# DIGITAL EQUIPMENT CORPORATION

# HEALTH STUDY

## FINAL REPORT

## EXECUTIVE SUMMARY

University of Massachusetts
Division of Public Health

November 7, 1986

# INTRODUCTION

This report presents the results of a health study of employees of the D.E.C. Hudson L.S.I. facility conducted by the University of Massachusetts School of Public Health (E. Calabrese and H. Pastides, Co-Principal Investigators). This summary presents, in abbreviated form, the major study findings. A comprehensive report including further background information, methodologic details and complete results follows this summary. All tables presented in this summary are also found in the complete report.

This investigation was initiated by management in response to concern raised by one or more employees about the possibility of an elevated risk for spontaneous abortion among manufacturing employees. While this adverse health outcome was the study's main focus, a wide variety of reproductive outcomes as well as the prevalence of general health measures were examined.

All current employees at the time of the study, as well as all former L.S.I. Hudson manufacturing workers (not terminated for cause) were eligible for study. During two phases of interviewing, useable data were collected from a total of 744 employees. Spouses of currently married male employees were interviewed by telephone to identify their history of pregnancy outcomes.

Three groups of employees were compared with respect to the occurrence of reported health outcomes: Photo employees refer to manufacturing and other workers exposed to a wide array of chemicals including glycol ethers used in a photosensitive process of semiconductor manufacture. Diffusion employees refer to manufacturers and other workers exposed to chemicals not including glycol ethers and involving other activities in semiconductor manufacture. Non-exposed employees refer to workers with a wide variety of occupational responsibilities at the Hudson facility exclusive of jobs involving chemical exposures. This group included clerical staff, engineers, administrative employees, and others.

## Reproductive Outcomes

For the purposes of this report "abortion" refers to induced abortions reported by respondents; "miscarriage" refers to reported spontaneous abortions prior to 28 weeks of gestation; and "stillbirth" refers to spontaneous abortions after 29 weeks of gestation or a fetus pronounced dead at time of birth. For workers in the Photo and Diffusion groups, only pregnancies occurring after date of first employment at Hudson were considered in the following presentation of results since prior pregnancy outcomes could not be attributable to Hudson occupational exposures. For the Non-exposed group, however, all pregnancies were considered. This was done to enhance the precision with which quantitative comparisons could be made.

Table 1 presents the reported pregnancy outcomes in the three groups. The miscarriage ratio among females in the Diffusion group, defined as the proportion of total pregnancies resulting in a miscarriage, was found to be slightly more than twice the rate found among Non-exposed females (38.9% vs. 17.8%). This translates into a Relative Risk of 2.18 (the ratio of Diffusion miscarriages to Non-exposed miscarriages); this risk was significantly greater than a difference likely to have been due to chance alone. The miscarriage rate among Photo females was found to be 29.4%, translating to a Relative Risk of 1.65 when compared to the Non-exposed females. This ratio, while elevated, was not found to be significantly different in a statistical sense from the miscarriage ratio in the Non-exposed females.

TABLE 1

PREGNANCY OUTCOME AMONG FEMALE EMPLOYEES BY EXPOSURE GROUP

| EXPOSURE GROUP | ABORTIONS N | ABORTIONS RATIO | STILLBIRTHS N | STILLBIRTHS RATIO | MISCARRIAGES N | MISCARRIAGES RATIO | LIVEBIRTHS N | LIVEBIRTHS RATIO |
|---|---|---|---|---|---|---|---|---|
| PHOTO | 2 | (11.8) | 0 | ( 0.0) | 5 | (29.4) | 10 | (58.8) |
| DIFFUSION | 1 | ( 5.6) | 0 | ( 0.0) | 7 | (38.9) | 10 | (55.6) |
| NONEXPOSED | 35 | ( 8.8) | 2 | ( 0.5) | 71 | (17.8) | 290 | (72.9) |

Ratios expressed as a number of events per 100 pregnancies.

Relative risk of miscarriage comparing Photo to Nonexposed women = 1.65; 95% CIE = (0.77, 3.55).

Relative risk of miscarriage comparing Diffusion to Nonexposed women = 2.18; 95% CIE = (1.18, 4.04).

Relative risk of miscarriage comparing combined exposure groups (Photo + Diffusion) to Nonexposed women = 1.92; 95% CIE = (1.16, 3.18).

Miscarriages in the Diffusion group females were reported to occur at an earlier time, on average, than those in females in the Photo and Non-exposed groups (6.3 weeks vs. 10.2 and 11.6 weeks, respectively). These results are reported in Table 2.

TABLE 2

DISTRIBUTION OF GESTATIONAL AGE (WEEKS) FOR MISCARRIAGES OCCURRING AMONG FEMALE DEC EMPLOYEES

| PARAMETER | PHOTO | DIFFUSION | NONEXPOSED | ANOVA |
|---|---|---|---|---|
| MEAN | 10.2 | 6.3 | 11.6 | F = 2.630 |
| STD. DEV. | 2.49 | 1.38 | 6.31 | p = 0.079 |
| 95% CIE | ( 7.1, 13.3) | ( 5.0, 7.6) | (10.1, 13.1) | |
| RANGE | 6.0, 12.0 | 4.0, 18.0 | 1.0, 28.0 | |
| MEDIAN | 11.0 | 6.3 | 11.5 | |
| NUMBER | 5 | 7 | 71 | |

In order to determine whether the reported differences in miscarriage ratios could be attributed to any other factors potentially related to the risk of miscarriage and to exposure group, multivariate statistical procedures were employed. Factors which were taken into account included: age at pregnancy, number of previous pregnancies, presence of prior induced abortions, smoking during pregnancy, alcohol consumption during pregnancy, caffeine consumption during pregnancy, and others. No substantial deviations from the relative risks reported above were identified in these analyses. In no case did the risk of miscarriage among Diffusion females become lower than that reported in Table 1; in multivariate analyses the risk was in the range of 2.8 to 3.4.

Similarly, in no analysis did the risk for Photo females become lower than that reported in Table 1; the risk of miscarriage ranged from 2.1 to 2.6.

To explore whether the relative risk identified could have been due to differences in miscarriage risk present prior to Hudson employment, pregnancy outcomes before first Hudson employment were compared. As seen in Table 3, no meaningful differences in risk were identified; miscarriage rates in all three groups were between 12.5% and 16.8%.

With respect to other reproductive outcomes, no differences were identified in the reported occurrence of congenital anomalies, mean birth weight of live births, infertility, or spotting or bleeding during pregnancy (apart from miscarriage).

When pregnancy outcomes of spouses of male Hudson employees were compared, no significant differences in the ratios of reported miscarriage were identified (Table 4). The ratios were between 5.9% and 13.3%; given the relatively small numbers of events, these differences could have been attributable to chance.

TABLE 3

PREGNANCIES OCCURRING PRIOR TO DEC EMPLOYMENT AMONG FEMALE EMPLOYEES

| EXPOSURE GROUP | ABORTIONS N | ABORTIONS RATIO | STILLBIRTHS N | STILLBIRTHS RATIO | MISCARRIAGES N | MISCARRIAGES RATIO | LIVEBIRTHS N | LIVEBIRTHS RATIO |
|---|---|---|---|---|---|---|---|---|
| PHOTO | 4 | (50.0) | 0 | ( 0.0) | 1 | (12.5) | 3 | (37.5) |
| DIFFUSION | 3 | (50.0) | 0 | ( 0.0) | 1 | (16.7) | 2 | (33.3) |
| NONEXPOSED | 30 | ( 8.5) | 2 | ( 0.6) | 59 | (16.8) | 261 | (74.1) |

Ratios expressed as a number of events per 100 pregnancies.

Relative risk of miscarriage comparing Photo to Nonexposed women = 0.75; 95% CIE = (0.12, 4.73).

Relative risk of miscarriage comparing Diffusion to Nonexposed women = 0.99; 95% CIE = (0.16, 6.04).

Relative risk of miscarriage comparing combined exposure groups (Photo + Diffusion) to Nonexposed women = 0.85; 95% CIE = (0.23, 3.14).

TABLE 4

PREGNANCY OUTCOME AMONG SPOUSES OF MALE EMPLOYEES, BY EXPOSURE GROUP

| EXPOSURE GROUP | ABORTIONS N | ABORTIONS RATIO | STILLBIRTHS N | STILLBIRTHS RATIO | MISCARRIAGES N | MISCARRIAGES RATIO | LIVEBIRTHS N | LIVEBIRTHS RATIO |
|---|---|---|---|---|---|---|---|---|
| PHOTO | 0 | ( 0.0) | 0 | ( 0.0) | 2 | (13.3) | 13 | (86.7) |
| DIFFUSION | 0 | ( 0.0) | 0 | ( 0.0) | 1 | ( 7.7) | 12 | (92.3) |
| NONEXPOSED | 1 | ( 5.9) | 0 | ( 0.0) | 1 | ( 5.9) | 15 | (88.2) |

Ratios expressed as a number of events per 100 pregnancies.

Relative risk of miscarriage comparing Photo to Nonexposed women = 2.27; 95% CIE = (0.23, 22.56).

Relative risk of miscarriage comparing Diffusion to Nonexposed women = 1.31; 95% CIE = (0.09, 19.00).

Relative risk of miscarriage comparing combined exposure groups (Photo + Diffusion) to Nonexposed women = 1.82; 95% CIE = (0.21, 16.14).

General Health Outcomes

The examination of differences between the prevalence of reported symptoms and illnesses between males and females in the Photo, Diffusion, and Non-Exposed groups was conducted to identify general associations with occupational group; symptoms occuring any time during the most recent five years (the approximate history of the Hudson facility) were inquired about. Table 5 presents a summary of the significant associations found. When compared to females in the Non-exposed group, females in the Photo group were more likely to report frequent or severe nausea, sore throats or rash, arthritis and diabetes. Females in the Diffusion group were significantly more likely than their Non-exposed counterparts to report frequent or severe sore throats or headaches and back problems other than slipped disk. Males in the Diffusion group were more likely than Non-exposed males to report frequent or severe nausea.

TABLE 5
SUMMARY TABLE FOR SYMPTOMS SIGNIFICANTLY ASSOCIATED *
WITH EXPOSURE, BY SEX GROUP

| EXPOSURE GROUP | REPORTED SYMPTOM | SEX GROUP | RELATIVE RISK | 95% CIE (LL, UL) |
|---|---|---|---|---|
| PHOTO | SORE THROAT | FEMALES | 2.73 | (1.13, 6.57) |
| DIFFUSION | SORE THROAT | FEMALES | 3.07 | (1.32, 7.11) |
| PHOTO | RASH | FEMALES | 2.38 | (1.12, 5.02) |
| PHOTO | NAUSEA | FEMALES | 2.94 | (1.20, 7.20) |
| DIFFUSION | NAUSEA | MALES | 8.73 | (1.09, 69.65) |
| DIFFUSION | OTHER BACK PROBLEMS | FEMALES | 0.42 | (0.19, 0.94) |
| DIFFUSION | HEADACHE | FEMALES | 2.16 | (1.56, 3.00) |
| PHOTO | ARTHRITIS | FEMALES | 2.32 | (1.16, 4.63) |
| PHOTO | DIABETES | FEMALES | 7.55 | (1.29, 44.29) |

* A symptom with a relative risk whose confidence interval estimate does not include 1.0.

## Discussion

The finding of a significantly increased risk of miscarriage among female Diffusion employees, and a non-significantly higher risk among female Photo employees, at the DEC Hudson facility when compared to an internal Non-exposed group needs to be considered in light of general medical knowledge about this reproductive outcome and also in light of the limitations of the present study.

Retrospective surveys of past pregnancies have contributed the largest amount of information known about population rates of spontaneous abortion. The completeness of such research depends on the willingness and ability of respondents to report past events of this type. Reasons for underreporting could include: fear that it might be thought of as having been induced; incomplete recall; and lack of knowledge that such an event occurred, especially if very early in pregnancy. The assessment of gestational age at miscarriage is further complicated in that fetal death might have occurred well before expulsion.

The miscarriage ratio (total number of miscarriages divided by total number of pregnancies) is the usual index used to examine population risk (1). General population surveys, as well as specific research studies, have generally found miscarriage ratios in the 10-20% range (2-11).

Known and purported causes of miscarriage include malformation, chromosomal abnormalities, gynecologic pathology, immunological factors, progesterone defficiency, infectious disease, IUD use, smoking and alcohol during pregnancy, maternal age and birth order, and chemicals and other environmental exposures. While this study collected and analyzed information on several of these risk factors in light of occupational group, it would be impossible to completely examine all possible risks in detail. The attribution of the observed increased risk in this study cannot, therefore, be causally linked with occupation. The inherent weakness of working with self-reported data from human populations often prelcudes a "proven" or "cause and effect" appraisal.

The data reported here, nevertheless, do indicate a positive association between occupation in the Diffusion area and risk for spontaneous abortion among females, beyond that which would be expected by chance. The observed rate of miscarriage of this group was higher than in the comparison group and also higher than the level observed among these women prior to employment at the Hudson facility. This relation persisted even after controlling for a variety of risk factors for which data were available. The elevated risk among females in the Photo group, while not statistically significant, corresponds to a 29.4% occurrence of spontaneous abortion; this is higher than that observed in most population surveys.

While only a small proportion of reported miscarriages were verified by physician records it is much more likely that these events would be underreported rather than overreported by respondents; this would not, therefore negate the findings of this report unless the underreporting were substantially greater in the Non-exposed group than in the Diffusion group, an unlikely premise.

The fact that women who continue working are sometimes at higher risk for miscarriage than those who terminate employment (to care for the infant) has been identified by Axelsson (12). This study attempted to address this issue by identifying former employees, not terminated for cause, and collecting information on health outcomes by telephone interview. The number of such employees was small, however, and did not substantially affect the results.

Studies to date have identified the testicular toxicity of acute glycol ether exposure in mice, rats, and rabbits (13-20). Observed toxic effects include atrophy in size and weight of testes, and degeneration of germinal epithelium. Reversible fertility loss has also been identified in these male species (16,21), as has teratogenicity (22-25). The nature and severity of events has varied depending on dose and route of administration. The fact that animal experiments indicate that a biological effect of glycol ether was to cause spontaneous abortion through its action on male gametes should not be viewed as an argument against a potential effect on the human female, since sufficient studies of females have not been conducted.

Finally, one needs in the future to better account for actual exposure levels encountered in the Hudson occupational setting. Only with better monitoring will exposure information be valuable enough to include in an analysis of the data. With respect to glycol ethers, for example, previous Hudson industrial hygiene monitoring data indicated only trivial or non-discernable exposure levels among persons in the Photo area. This should not be used to discount the present association, but should, instead, underscore the need to conduct more complete monitoring. Additionally, the results of this study should bear replication in future investigations using comparably exposed groups of workers.

## REFERENCES


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To: Belle Manzo
Re: Pre-placement and Periodic examinations for Mod-8 (wafer fabricaton) employees
Date: July 2, 1986

As you have requested I have reviewed the potential chemical exposures for employees in the new "Mod-8" wafer fabrication facility.

Although we do not have complete data on the ingredients in the photoresists, some general conclusions can be drawn. There is apparently no anticipated use of Arsine or other arsenic containing compounds. According to Bob Wheaton, the photoresists typically contain 4 components: zylene, toluene, N-butylacetate, and a glycol ether, usually cellusolve acetate. Other potentially significant exposures include acids (hydrofluoric and hydrochloric), and a variety of solvents used in cleaning operations.

Some of the chemical listed above do have potentially significant health effects associated with uncontrolled exposure, but none of them appears appropriate for biological monitoring. Therefore, I recommend the following examination protocol:

PRE-PLACEMENT EXAMINATIONS

1. Medical History
2. Past exposure and Occupational History
3. Vital Signs and Physical Examination by Nurse
4. Urine dipstick and hematocrit
5. Record review by medical consultant

PERIODIC EXAMINATIONS

1. Updated medical history,
2. Vital signs and physical examination by nurse
3. Hematocrit and urine dipstick
4. Other specific laboratory tests if indicated after discussion with medical consultant.

For those workers who routinely wear respirators, or are occasionally required to use respirators (e.g. spill team members) I would add a respiratory history and annual spirometry testing.

Obviously we will need to review these recommendations as any process of formulation changes are introduced in this area. I plan to discuss these recommendations with Bob Wheaton and Richard Porter before their finalization. Your comments will be appreciated.

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