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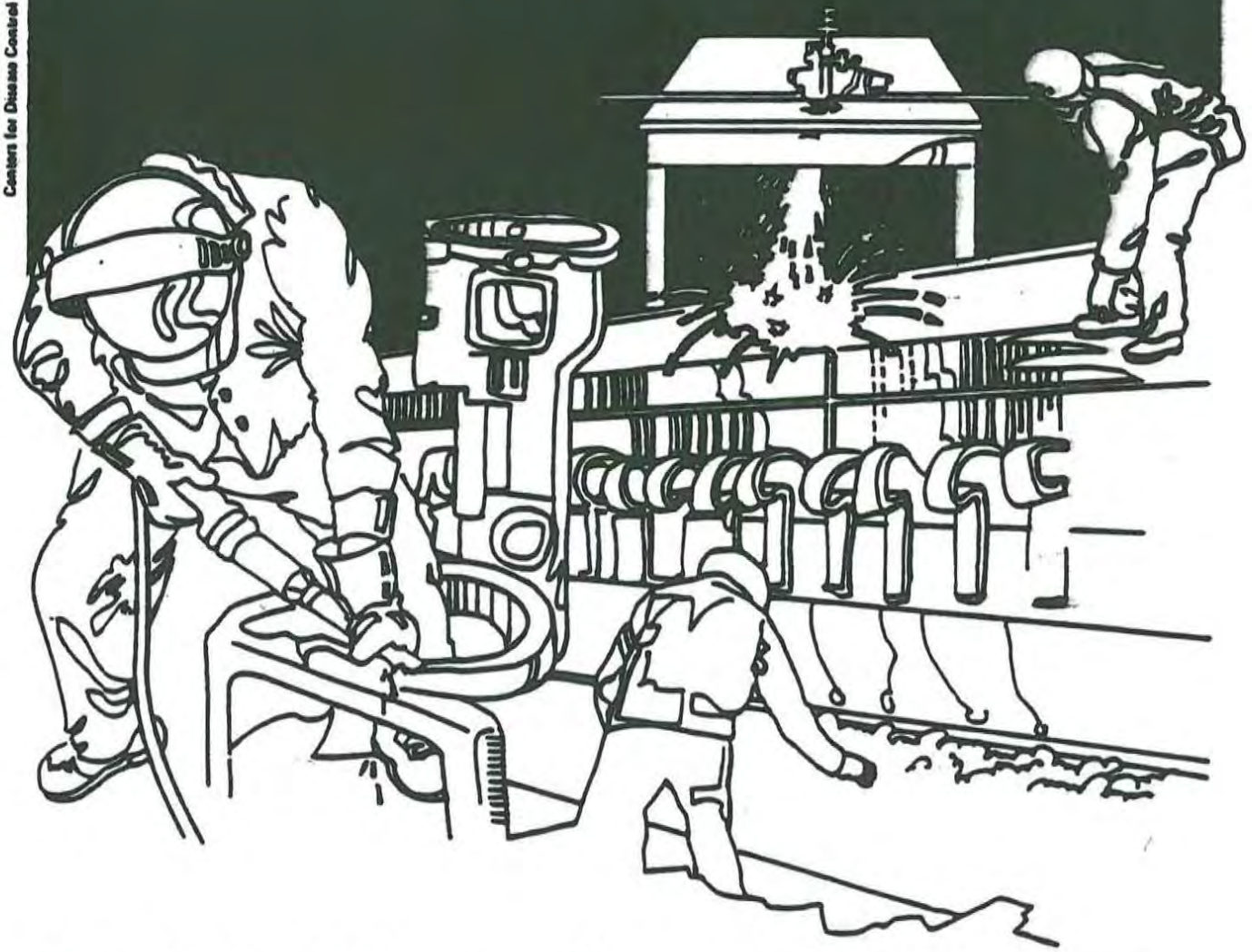

Health Hazard Evaluation Report

HETA 84-415-1688
PRECISION CASTPARTS CORPORATION
PORTLAND, OREGON

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.

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PRECISION CASTPARTS CORPORATION
PORTLAND, OREGON

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I. SUMMARY

In June, 1984, the National Institute for Occupational Safety and Health (NIOSH) received a request to conduct a Health Hazard Evaluation of possible reproductive effects among male workers exposed to the solvent 2-ethoxyethanol (2EE) at the Precision Castparts Corporation in Portland, Oregon.

2EE is used in a binder in the preparation of ceramic shells used to cast precision metal parts from wax molds. Approximately 80 male workers engaged in this process are potentially exposed to 2EE. An industrial hygiene survey conducted by NIOSH in April and June, 1984, showed full-shift breathing zone airborne exposures to 2EE ranging from non-detectable to 23.8 ppm. Because of the potential for skin exposure to 2EE, urine measurements of the metabolite of 2EE, ethoxyacetic acid (EEA), were also conducted among potentially exposed men, showing urine excretion of EEA ranging from non-detectable to 163 µg/g creatinine. Blood samples were also collected from a few workers to determine 2EE concentrations but analysis of all samples revealed non-detectable levels.

In June, 1984, NIOSH conducted a cross-sectional evaluation of semen quality (sperm concentration, pH, volume, viability, motility, velocity and morphology) among 37 men exposed to 2EE. The evaluation included a comparison group of 38 men elsewhere in the plant who were not exposed to 2EE. A questionnaire to determine personal habits, medical and work histories and a brief examination of the urogenital tract were also administered.

The average sperm count per ejaculate among the 2EE - exposed workers was significantly lower than that of the unexposed group (113 v. 154 million sperm per ejaculate; $p < 0.05$) after consideration of abstinence, sample age, subjects' age, tobacco, alcohol and caffeine use or history of urogenital disorders, fever and other illnesses. Further, it should be noted that the average sperm concentrations of both groups were lower than the average for other occupational populations studied by NIOSH researchers; for 2EE - exposed workers, this difference was statistically highly significant ($p < 0.001$).

The two groups did not differ significantly with respect to other semen characteristics or testicular size; consideration of other factors which could affect semen quality did not alter these results.

Based on the results of this study, NIOSH investigators conclude that there is a possible effect of 2EE on sperm count among these workers, although the possibility that other factors may be affecting the semen quality of boththe exposed and unexposed workers in this study cannot be ruled out. Given the known testicular toxicity of 2EE in animals, the limiting of exposure to 2EE to the fullest extent feasible is recommended as a prudent course of action. Recommendations for environmental and medical surveillance follow-up are incorporated in Section VIII of this report.

Keywords: SIC 3369 Cellosolve CAS # 110-80-5.
2-ethoxyethanol; ethylene glycol monoethyl ether
2-ethoxyacetic acid; metal casting
semen quality; reproductive health.

II. INTRODUCTION.

On June 15, 1984, the management of the Precision Castparts Corporation at Portland, Oregon, submitted a Health Hazard Evaluation request regarding a possible reproductive health hazard to male workers potentially exposed to 2-ethoxyethanol (2EE) in the binding slurry used in the preparation of ceramic shells used to manufacture metal parts from wax molds. An industrial hygiene survey conducted during a previous site visit in April, 1984, had demonstrated full shift breathing zone exposures of up to 19 ppm (mean 9 $\pm$ 5.6 ppm). Due to concern regarding animal evidence of impaired spermatogenesis and infertility and testicular atrophy due to 2EE, NIOSH investigators conducted a cross-sectional evaluation of semen quality among volunteers from exposed workers and a comparison group of unexposed workers. The field study was conducted between June 18-29, 1984.

III. BACKGROUND.

Description of Process and Workforce

Precision Castparts Corporation, first incorporated in 1956, is located on two separate sites in the vicinity of Portland, Oregon. The company is principally engaged in manufacturing precision cast parts including pumps, compressors, turbochargers and devices for surgical bone repair and replacement at three separate facilities. The Clackamas plant (Building A) is the newest and most automated plant where smallcastings are made. The Portland plant (Building B) is the original facility and primarily manufactures large castings. The Titanium plant (Building C) is a recently remodeled building dedicated to the manufacture of titanium castings.

Investment casting, also called the "lost wax" process, begins with a wax replica of the part which is to be cast in metal. The wax replica is prepared by injecting wax under pressure into a die machined by the tool and die department. A wax replica must be prepared for each final cast part produced. The smaller wax replicas are assembled into "trees" or clusters to ease handling of large quantities of small parts. Larger wax parts are handled individually.

The wax replicas serve as molds for preparing a ceramic shell used to cast the metal part. The shells are made by repeatedly immersing the mold in a binder slurry composed of approximately 50% ethanol and 50% 2EE and dipping it in a sand shower to build up a thick shell on the outer surface of the wax. Between dips, shells are suspended from an overhead conveyor system or stored on open racks in the investing room to dry. Fans are used to keep the room air in constant motion. The air is conditioned for temperature and humidity control and recirculated by a large air handling system.

After the desired thickness of ceramic shell is achieved, the next step is to remove the wax from the shell in a steam autoclave. Then the shells are heated to condition them for the pour of molten metal. After pouring, shells are cooled and removed from the newly formed metal part. Cast parts are cleaned and repaired as necessary following several inspections.

Approximately 80 male workers are employed in the investing departments at each of the three sites where ceramic shells are prepared from wax molds and dried and are potentially exposed to 2EE. These include men engaged in the making up of the binder slurry, hand dippers and grabber operators who dip the wax molds in the slurry, shell processors who prepare and handle the ceramic shells, supervisors, and process engineers who regularly enter the investing rooms. All of these workers are potentially exposed to airborne levels of 2EE by inhalation due to evaporation of 2EE from the binder slurry tanks and drying shells; it is circulated throughout the investing department room by the fan and air conditioning system designed to promote drying. There is also the potential for absorption of airborne 2EE vapor through the skin. A proportion of these workers, principally those engaged in the making up of the binder slurry and the hand dipping of molds, also have the opportunity for skin exposure through splashes and spills. Gloves were worn by some workers, but no other personal protective equipment or respirators were used.

IV. EVALUATION DESIGN AND METHODS

A. ENVIRONMENTAL

Air samples were collected and analyzed in accordance with NIOSH Method 1403 (1). Two types of sampling pumps were used. MDA Accuhaler^{tm} pumps were used for most samples operating at 50 ml/min as recommended (1). To ensure a greater likelihood of detecting 2EE in various areas of the plants, a few samples were collected at higher flow rates to achieve a larger sampling volume and thus a larger quantity of contaminant on the sample media. For these samples, DuPont P 200^{tm} pumps were used at a flow rate of 200 ml/min.

Most samples were breathing zone (BZ) samples collected by attaching the sample media to the worker's collar. The pump and tube were connected by a length of tygon tubing for comfortable positioning of the pump on the worker's belt after looping the tubing across the worker's back.

Blank and spiked samples were prepared on this survey as a check on field practices and laboratory performance. Spiked samples were prepared in the field by injecting a known quantity of 2EE directly onto the sample media using a microsyringe. As an additional check, the NIOSH quality control laboratory in Cincinnati provided precision spikes for inclusion with the field samples and laboratory samples.

Air samples were collected in all three plants. At least one full shift personal breathing zone sample was collected for each specific job title in the investing department. Samples were repeated on at least two separate work days. Area samples were collected in areas where unique exposure levels were expected. No short term personal samples were collected since the nature of the process did not indicate any likelihood of sudden releases of 2EE or other sources of peak exposure. All samples were analyzed by gas chromatography (1).

Since studies of 2EE exposure in animals have shown that the parent compound can be detected in blood and its metabolite (2 ethoxyacetic acid) in urine (2), both blood and urine samples were collected in this study. Five ml blood samples were collected one time at the end of a work shift, using vacutainers equipped with disposable needles. Blood samples were chilled (not frozen) and hand carried to the laboratory for analysis. Spot urine samples were collected in 200 ml plastic bottles which participating workers marked at the time of void. A portion of the urine was transferred to 20 ml scintillation vials and frozen for shipment to the laboratory for analysis. Samples were analyzed as described in Smallwood et. al. (2).

B. MEDICAL

1. Selection of Participants.

Exposed Subjects: Personnel lists of all workers at each of the three plants were made available to NIOSH investigators at the beginning of the field study. In cooperation with the plants' industrial hygienist, all male workers who could be potentially exposed to 2-ethoxyethanol (other than occasionally) were identified. Each man (a total of 79 available at the time of the study) was given a personal confidential interview by a NIOSH investigator to describe the purpose of the study and the medical procedures to be used and to solicit participation. Six workers were ineligible due to vasectomies or employment in one of the

above job categories for less than one month. Fifty eligible potentially exposed men (68%) agreed to participate of whom 37 provided semen samples (50% of the men eligible for study).

Unexposed Workers.

Randomly selected workers from elsewhere in the plant, including workers in the wax mold preparation and metal casting departments, x-ray and finishing departments quality controllers and process engineers, were interviewed to solicit participation. (Due to time constraints, it was not possible to systematically interview all unexposed workers randomly selected from personnel lists.) Fifty of approximately 150 unexposed men interviewed agreed to participate, of whom 39 (26%) provided semen samples. Men who had previously worked in the investing department (i.e. with previous potential exposure to 2EE) were excluded.

C. Questionnaire, Physical Examination and Semen Collection.

Each participant was given a detailed consent form and questionnaire by personal interview to provide data on demographic characteristics, personal habits (including tobacco, alcohol and caffeine consumption), medical history, work history and history of current and previous exposures to chemical and physical hazards. Participants underwent a brief physical examination concentrating on the urogenital tract and were given a coded, clean glass jar and thermos with verbal and written instructions on the method of semen sample collection. Subjects were asked to provide a semen specimen at home by masturbation into the jar, after a minimum of two days of sexual abstinence, and to bring the sample in the thermos to the workplace within an hour of collection. The date and time of ejaculation, abstinence period and spillage (if any) were recorded by the subject on the jar label.

D. Semen Analysis Methods

Semen analyses were conducted in two phases. Video recordings, viability assessments, sperm counts, volume and pH measurements, fixation of slides and cryopreservation of seminal plasma were conducted at the field study location. Morphology and morphometry analyses of slides and motility and velocity analyses of video tapes were conducted at the NIOSH laboratories. All samples were processed and analyzed in blind fashion by the investigators.

1. Sperm Velocity and Motility

Seven microliters of the semen sample were placed on a glass microscope slide and covered with a glass coverslip. The sample was placed on a microscope stage warmed to 37°C by a heat curtain (Model #ASI 400, Nicholson Precision Instruments, Bethesda, Maryland). Five to eight fields selected arbitrarily were video recorded using a 25x phase objective (Carl Zeiss Inc., NY). The video equipment consisted of a Panasonic NV 8200 video recorder, time-date generator (Panasonic WJ-810), vertical enhancer (Hitachi VE 102), MTI black and white high resolution camera and Hitachi high resolution monitor (model VM 1290). The individual sample number was voice recorded concurrently on the videotape. The time from ejaculation to videotaping (sample age) was recorded. Video tapes were analyzed using a Zeiss Videoplan (Carl Zeiss Inc., NY) semiautomatic image analysis system with video overlay and digitizing tablet. For sperm velocity measurements, thirty motile sperm from each sample were randomly selected and the path of each was traced according to Albertson et. al. (3). The start and stop times (to the nearest 0.01 second) for each tracing were recorded and superimposed on the videotape.

Sperm velocity estimates involve two approaches; velocity along the actual sperm path and straight line (point to point or distance) velocity (4, 5). The ratio of path length velocity to distance velocity, termed the forward progression ratio, can be used to describe the motility pattern of the sperm. The ratio is a number between 0-1, where numbers closer to 1 indicate a more linear progressive path. The software of the microcomputer permitted calculations of path length and distance velocity and forward progression ratio of each tracked sperm.

The percentage of motile sperm was determined by marking all sperm observed in one video frame, then advancing the video tape to identify motile and non-motile sperm. This process was repeated for a minimum of five fields, so that an average of 200 sperm were scored.

2. Semen pH and Volume

The pH of the semen sample was determined using an Orion (model 701) pH meter equipped with a gel filled plastic pH electrode (model E-5M, Fisher Scientific). The volume was measured using a 5 ml plastic disposable syringe.

3. Sperm Morphology and Morphometry

Four air-dried smears were prepared from each whole semen sample, fixed in absolute ethanol for ten minutes, and stored for later analysis. Air-dried slides were stained in Papanicolau stain according to the WHO semen analysis guidelines (6). Sperm morphology was scored according to Zaneveld and Polakoski (7), reading 200 cells on each of 2 slides. The remaining two slides were used for objective analysis of sperm head shape (morphometry) using the Videoplan system (8). A 63x dry objective and HMI video camera with a 4x enlarger were used to evaluate 100 sperm on each of 2 slides. Individual sperm heads were outlined using the digitizing tablet and the microcomputer software allowed calculations of area, perimeter, length, width, width/length ratio, and 4pi (area)/perimeter^2 (Pi factor) as indices of sperm head shape.

4. Sperm Viability

Viability by stain exclusion [modified from Eliasson and Treichl (9)] was determined by mixing 100 µg of semen with 100 µl of 0.5% (w/v) eosin y stain in Tyrodes buffer (Difco). Seven µl of this suspension were placed on a microscope slide and 200 sperm were counted and classified as unstained (viable) or stained (nonviable). Viability by hypoosmotic swelling (10) was analyzed by mixing 100 µl of semen with 1.0 ml of a solution containing 150 milliosmolar sodium citrate and 150 milliosmolar fructose. After an incubation of at least 30 minutes, (after which further swelling does not occur), 7 µl were placed on a slide, and 200 sperm were classified as swollen (viable) or unswollen (nonviable) using differential interference contrast (DIC) microscopy.

5. Sperm Concentration

100 µl of semen were mixed with 100 µl of distilled water. Five microliters of this suspension were placed on a Makler Chamber (Sefi-Medical Instruments Haifa, Israel) and the sperm were counted using DIC microscopy. Replicates were prepared and counted for each sample.

D. Statistical Analysis

Data for each semen characteristic were tested for normality using the Shapiro-Wilk statistic for samples sizes of less than 51 (11).

A square root transformation was used for sperm concentration, and logistic transformations for proportions, i.e. percentage motility, viability and normal sperm morphology. Data for exposed and unexposed groups were compared using a two-sided t test. The presence of factors associated with semen characteristics and with exposure that may distort comparisons using the t-test were tested using a multiple linear regression model. This multivariate technique determines the ability of exposure and other variables to predict the outcome measure (semen characteristic).

In the case of abnormal sperm morphology classifications, data were analyzed using the FUNCAT procedure (12) which permits multivariate modeling of categorical frequency data and produces approximate chi-square statistics.

V. EVALUATION CRITERIA

A. ENVIRONMENTAL

The Occupational Safety and Health Administration (OSHA) has promulgated an 8 hour time weighted average permissible exposure limit (PEL) of 200 ppm for 2EE (13). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Threshold Limit Value (TLV) of 5 ppm (14). Both the OSHA PEL and the ACGIH TLV bear the "skin" notation indicating the potential for absorption of toxic amounts of 2EE through the intact skin (see also ref. 15). NIOSH does not recommend a specific air concentration standard for 2EE, but recommends that exposure be reduced to the lowest extent feasible (16).

B. TOXICOLOGICAL

2EE is one of a family of glycol ethers, several of which have been shown to produce adverse reproductive effects in both male and female animals (16). With respect to the male reproductive toxicity of 2EE, testicular atrophy and microscopic testicular changes (including degeneration of seminiferous tubules and damage to dividing spermatocytes and spermatids) have been reported in rats given 900 mg/kg 2EE in the diet for two years (17); in rats and dogs treated orally with 186 mg 2EE kg/day for 13 weeks and rats given 372 and 744 mg 2EE/kg/day subcutaneously for four weeks (18); in

rats dosed orally with 460-1000 mg 2EE/kg/day orally for 11 days (19, 20); in mice given 1000-2000 mg/kg/day orally for five weeks (21) and in rabbits exposed to 400 ppm 2EE (6 hr/day, 5 days/week) by inhalation for 13 weeks (22).

Oudiz et al (23) intubated rats with 936, 1872 and 2808 mg 2EE/kg for five days and analyzed semen at periods ranging from 1-14 weeks after cessation of dosing, and found azoospermia or severe oligiospermia among the two highest dose groups and a significant increase in abnormal sperm morphology in the lowest dose group by the seventh week. Partial or complete recovery of sperm counts and morphology were observed by the fourteenth week. Finally, Lamb et al (24) found dose related decreases in sperm motility, an increase in the percentage of morphologically abnormal sperm and decreases in testicular weight in mice given 1-2% 2EE in their drinking water for 14 weeks. A significant reduction in fertility (number of live pups per litter) among untreated females mated with the males treated with 2% 2EE was also observed.

Based on the animal evidence of the reproductive toxicity of 2EE, NIOSH has recommended that the current OSHA PEL of 200 ppm (8 hour TWA) be reexamined and that exposures to 2EE be reduced to the lowest extent feasible (16).

There are no previous studies of the reproductive effects of 2EE in humans.

VI. RESULTS

A. ENVIRONMENTAL

Air Samples

The results of the spiked samples for the April and June surveys are shown in Table 1. For the April survey, the spiking data are divided into three sets. In order to investigate the possibilities of losses in analyte recovery (since 2EE is known to be unstable on the sampling media), a local laboratory was selected to analyze two spiked samples and a blank sample. The local laboratory was near the plant and was frequently used by the plant for analysis of their routine industrial hygiene samples. This set was analyzed overnight following the first day of sampling (labeled 'overnight analysis' samples in Table 1). Two additional sets of spiked samples were prepared for shipment along with the field samples; one set prepared in the field ('field spikes')and one set prepared before the survey by chemists at the NIOSH laboratories ('QC spikes'). These spiked samples were labeled identically as field samples, frozen, and shipped to the NIOSH analytical laboratory for routine analysis. Analysis was completed approximately six weeks later.

The results indicate considerable variability in analyte recovery due in part to time in shipment and handling as well as spiking technique. The two spikes analyzed overnight on-site reflect an average recovery of 150%. The field spikes showed average recoveries below 100%. The analysis of the three QC spikes (prepared under laboratory conditions) resulted in a consistent 60% recovery. These results, while highly variable, suggest that recovery of analyte from field samples (shipped to an analytical laboratory and stored for extended periods) will be less than 100% and as low as 60%. The spiking data was not used to correct any of the actual exposure measurements, but these data suggest that the exposures reported in these surveys could be significantly higher than the results shown.

All of the blank samples (not exposed to 2EE but handled as field samples) were analyzed as non detectable. Thirteen blank samples were submitted for analysis, five in the April survey (one blank was sent to the overnight laboratory) and eight in the June survey. The absence of any detectable quantities of 2EE on the blank samples confirms the absence of contamination either in preparation, shipping, and laboratory analysis.

Full shift time weighted average area (bulk air) samples were collected to investigate general background levels of 2EE in major working locations where 2EE was in use (Table 2). In the April survey, two of three buildings were investigated; while in the June survey all three buildings were sampled. In the April survey (when 2EE was in full use in all plants), the highest levels, approaching 20 ppm, were found in the investment rooms of both buildings where open tanks of 2EE slurry were located. Concentrations of 2EE were higher in Building A than Building B, due to the physical features of the buildings. Building A is a newer building where the investment room is tightly closed and conditioned air provided by a modern air handling system. As expected, investing room exposures at both buildings were generally higher than chemical storage and mixing areas, where 2EE was not in daily use and storage drums were tightly closed.

During the June survey, 2EE use was suspended in Buildings A and C (although some trace quantities of 2EE were still in the process stream). The concentrations in Building A clearly declined after 2EE was discontinued. Sampling in Building C also reflected a reduction in 2EE concentration, although in both buildings, individual area samples ranged as high as 28 ppm and 14 ppm, respectively, after the suspension of 2EE. These high measurements may have reflected placement of area samplers near single point sources of 2EE which had not yet been eliminated.

As expected, the background area sampling in Building B revealed concentrations in the June survey similar to results found in the April survey. The use of 2EE in this building was not discontinued and production was continuing at a similar level.

The personal exposure data demonstrates exposures similar to the area bulk air samples (Table 3), especially in Building A which is a relatively new, tightly closed building. Hand dippers appeared to have the highest exposures of the job categories sampled. These workers spent the entire day dipping small molds by hand into open slurry tanks, then inserting wet molds into a sand shower to build up the shell covering over the wax replicas. Hand dipping was done only in Building A, where small parts were processed. Large parts were processed at Building B where parts were handled with forklift trucks (auto shell processor) and dipping was performed by robot dipping machines (grabber operators).

Utility investor and shell processor exposures were less than those for hand dippers. Utility investors prepare and check the slurry during the work shift. Periodically during the day, these workers would approach slurry tanks and dip out a small quantity for testing, but did not spend the entire day directly adjacent to a slurry tank. Shell processors were responsible for handling finished ceramic shells and rarely approached the open slurry tanks.

Exposures were generally less at Building B than Building A. This result is seen in both area bulk air samples and personal samples. As noted earlier, this difference was most likely due to construction differences between the buildings. Building A is newer and tightly built with a closed ventilation system. Also, the investment department at Building A is physically isolated from the remainder of the building. At Building B, outside doors were typically left open to encourage cross ventilation and all departments were interconnected.

Biological Samples

In the April survey, seventeen (17) blood samples were collected from individual workers in Building A. Nine (9) exposed workers and four (4) controls participated by providing at least one blood sample. Four (4) exposed workers provided two samples each (two vials of blood from the same needle stick) for replicate samples. All blood samples were analyzed for parent compound (2EE) by an experimental method which has not been previously attempted as a method for estimating 2EE exposures in humans (2). In the animal experiments used to develop the method, 2EE was applied directly to the skin. None of the workers who submitted blood samples reported any direct skin contact with 2EE and exposure was deemed to occur only by inhalation or from airborne vapor condensing on the skin.

The analysis of the blood samples revealed no detectable levels of 2EE in any of the field samples submitted. As a part of the analysis of the submitted samples, the laboratory prepared spiked blood samples for a recovery study. The results of five spiked samples (spiked at 25 µg 2EE/g blood) averaged 100 % recovery, suggesting that the method was in control at that level. The limit of quantitation (LOQ) of the method was established in previous studies, and for reporting purposes, the results of controls and exposed worker samples are expressed as less than the LOQ, or less than 10 µg 2EE/g blood.

Urine monitoring did reveal positive evidence of 2EE absorption (Table 4). In the April survey, individual urine voids were collected from three (3) exposed workers and two controls (Building A) as voided throughout a 24 hour sampling period. The number of voids varied from worker to worker. The total urine volume voided by each individual during the 24 hour study period is tabulated. The two hand dippers and the supervisor reported in Table 4 are the same workers whose personal breathing zone exposures were reported in Table 3 (April survey). The control subjects were workers who were employed outside of the investment department where there was no source of exposure to 2EE.

The EAA concentrations in urine for the exposed workers were observably different from the controls (no statistical testing was attempted with these few data points). Furthermore, the hand dippers' results are higher than the supervisors' results, suggesting agreement with the environmental sampling reported in Table 3.

In the June survey, additional urine samples were collected from cooperating workers in Building B with the intent of studying variation over an extended period. These samples were spot samples collected over a seven day week. While some workers agreed to give one sample, seven workers agreed to provide multiple spot samples throughout the week. The logistics of worker cooperation, sample collection and handling prevented more frequent sampling or sampling from more individuals. The goal of the extended sampling was to determine if trends in the concentration of EAA in urine occurred either during a work shift, or over a work week.

In the seven cooperating workers, it is possible to examine trends during shifts and over the work week. Results for the investment room supervisor, who was in and out of the investment department, were variable, but generally lower than workers who remained in the investment department continually. Grabber Operator 1 (the worker who provided the most samples) submitted samples which reflected increases during a given shift; although no pattern was evident during the work week. The worker with the highest urine concentrations (grabber operator 2), was observed cleaning slurry

containers the night before the urine samples were submitted. None of the samples submitted by control subjects contained detectable concentrations of EEA in submitted samples. A few spot samples were collected from workers in Buildings A and C (where 2EE use was suspended) and most of these urine samples contained no detectable concentrations of EEA. For the few urine samples from these workers with detectable amounts of EEA in urine, the concentrations were all below 8 mg EEA per gram creatinine (which is close to the limit of detection of the analytical instrumentation). The trace quantities found in these urine samples corresponds to trace levels of 2EE found in the environmental samples; while the plant had eliminated 2EE use in these buildings, some evidently remained in the process stream.

B. MEDICAL

Characteristics of the groups

The characteristics of the exposed and unexposed groups determined by questionnaire and physical examination were generally similar (Table 6). [Note: One unexposed subject was found to be severely oligospermic; on physical examination, the cause was determined to be small testicular size unrelated to occupational factors. This subject was eliminated from further analysis. Three exposed men declined the physical examination.]

Exposed subjects ranged from 19-45 years of age (mean 30.1 $\pm$ 7.0 years); unexposed subjects ranged from 21-58 years of age (mean 30.3 $\pm$ 7.5 years). The mean ages of the two groups were not significantly different. All subjects (except one unexposed man) were white. The average duration of employment at the company was 5.2 years (range less than 1 to 20 years) for unexposed men and 7.3 years (less than 1 to 19 years) for exposed men. The average duration of potential exposure to 2EE among the exposed group (excluding prior periods of employment in parts of the plant where 2EE was not used) was 4.9 years (range less than 1 year - 18.5 years).

The two groups did not differ significantly with respect to alcohol, caffeine, cigarette or prescription medication consumption or history of recent fever, urogenital disorders or other medicalconditions which could affect normal spermatogenesis (Table 6). Eleven exposed and 6 unexposed men had evidence of a mild varicocele on physical examination.

The mean testicular sizes of exposed and unexposed subjects were 20.7/21.5 and 21.1/22.1 ml (left/right) respectively and did not differ significantly between the two groups. The average number of days of sexual abstinence and time from ejaculation to semen analysis did not differ significantly between the two groups.

Semen Analysis

The mean semen volume and sperm concentration among the exposed group were lower than among unexposed workers, but the differences were not statistically significant before or after correction for the effect of other factors that could affect semen quality and which differed between the two groups (Table 7). The sperm count per ejaculate, however, [calculated as sperm concentration (millions/ml) multiplied by semen volume (ml)] was marginally significantly lower among 2EE - exposed men ($p = 0.047$) after consideration of other factors. The proportion of men with oligospermia (a sperm concentration of 20 million/ml or less) was higher in the exposed group than in the unexposed group (16.2% v. 10.5%) but this difference was not significant ($p = 0.516$ by Fisher's exact test) (Table 7). Similarly, no significant differences between exposed and unexposed men were found with respect to measures of sperm pH (Table 7), sperm viability, percentage motility or velocity (Table 8) the overall proportion of sperm with normal morphology (oval heads and normal tails) (Table 9) or morphometry (Table 10), after adjustment for significant confounding variables where specified in the tables. (In the case of sperm viability, motility, velocity morphology and morphometry, none of the independent variables included in the regression models were significant confounders).

In the case of abnormal sperm forms, exposed men had a significantly lower proportion of double headed sperm and a significantly higher proportion of immature forms ($p = 0.001$ was taken as an acceptable level of significance for the chi square test used in this FUNCAT procedure).

No effect of duration of exposure (calculated as the total number of months of potential exposure to 2EE) on the various semen characteristics was observed when a test for linear trend was performed. It should be noted, however, that a number of currently exposed workers had not had continuous potential exposure to 2EE since the start of employment due to periods spent in other departments or lay offs. Workers with potentially higher exposure to 2EE through skin contact, i.e. hand dippers and slurry preparers ($n = 10$) were also compared separately to workers with potentially lower exposure and unexposed men in the regression analyses. No differences in semen characteristics due to potential intensity of exposure were observed; the number of workers in each exposure group may, however, be too small to detect an effect.

VII. DISCUSSION

These data indicate a statistically significant decrease in the mean sperm count per ejaculate among workers exposed to 2EE compared to unexposed workers from the same plants. No statistically significant differences in semen volume, sperm concentration, semen pH, viability, motility, velocity and normal morphology were observed between exposed and unexposed men. These results did not change when the potentially confounding effects of abstinence, sample age, caffeine, alcohol and tobacco consumption, urogenital and other medical disorders and other factors were considered. The two groups differed with respect to the proportion of certain categories of abnormal sperm shapes, exposed men having a significantly higher proportion of immature forms and a lower proportion of double - headed forms. (Note that the acceptable level of significance for this analysis is $p < 0.001$ as discussed above.) It is possible that these differences may be due to 2EE exposure or to factors affecting both the exposed and unexposed group. In view of the small absolute differences in these proportions, and the lack of consistency of an exposure effect, however, there is insufficient evidence from these data to conclude that 2EE adversely affects sperm morphology in this group. No effect of duration of 2EE exposure on semen quality was observed.

There are a number of methodological and biological considerations which should be taken into account in interpreting these results. A highly conservative approach to the statistical interpretation of data where multiple tests are compared is to make a downward adjustment of the acceptable level of significance based on the number of comparisons made. In such a case, the effect of 2EE exposure on sperm count could be considered to be of borderline or no significance. Leaving aside strict statistical interpretations, however, the fact that the effect of exposure on semen volume, sperm concentration and count, and the proportion of oligospermic men is consistently in the direction hypothesized supports the view that 2EE may affect spermatogenesis and, less certainly, seminal fluid production. (See also comparison with other occupational groups, below).

The number of subjects studied may limit the ability to detect small changes in certain semen characteristics due to exposure even if underlying differences are present. Our sample of 37 exposed and 38 unexposed men was sufficient to have had an 80% chance of detecting an approximately 39% or greater decrease in mean sperm concentration compared with the adjusted mean for the unexposed group of 53 million/ml. For semen volume, our sample size permitted an 80% chance of detecting at least an approximately 20% decrease in volume compared with the adjusted mean of 3.0 ml in the unexposed group. Similarly, for sperm motility and velocity, an approximately 26 and 10% difference (respectively) could have been detected; for the proportion of normally

shaped sperm, an approximately 15% difference could be detected in exposed workers. Thus, the possibility that smaller true differences in semen characteristics exist between the groups cannot be determined with confidence in this study population.

It is possible that the results of the study may be biased if systematic differences exist between the two groups with respect to participants and nonparticipants; for example, if men with suspected reproductive problems were more likely to participate in the exposed group than the unexposed group or vice versa. All potentially exposed men were interviewed in the same manner to solicit participation and volunteers for the comparison group workers were recruited randomly from the pool of unexposed workers, which minimized the possibility of systematic bias at the sample selection stage. There were no clear differences between participants and nonparticipants in the exposed group for demographic characteristics for which information was available to the investigators. (Inadequate information on unexposed nonparticipants was available). Further, the reasons given for not participating were generally unrelated to factors which may potentially affect semen quality.

Finally, the question arises as to whether a possible effect of 2EE on certain semen characteristics may not have been observable at the time of the study due to recent withdrawal of the use of 2EE in two of the three buildings. As the data in Table 2 indicates, the airborne levels of 2EE were lower in Building A at the time of the semen study (June) than in April (approximately 3 ppm vs. 17 ppm), and were comparable to those in Building C, where 2EE use was also suspended. In contrast, air levels in Building B, where 2EE use had not yet been discontinued, were similar at both sampling dates (approximately 11 and 15 ppm respectively). Since, however, this reduction in potential exposure occurred within the average length of a spermatogenic cycle (of approximately 70 days), it is likely that an effect on semen quality would still be observable at the time of study, even assuming complete reversibility of a putative effect.

Of greater concern in the present study, however, is the possibility that the semen quality of both groups in the plant may be affected. The pooled mean sperm concentration among unexposed workers previously studied by NIOSH researchers (termed hereafter 'historical controls') is 71 million/ml (n=104), which is similar to reported values from other occupational and non-occupational populations. (For example, Steinberger and Rodriguez-Rigau (25) calculated the average 'normal' sperm concentration to be 70 million/ml, based on data on several large populations of allegedly fertile U.S. males.) This mean may be compared to the mean sperm concentration of 60 million/ml (unexposed group) and 48 million/ml (2EE exposed group) in the present study. The difference between the mean sperm concentration of the group exposed to

2EE and historical controls is highly significant ($p < 0.001$ using square root transformation of the data and adjusting for abstinence); the mean sperm concentration for unexposed workers in this study is also significantly lower ($p = 0.040$) than that of the historical controls. Further, the proportion of men with oligospermia (sperm concentrations $\leq$ 20 million/ml) in the 2EE - exposed group is significantly higher than among historical controls (16.2% vs. 3.9%, $p = 0.021$ by 2-sided Fisher's exact test), although not for unexposed workers in this study (10.5 vs. 3.9%, $p = 0.207$). Thus, if the sperm concentrations of both groups in this study are adversely affected by occupational or other factors which could not be addressed directly in the present study, it may not be possible to distinguish a specific effect due to 2EE alone given the limited sample size and large interpersonal variations in this characteristic. The mean values for other semen characteristics (i.e., sperm viability, motility, velocity, morphology) were not significantly different from those of the historical controls measured using identical methodologies.

In conclusion, our findings suggest a possible effect of 2EE exposure on semen quality in these workers. In view of the low sperm concentrations observed in both groups and particularly among 2EE-exposed workers, it is possible that control workers are or have in fact also been exposed and affected by 2EE or that some other, unknown, agent(s) is affecting both groups. Given the toxicological evidence which clearly demonstrates the testicular toxicity of 2EE in a number of species, prudent interpretation of the results of this semen study would suggest strictly limiting exposure. Confirmatory studies in other populations would be useful.

VIII. RECOMMENDATIONS.

A. The withdrawal of the use of 2EE in the slurry mix is recommended as a prudent preventive measure. Efforts should be made to ensure that the acute toxicity, carcinogenicity and reproductive toxicity of substitution products be evaluated prior to their introduction, and that toxicity information be made available to employees.

B. Due to concern regarding the sperm concentrations observed among employees, and particularly among 2EE exposed men, it would be advisable to assure that there is no continuing problem by monitoring the incidence of reproductive problems (in particular infertility) among these workers. If follow-up monitoring indicates an increased rate of infertility or adverse reproductive outcomes, further medical testing of workers, which might include reevaluation of semen quality, would be advisable.

C. The personal protective equipment (PPE) program at Precision Castparts Corp. should be evaluated. Workers were observed in investment rooms with varied types of clothing. Since high concentrations of solvents are present (with possible skin absorption properties), long sleeved coveralls are recommended for all workers. These garments should be laundered regularly and not worn home. Gloves are currently in use by most employees in the investment departments, but the permeability of the glove material to the solvents in use should be evaluated. Damaged and/or saturated gloves should be replaced. Shoes can become saturated with solvents and can be a source of exposure for solvents absorbed through the skin. Shoes should be examined periodically and replaced if saturated. Employees who work with concentrated solvents (e.g., while mixing slurry) should wear a properly fitted, approved respirator.

D. The functioning of the ventilation systems in all investment rooms should be evaluated. In the newest building (with the most modern air handling system), 2 EE concentrations were highest, suggesting that the current system increases levels of solvent in the workroom air. One method of reversing this result is an investigation of the current filtration media. More efficient filtration media (if available) should be substituted, or saturated media should be replaced more frequently. An increase in make-up air could dilute solvent concentrations (although this step may be expensive since make-up air must be tempered and dehumidified). The ventilation system in the investment room in the oldest building is inadequate. Employees typically leave outside doors open to encourage natural ventilation with unsatisfactory results.

E. A continuous program of industrial hygiene assessment should be instituted for the investment departments. Since solvents are used in large quantities (with unknown health consequences), frequent sampling for exposures is essential. Where available, biomonitoring methods should be employed (blood, urine sampling). With solvents such as 2EE, skin absorption is a more likely route of exposure than inhalation and air sampling is inadequate for estimating skin absorption accurately.

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Copies of this report are currently available upon request from NIOSH, Division of Standards Development and Technology Transfer, Publications Dissemination Section, 4676 Columbia Parkway, Cincinnati, Ohio 45226. After 90 days, the report will be available through the National Technical Information Service (NTIS), 5285 Port Royal, Springfield, Virginia 22161. Information regarding its availability through NTIS can be obtained from NIOSH Publications Office at the Cincinnati address. Copies of this report have been sent to:

1. Precision Castparts Corporation
2. NIOSH, Region X
3. OSHA, Region X

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

TABLE 1

RESULTS FOR SPIKES AND BLANKS

	No. of Samples (N)	Avg. Recovery (%)
April 1984 Survey		
Overnight analysis	2	150
Field Spikes	4	69
QC Spikes	3	60
Blanks	4	0
June 1984 Survey		
Field Spikes	14	86
Blanks	8	0

TABLE 2
RESULTS FOR FULL SHIFT AREA SAMPLES
(ppm)

Location	April 1984 Survey			June 1984 Survey		
	gm	gsd	n	gm	gsd	n
Building A:						
Investment room	16.9	(1.0)	(3)	3.0	(6.8)	(3)
2EE mix/stg. rooms	4.8	(2.0)	(2)	na		
Building B:						
Investment room	10.7	(1.3)	(3)	14.9	(1.0)	(4)
2EE mix/stg. rooms	6.6	(1.4)	(4)	na		
Building C:						
Investment room	na			2.4	(5.5)	(5)

Notes: gm = geometric mean
gsd = geometric standard deviation
n = number of samples
na = not applicable or not sampled

TABLE 3
RESULTS FOR FULL SHIFT PERSONAL SAMPLES
(ppm)

Location	April 1984 Survey	June 1984 Survey
	gm gsd n	gm gsd n
Building A:		
Hand dipper	14.5(1.2)(5)	na
Shell processor	3.0(4.7)(2)	na
Utility Investor	8.5(1.6)(3)	na
Building B:		
Grabber Operator	6.5(1.1)(2)	10.0(2.9)(7)
Auto shell processor	na	8.5(2.4)(6)
Investment supervisor	6.0(1.0)(2)	5.0(1.0)(1)
Building C:		
Grabber operator	na	5.7(2.5)(2)
Auto shell processor	na	1.6(2.2)(3)

Notes: gm = geometric mean
gsd = geometric standard deviation
n = number of samples
na = not applicable or not sampled

TABLE 4
RESULTS OF INDIVIDUAL WORKER URINE MONITORING

April 1984 Survey
Building A

Job Code	Total 24Hr Void (L)	Individual Voids (mg EAA/g Creatinine)					
		1	2	3	4	5	6
Hand dipper Bldg. A	1107	ND*	26	37	40	46	55
Hand dipper Bldg. A	1469	21	21	40	38	31	
Supervisor Bldg. B	1110	18	27	28	35	32	
Control Bldg. A	824	ND	ND	ND	ND	ND	
Control Bldg. A	1089	ND	ND	ND	ND		

*Limit of Quantitation = 10 mg/L (before creatinine adjustment)

TABLE 5
EXPOSURE RESULTS: INDIVIDUAL URINE MONITORING
PRECISION CASTPARTS CORP.
mg EEA/g Creatinine

June 1984 Survey
Building B

	Day of collection						
Person/Job	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Supervisor	29 40		30		16* 20* 16*		
Grab. Opr.	1	101 106	70 102	97	68	59	108
Grab. Opr.	2		163	121	52	59	79
Grab. Opr.	3			74	55	45	
Shell Proc.	1	79					ND**
Shell Proc.	2		78	87			
Shell Proc.	3						61 60

Notes: data shown is concentration for sequential voids during a work shift
*after one day off work
**after two days off work

TABLE 6
CHARACTERISTICS OF UNEXPOSED AND EXPOSED WORKERS

Characteristic	Unexposed (N=38)	Exposed (N=37)
Age of subject(years)	30.3 ± 7.5	30.1 ± 7.0
Cigarette smokers(%)		
Current	44.7	43.2
Ex.	18.4	18.9
Non	36.9	37.9
Alcohol consumption(drinks/ week)	7.2 ± 10.0	12.5 ± 14.6
Caffeine consumption(cups tea/ tea/coffee/day)	2.5 ± 2.8	2.7 ± 3.2
Duration of employment(years)	5.2 ± 5.0	7.3 ± 5.5
Duration of employment in 2EE exposed jobs		4.9 ± 4.1
Use of prescription medication in previous year(%)	26.3	16.2
History of fever in preceding 3 months(%)	7.9	13.5
History of urogenital disorders[1](%)	23.7	29.7
Presence of varicocele(%)	15.8	32.4[2]
Other abnormal medical history (%)[3]	8.1	10.8
Testicular size (ml) Right	22.1 ± 4.0	21.5 ± 4.7[2]
Left	21.1 ± 3.8	20.7 ± 5.0[2]
For semen analysis:		
Length of sexual abstinence(days)	3.7 ± 4.9	2.8 ± 2.2
Age of semen sample at analysis (mins)	54.2 ± 32.1	55.8 ± 33.2

1 Urinary tract infection, venereal disease or testicular trauma
2 n=34
3 spermatic cord, history of diabetes, hepatitis, rheumatic fever

NOTE: All differences between exposed and unexposed groups not significant ($p > 0.05$)

TABLE 7
SEMEN CHARACTERISTICS OF UNEXPOSED AND EXPOSED WORKERS

	Unexposed (n=38)		Exposed (n=37)		Significance
Characteristics	Mean	SD	Mean	SD	(p value)
Semen pH	8.08	0.18	8.03	0.17	
adjusted mean[1]	8.09		8.01		0.060
Semen volume (ml)	3.1	1.4	2.8	1.3	
adjusted mean[2]	3.0		2.9		0.538
Sperm concentration (millions/ml)	60.2	37.0	48.5	30.2	
Adjusted mean[3]	53.3		45.0		0.207
Sperm count (millions/ ejaculate)	178.6	118.0	123.4	81.7	
Adjusted mean[4]	153.9		112.7		0.048
% subjects with sperm concentration ≤ 20 million/ml	10.5		16.2		0.516

SD=standard deviation of the mean

1 adjusted for abstinence and presence of varicocele
2 adjusted for abstinence and subject's age
3 adjusted for prescription medication use and presence of varicocele
4 adjusted for prescription medication use and presence of varicocele

TABLE 8
SPERM VIABILITY, MOTILITY AND VELOCITY
IN UNEXPOSED AND EXPOSED WORKERS

Characteristics	Unexposed (n=38) Mean	SD	Exposed (n=37) Mean	SD	Significance (p value)
Viability by stain exclusion(%)	71.2	9.1	71.5	10.1	
Adjusted mean[1]	72.1		72.3		0.931
Viability by hypoosmotic swelling(%)	66.8	10.2	68.6	7.6	
Adjusted mean[1]	67.5		69.4		0.348
Motility(%)	40.4	12.3	43.9	10.5	
Adjusted mean[1]	39.8		43.6		0.213
Velocity(path length) (μm/sec)	65.2	14.2	65.6	13.3	0.916
Velocity(distance)(μm/sec)	39.8	8.8	40.2	7.7	0.817
Rates of length/distance velocity	0.7	0.1	0.7	0.1	0.906

SD=standard deviation of the mean

1 adjusted for abstinence and presence of varicocele

Table 9

SPERM MORPHOLOGY CLASSIFICATIONS[1]
IN UNEXPOSED AND EXPOSED WORKERS

Category	Unexposed (n=38) Mean	SD	Exposed (n=37) Mean	SD	Significance p value[2]
Oval(normal)heads(%)	79.42	± 10.59	78.02	± 9.47	0.455
Macrocephalic(large) heads(%)	1.40	± 2.39	0.95	± 0.70	0.016
Microcephalic(small) heads(%)	0.40	± 0.56	0.36	± 0.37	0.752
Absent heads(%)	1.78	± 1.46	1.97	± 1.70	0.310
Tapered heads(%)	3.58	± 4.24	3.65	± 3.55	0.679
Double heads(%)	1.65	± 3.16	0.95	± 1.11	<0.001
Amorphous heads(%)	1.00	± 1.92	1.18	± 1.01	0.244
Abnormal tails(%)	3.38	± 3.15	4.05	+ 3.89	0.0220
Immature forms(%)	7.40	± 6.22	8.82	± 6.71	0.001

SD=standard deviation of the mean

1 Mean % of 2 slides: 200 cells read/slide
2 p value of 2-sided t test (normal forms) and chi-square (all abnormal forms).

TABLE 10

SPERM MORPHOMETRY IN UNEXPOSED AND EXPOSED WORKERS

	Unexposed (n=38)		Exposed (n=37)		Significance
Category	Mean	SD	Mean	SD	(p value)
Area(μm^2)	9.0	1.0	9.0	0.8	0.993
Perimeter (μm)	11.4	0.6	11.5	0.6	0.579
Length (μm)	4.4	0.3	4.5	0.3	0.265
Width (μm)	2.6	0.2	2.6	0.1	0.399

SD=standard deviation of the mean