol (DES) is shown for comparison.

charging ports, transfer points, sampling ports, and in filtering and drumming operations. Opportunities existed for chemical absorption via respiratory, dermal, and, possibly, oral routes.

Study Population

The study population consisted of 5 distinct work groups in the production area. Each work group stayed together as a unit, 4 of them rotating their work schedule every week (1 week of mornings, 1 week of evenings, 1 week of nights, 1 week off; repeat). One of the work groups was a non-rotating group that worked the day shift. Each of the 5 groups had a supervisor who remained with his assigned group. In the rotating groups 1, 2, 3, and 4, there were 10, 9, 11, and 9 men, respectively. Group 5, the non-rotating group, consisted of 5 workers with greater seniority.

Health Status Questionnaire and Physical Examination

A health history questionnaire focusing on sexual and reproductive history was administered by male physicians to 45 men and 4 women currently employed in the stilbene-derivative manufacturing area. Responses on sexual function were categorized into outcomes of *current impotence* (defined as a 25% or greater failure rate in obtaining or sustaining penile erection for at least 6 months prior to the study); *past impotence* (a 25% or greater rate of penile erectile dysfunction for at least a 6 month period in the past, but not within the last month before this study); *other potency problems* (current problems with penile erection for at least 6 months' duration but a failure rate less than 25%); and *loss of libido* (decreased desire for intercourse or masturbation leading to a 25% or greater decline in the frequency of these sexual acts during the 2 years prior to this study), all since beginning work in the stilbene-derivative production area. Our definition of current impotence is similar to Masters and Johnson's definition of secondary impotence as a 25% or greater failure to obtain and sustain an erection, although their definition does not specify an absolute time duration for symptoms [Masters and Johnson, 1970]. Primary impotence, defined as "never able to achieve and/or maintain an erection quality sufficient to accomplish successful coital connection" [Masters and Johnson, 1970] was also evaluated.

In addition, the questionnaire assessed the presence of other factors that may be associated with secondary impotence including diabetes mellitus, thyrotoxicosis, obesity, alcohol ingestion, antihypertensive, amphetamine, and non-prescription drug ingestion including marihuana and cocaine, serious physical or psychological stress, and genitourinary, endocrine, cardiovascular, or neurologic disease [Masters and Johnson, 1970; Slag et al., 1983]. A smoking history was taken also. The questionnaire was administered and evaluated in a previous workplace investigation of impotence among chemical workers.

Serum Hormone Evaluations

Blood samples were taken for complete blood count and serum biochemistry. Serum testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and thyroxin concentrations were measured. The first set of blood samples were drawn at various times of day throughout each work shift; a second set were drawn at a time standardized with regard to time of day and work shift. Hormone levels were determined by radioimmunoassay [Chen et al., 1971]. Quality control for the hormone measurements included the analysis of standard samples (provided by the College of American Pathologists' Quality Assurance Program) with each assay. For all male subjects, physical examinations were performed, which consisted of an evaluation of secondary sexual characteristics, genitalia, and the peripheral nervous system including the bulbocavernosus reflex (anal contraction when pressure is applied to the glans penis).

Industrial Hygiene Assessment

A preliminary industrial hygiene assessment was conducted primarily to develop and evaluate air sampling and analytical methods. Subsequent environmental sampling and work practice evaluation which had been planned for the follow-up study, was disallowed. Work practices were observed for each workshift, and work histories were compiled for each person who worked in the area. Personal total

airborne particle samples were collected on Teflon-coated fiber glass filters for selected individuals on all shifts. One area sample was collected with a high-volume sampler. In addition, bulk samples of chemical at various stages of the process were collected to determine the relative concentrations of PNTSA, DNS, and DAS. All samples were stored, refrigerated in the dark, and analyzed for DNS, PNTSA, and DAS according to methods described elsewhere [Hammond et al., 1987].

RESULTS

Health Status Questionnaire and Physical Examination

Complete health status questionnaire data were obtained from the 45 men and 4 women, and blood samples were obtained from all subjects except one of the men employed in a supervisory job. Because the 4 women reported no health complaints and had normal blood chemistry and serum hormonal findings, they are not discussed further. One man (aged 46 years) with current impotence for 3 years had been treated for thyrotoxicosis 10 years before. He was currently euthyroid, as assessed by a normal serum thyroxine level, and his serum testosterone, LH, FSH, and prolactin concentrations were also normal. Nonetheless, because thyrotoxicosis is a known cause of impotence and may have contributed to his current symptoms, this man's data were excluded. This report of the study population is confined to the 44 men (43 with blood analyses) aged 20–57 years (mean 37 ± SD 8 years).

Since beginning work in the production area, 14% of the men (6/44) reported current impotence, an additional 7% (3/44) had past impotence, and 4% (2/44) had other potency problems; loss of libido occurred in 36% of the men (16/44). No individual reported primary impotence. Physical examination of the impotent subjects showed no abnormalities of the external genitalia or testes. There was no evidence of feminization; in particular, body and facial hair were normal and there was no evidence of gynecomastia. The bulbocavernosus reflex, testing neurologic impairment in the spinal nerve ennervating the penis, was present and full in all subjects tested. No significant difference in the other health-related factors that may be associated with impotence, including alcohol consumption, drug ingestion, serious physical or psychological stressors, obesity, or underlying cardiovascular, neurologic, or genitourinary disease, was found between the symptomatic and asymptomatic workers, and no differences existed among the different work groups. The smoking histories of the symptomatic and asymptomatic groups were also similar. No subject had biochemical evidence (total protein, albumin, bilirubin, alkaline phosphatase, and SGOT) of chronic liver disease, and none had the physical findings of alcoholic cirrhosis.

Serum Hormone Evaluations

The mean serum testosterone concentration for the entire study population was 448 ± 170 ng/dl. Thirty-seven percent (16/43) of the study population had serum testosterone concentrations less than 350 ng/dl, the lower limit of the normal range for our laboratory [Spark et al., 1980]. The serum LH concentrations (mean = 10.9 mIU/ml ± 7.0 mIU/ml) showed considerably greater variability than testosterone, which is consistent with published data showing pulses of LH secretion that are not usually accompanied by a testosterone pulse [Van Cantor and Aschoff, 1989]. Examination of the results for serum LH concentrations among the 15 men who had low

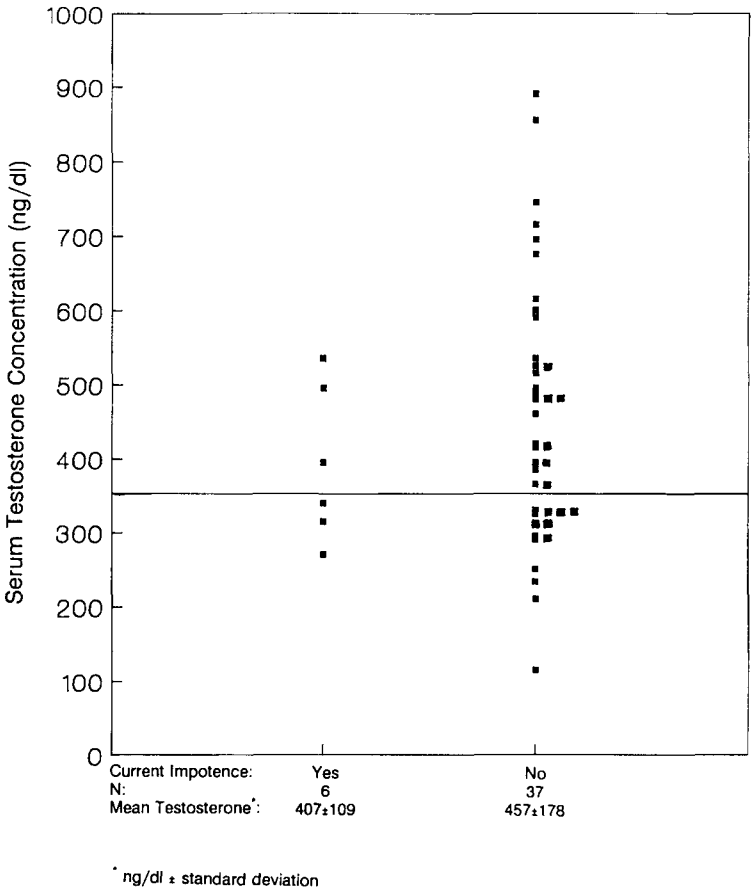

Fig. 2. Distribution of serum testosterone concentrations for men reporting current impotence and those not currently impotent.

testosterone values showed that the LH levels were generally within the normal range (5–20 mIU/ml). The lowest serum testosterone level was 115 ng/dl and occurred in a 47-year-old man whose only symptom was decreased libido; his LH level (4.2 mIU/ml) was just below the lower limit of normal. Measurements of serum FSH, prolactin, and thyroxine concentrations were within the normal ranges for all subjects.

The difference between the mean serum testosterone concentrations for those reporting symptoms of current impotence, 407 ± 109 ng/dl (n = 6), and those reporting no impotence, 457 ± 178 ng/dl (n = 37) was not significant (2-sample t-test, 41 df, p = .39) (Fig. 2). The means and distributions of serum testosterone concentrations by work group are shown in Figure 3. Rotating work groups 2, 3, 4, and non-rotating work group 5 contained all of the cases of impotence and had similar mean serum testosterone concentrations, while rotating work group 1, which included no individual with a potency problem, had the highest average testosterone level (Fig. 3). Analysis of variance showed a significant difference in serum testosterone among work groups ($F = 5.10$, $p < .002$). The mean ages for the shifts were similar, 36,

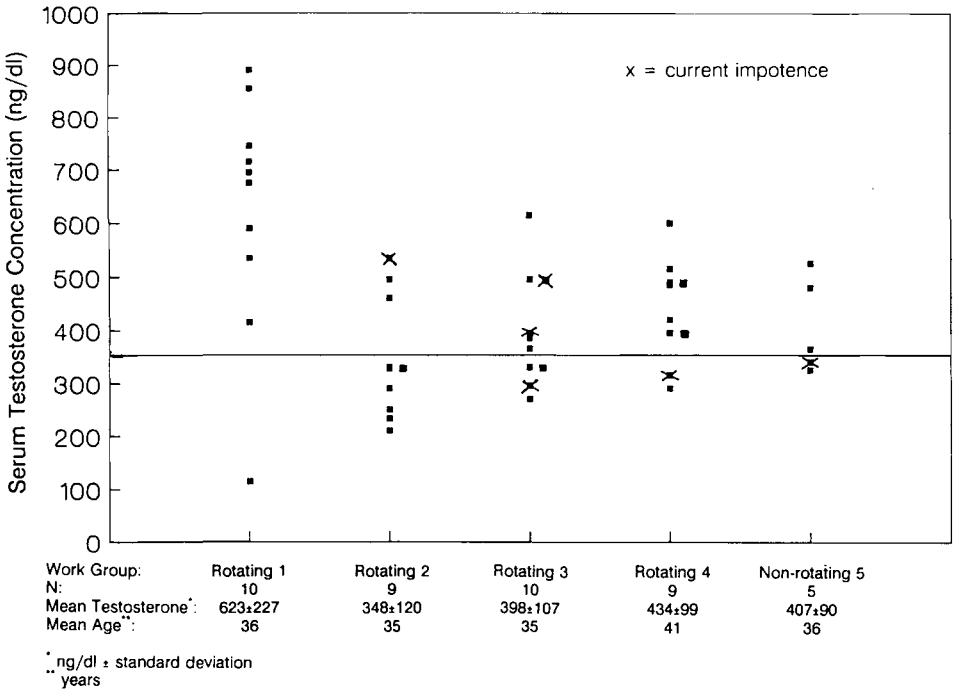

Fig. 3. Distribution of serum testosterone concentrations by work group.

35, 35, 41, and 36 years, respectively (analysis of variance $F = 0.70$, $p = .63$). The average length of employment in the area was 4.7 years. A regression analysis showed a negative association between serum testosterone concentration and duration of work in the production area, although this association was not strong (b, the regression slope, $= -12.0$ ng/dl/year, $p = .14$). There was a weak association between age and serum testosterone concentration ($b = -3.6$ ng/dl/year, $p = .26$). The mean body weights of those with decreased testosterone and those with normal testosterone values were not statistically different (2-sample t-test, $p = .13$).

To address the potential confounding effects that circadian rhythm and rotating shift work may have on the serum testosterone measurements, blood samples were redrawn to verify and standardize the results with respect to time of day. Since studies using single and pooled blood samples have found that normal young men exhibit a circadian rhythm in serum testosterone, with the highest levels around 0800 hours and the lowest between 1900 and 2100 hours [Bremner et al., 1983], all blood samples were drawn between 0800 and 1030 hours on the final day of the workers' day-shift rotation (that is, after each worker had been on the same schedule for 2 weeks: off 1 week, day shift 1 week). Thirty-seven of the workers were available for retesting. To minimize possible moment-to-moment variations in the serum concentrations of testosterone, two 10 ml specimens of blood were taken from each worker (each drawn slowly over 2 minutes) about 10 minutes apart. Samples were analyzed for testosterone and LH separately and pooled according to the same analytic procedures as the initial set. The results of the individual measurements did not differ significantly from the pooled results, and so the pooled values are discussed here.

The repeat testing of serum testosterone showed that the number of subjects with low serum testosterone was approximately the same, although some changes in individual values occurred. The two sets of serum testosterone values were closely correlated ($r = 0.73$). There was a statistically significant increase in the mean serum testosterone concentration in the retested group (56 ng/dl, $p = .02$ in a paired t-test). The largest difference was found for individuals in rotating shift 3 who had been working the night shift during the initial blood sampling.

Repeat analyses of serum LH concentrations showed no significant changes. In those individuals with a decreased serum testosterone, LH levels were again within the normal range.

Industrial Hygiene Assessment

Environmental samples were used to assess airborne exposures to total particulate matter, PNTSA, DNS, and DAS. (PNT was not sampled because it was used primarily outside the work area.) Nineteen personal samples and one high-volume area sample were analyzed. Total particle concentrations ranged from 50 to 305 $\mu g/m^3$, 8-hour time weighted average (TWA). Only one personal sample had a detectable amount of DAS (detection limit approximately 20 $\mu g/m^3$); this sample was from the operator of a filter press where iron oxide was filtered from a solution of DAS. Thirty-eight percent of the samples had detectable levels of DNS, and 24% had detectable levels of PNTSA. All exposure concentrations were near the limits of detection (approximately 10 $\mu g/m^3$ for DNS and PNTSA). Qualitatively, the airborne exposures were consistent with job categories, although it was observed that most jobs required regular movement throughout the work area. For example, the highest PNTSA exposure was found for the worker who filtered PNTSA in a separate building, and his personal exposure sample showed no detectable levels of DNS or DAS. The high-volume filter was placed near the filter press where iron oxide was separated from the DAS in solution. Not surprisingly, more DAS (1.6 $\mu g/m^3$) was found here than DNS (0.25 $\mu g/m^3$) or PNTSA (0.18 $\mu g/m^3$).

DAS was visible as a fine, yellowish film on some of the equipment and on many of the surfaces, such as handrailings, throughout the work area.

DISCUSSION

The present investigation found a 14% prevalence of current impotence, a 7% prevalence of past impotence, and a 36% prevalence of decreased libido in men aged 20–57 years. In addition, 37% had serum testosterone concentrations that measured less than 350 ng/dl, the lower limit of the normal range. Since there are limited published population data on impotence, a study was planned to compare the population investigated here with an unexposed group of men of similar age employed at the same plant. The company would not permit further study, however, and so population-based data are used for comparison.

Comparisons to Population Norms

Information regarding the prevalence of impotence in normal populations is sparse and limited in its usefulness as comparison data because: 1) the methods for obtaining the study populations differ; or 2) the criteria for defining impotence, in particular, the frequency and duration of problems with erectile dysfuction, are not

reported; or 3) the reports of impotence are not stratified by age. The data of Kinsey et al. [1948] remain the most comprehensive population-based survey of male sexual behavior in the United States. Kinsey's age-specific data for impotence prevalence indicate that fewer than 3% of men younger than 45 years, and only 6.7% between 45 and 55 years are "more or less totally impotent." In a re-analysis of the Kinsey data, the prevalence of ever having had trouble getting or keeping an erection "more than incidentally" is 18.9% in non-college educated white males, 5.6% in college-educated white males, and 6.4% in black college-educated males all between the ages of 15 and 81 + years [Gebhard and Johnson, 1979]. No further breakdown of impotence rates by age is given. Frank et al. [1978] report a prevalence of 7% for the problem of difficulty in achieving an erection in men who participated in a survey of 100 predominantly white, well-educated U.S. couples. The mean age of the men in this study population was 37 ± 11 years. A study of 98 presumably normal white, male British volunteers aged 20–35 years and representing a range of social classes (Reading and Wiest [1984] in collaboration with the World Health Organization) found that 8.25% of the men reported impotence and 11% reported a decreased desire for or an interest in sex, both during the preceding 4 weeks. Regarding the issue of reporting bias, the authors conclude that a volunteer study population would be unlikely to introduce a bias in the direction of under-reporting or denial of problems, if there is bias at all.

The current impotence prevalence rate of 14% in the present population is more than twice that estimated by Kinsey for 45–55 year olds and four times that for men less than 45 years. The Kinsey findings used a set of questions to ascertain impotence that were considered comparable to the definition used in this investigation [personal communication, Dr. Gebhard, Director of the Institute for Sex Research, 1982]. The 14% current impotence prevalence also exceeds the findings of Frank et al. [1978] and Reading and Wiest [1984], and the present finding of 37% decreased libido for at least 2 years is in excess of the 11% decrease in desire for or an interest in sex during the preceding 4 weeks found by Reading and Wiest [1984]. While differences among the study methods do not make the results directly comparable, these studies do provide reasonable estimates for a range of sexual dysfunction prevalence rates among normal individuals.

The published values for the lower limit of the normal range of serum testosterone vary, depending on the analytic methods used, and range from 300 ng/dl [Rudman et al., 1988] to 420 ng/dl [Nankin and Calkins, 1986]. Dai et al. [1981] report that there is generally good agreement that serum testosterone concentrations of normal, mature adult males range between 350 and 1050 ng/dl. The lower normal limit for the laboratory measuring the serum testosterone concentrations in the present population was 350 ng/dl [Spark et al., 1980]. In healthy men, serum testosterone declines gradually with age, although the average level generally remains within the normal range until at least 65 years [Marcus and Korenman, 1976; Tsitouras et al., 1982; Rudman et al., 1988]. In a study of 243 healthy men (mean age 51 ± 5 years) who participated in a Multiple Risk Factors Intervention Trial (MRFIT) program, Dai et al. [1981] found a mean serum testosterone concentration of 727 ± 251 ng/dl. While the MRFIT population was specifically selected for their risk of heart attack, the authors concluded that the population was representative of the general population with regard to hormonal status. The study population reported here had a mean serum testosterone concentration of 448 ± 170 ng/dl and a mean age of 37 ± 8 years.

Sources of Bias

Symptoms. The self-reporting of sexual dysfunction may be subject to reporting bias. In general it has been observed that men under-report sexual inadequacies [Spark et al., 1980]. If this were the case, the true prevalence of sexual dysfunction could be greater than reported here. It is possible, however, that the observed increase could be accounted for by the over-reporting of symptoms. Unfortunately the nature and degree of reporting bias cannot be determined by this investigation. However, job dissatisfaction was not a likely motive for symptom over-reporting. The workers in this work area expressed a high degree of job satisfaction, choosing to transfer into the area when the opportunity arose. Job turnover was low relative to many other production jobs in the plant.

Serum testosterone levels. As expected there was a small, statistically significant increase in the average serum testosterone concentration (56 ng/dl) for the group of workers who were retested at a standardized time of day and, to some extent, standardized work shift schedule. The largest increase in serum testosterone concentrations was found for individuals in rotating shift 3 who had been working the night shift during the initial blood sampling. It would be expected that these workers would have been subject to the greatest diurnal and rotating shift effects. The 56 ng/dl increase is not large enough to account fully for the the observed effect of decreased serum testosterone.

Correlation of outcomes. In clinic-based or randomly selected population-based studies, impotence generally is not strongly associated with decreased serum testosterone. Impotence has numerous physiological, environmental, and psychogenic causes, only some of which also effect testosterone concentrations [Spark et al., 1980; Tsitouras et al., 1982; Slagg et al., 1983]. In addition to this lack of association in other studies, several factors may contribute to the fact that no significant difference was found between the serum testosterone concentrations in the men reporting impotence and in those who did not. First, the numbers in this population are small and it is difficult to conclude anything about the true relationship between serum testosterone and symptoms of impotence. Second, a potential association could be obscured by either over- or under-reporting of symptoms. Third, the time-course for the changes in sexual function and the changes in serum testosterone concentrations may differ so that their relationship is obscured when only one point in time is evaluated in each subject.

Work-Related Factors

The testosterone measurements showed significant differences among the work groups and these differences remained, even after standardizing the time of day and the shift schedule for the collection of blood samples used for the serum testosterone analysis. The highest mean value was in the rotating shift 1 and not in the non-rotating shift 5 as might have been expected if the symptoms were due to a rotating shift effect. Since the mean age of each shift was similar and, additionally, age was not a strong predictor of serum testosterone concentration in this population, the difference in mean serum testosterone concentrations by shift cannot be explained fully by an age effect. Observation of work practices and job-specific tasks during the industrial hygiene survey indicated that there were a number of differences in work practices and assignments among the work groups that could have accounted for varying

degrees of exposure to chemicals used in the production area. For instance, some foremen (who rotated shifts along with their work group) required the workers they supervised to stand at or near the reactor vessels for most of the work shift even after the vessel had been charged. Other foremen did not require such attentiveness, and workers were permitted to leave the reactor vessel area and sit in an enclosed control room. The observed work practice differences among groups could mean that certain groups had a greater risk of exposure than others. Owing to access limitations, insufficient industrial hygiene data were collected to study the relationship between work practices and exposures.

The possibility of an acute, transient effect due to a work-related exposure to the present population was raised during the interviews of three men who reported developing impotence after cleaning a reactor vessel containing DAS. One man was impotent for 6 months (and was classified as impotent), but the other two had symptoms for shorter periods and did not meet the criterion for impotence. This prevalence study could not evaluate acute, transient effects because we defined dysfunction as having at least a 6-month duration; using this definition, impotence lasting days or weeks would not be included as cases. The 6 months' duration of dysfunction was used as a criterion for the definition of impotence to make the clinical definition (which does not include a strict time limitation) more applicable to an epidemiological study of chronic exposures. The time criterion was overly restrictive if the effects of workplace exposures were acute and transient. Acute, transient effects on impotence have been reported previously with the use of certain antihypertensive drugs [Spark et al. 1980; Slagg et al. 1983] and Tomic et al. [1983] have reported significantly reduced serum testosterone concentrations in men 1 week and 3 months after receiving radiation treatment for prostatic cancer with the pre-treatment values returning within 6 months after the irradiation.

Industrial Hygiene Assessment

The industrial hygiene measurements showed relatively low airborne concentrations of the DAS, DNS, and PNTSA. There was evidence, however, for potential dermal exposure for workers in the area. The final product, DAS, was a very fine powder usually in wet cake form. While the wet cake did not have the tendency to become airborne, a fine yellowish film was observed on surfaces throughout the work area such as handrailings, equipment, and the floor in the area where the DAS was put into metal drums for transport. This film was visible on the hands and forearms of some of the workers. Dermal and even oral exposures may also have varied by work group depending on the work practices followed.

Toxicological Information

The toxic and other biological actions of PNT, PNTSA, DNS, and DAS have not received much study. Based on limited available information, all four substances appear relatively non-lethal, as the LD_{50}s estimated from mortality data in mice, rats, guinea pigs, and rabbits given oral doses of these chemicals varied from about 1.2 to 71 g/kg body weight (Registry of Toxic Effects of Chemical Substances, 1987). In addition, PNT is mutagenic in bacteria [Shimizu and Yano, 1986], topical application of PNTSA and DNS irritated the eyes and skin of rabbits, and oral doses of DNS and DAS impair hepatic and renal function in mice, rats, rabbits, and guinea pigs (Registry of Toxic Effects of Chemical Substances, 1987). No impaired hepatic function

was seen in the present study, while skin and eye irritation were experienced by a few workers.

The chemical structures of these substances are noteworthy. DNS and DAS have structural similarities to diethylstilbestrol (DES), a synthetic estrogen (Fig. 1). Adverse reproductive effects, including decreased serum testosterone concentrations, decreased libido, sexual impotency, and gynecomastia have been reported among men who had occupational exposures to DES or who were given DES for the treatment of prostatic cancer [Zaebst et al., 1980; Harrington, 1982; Leuprolide Study Group, 1984]. While we have found no published reports examining the estrogenic actions of either DNS or DAS, at least two structurally related diaminostilbenes have been reported to exhibit estrogenic actions in rats: 4,4′-diamino-a,b-diethylstilbene and 3,4-bis(p-aminophenol) hexane [Solmssen, 1945].

In light of the study findings and the pharmacologic information, it was hypothesized that one or more of the chemicals being processed in the work area may have estrogenic effects. To explore this hypothesis, animal assays for estrogenic activity were initiated on the four substances by one of the authors (E.R.S.). In preliminary experiments it was found that single intraperitoneal doses of DAS, but not DNS, produced estrogenic effects in immature female rats. Importantly, a sample of DAS obtained at the workplace under study was also estrogenic. Further characterization of the estrogenic responses and estrogen-receptor-binding properties of these substances is underway.

CONCLUSIONS

The present findings suggest that the men working in the stilbene-manufacturing area may be experiencing increased impotence, decreased libido, and low serum testosterone concentrations and that further investigation of this exposure situation is warranted. Since the major substance produced in the work area, DAS, has structural similarities to DES, an estrogen that produces the same three adverse health effects, and since preliminary experiments indicate that DAS has estrogenic activity in rats, it is hypothesized that DAS may have estrogenic effects in humans and may be related to the observed dysfunction. The health status of the workers in the area should be reassessed more thoroughly and compared to a group of unexposed workers of similar age who are employed at the same plant on the same rotating shift schedule. A more complete industrial hygiene investigation should be conducted to determine if significant routes of worker exposure exist and to recommend exposure controls if they are warranted. Further research is needed to characterize the extent of the estrogenic activity of DAS in animals and in humans. In addition, population-based surveys to collect normative data on sexual dysfunction are needed.

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