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ATTN: 8(e) Coordinator:

4,4-methylene bis (2-chloroaniline, CAS 101-14-4
See Also: 8ECAP-0025 Phase 1 Submission # 533 (9/10/92)

Enclosed for the Agency's records is a copy of the recently issued cross-sectional survey, "Bladder Health Survey of MOCA Workers". The study concludes that no bladder tumors associated with 4,4-methylene bis (2-chloroaniline) alone were found.

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8EHQ-92-8673
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Sincerely,

Mark H. Christman

20 Pgs.

BLADDER HEALTH SURVEY OF MOCA WORKERS

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MOCA =4,4' Methylene bis (2 chloroaniline)

SUMMARY

MOCA (4,4-methylene bis (2-chloroaniline)) was handled at Du Pont from 1954 through 1980. Active and pensioned Du Pont workers with potential MOCA exposure during this period were invited to participate in a bladder health survey. This survey was cross-sectional in design, a "snapshot in time" of the MOCA worker's bladder health status as of June 1988. The potential duration, intensity and frequency of MOCA exposure were not addressed by this survey.

Four hundred ninety-two workers (492) with potential MOCA exposure were identified. Of these, four hundred thirty five (435), or 88% participated in the survey, responding to questionnaires, providing urine samples, and having their medical records reviewed. Of the 57 not participating, 39 were employees who resigned or were terminated after a short time and no longer have ties with the company.

No bladder tumors associated with MOCA exposure alone were found. Three previously reported bladder tumor cases were found involving workers who had long term exposure to other known bladder carcinogens (i.e.. benzidine and or beta-naphthylamine) and short term MOCA exposure.

INTRODUCTION

MOCA process development began in 1954 and production was carried out sporadically from 1955 through 1961 on a pilot plant scale. In 1962, full scale manufacture was initiated. Based on the results of laboratory animal studies, a medical surveillance program was initiated in 1967. Pensioners or other employees who left employment were encouraged to continue the

surveillance program but at a lesser frequency. They were encouraged to leave a urine specimen annually for cytology and urinalysis including microscopic for hematuria. They were encouraged to have a complete annual physical examination.

Reductions in MOCA exposure potential evolved and can be categorized into 3 periods.

- o Prior to 1967 - Normal Du Pont handling practices with no special effort made to avoid skin contact. Included use of "Nomex" long sleeve work clothing, post-work showers before changing to street clothing, use of butyl gloves, eating areas separate from work areas.
- o 1968-1973 - In addition to normal handling practices special ventilation was installed to capture dust and vapors, respirators were required for certain jobs and emphasis was increased on keeping the area and work surfaces dust free.
- o 1973-forward - MOCA was treated as a "No contact" chemical with great emphasis on skin contact as the principal route of exposure.

After the manufacturing process was discontinued in 1979, our surveillance program for active employees was modified. It included an annual urine cytology as well as an annual physical examination with a complete urinalysis. The surveillance recommendations for pensioners remained the same. They were encouraged but not required to participate in an annual urinalysis and physical examination. Any individuals with abnormal cytology or hematuria were referred for further urologic diagnostic review including cystoscopic examination if so indicated.

This surveillance program remained as described until we were made aware (in 1987) of the discovery of the two (now three) cases at another company's[1] [2] MOCA handling facilities. After that notification, we decided to review the health status of our workers and made every attempt to bring everyone back into active surveillance. All sites updated their lists of MOCA workers. Workers lost to site follow up were referred to a central source for resolution. All pensioners were contacted and advised of the other company's experience. Urine cytology and complete urinalysis were performed and a medical history obtained.

SURVEY DESIGN

This document reports on a cross-sectional survey, a "snapshot in time", of the bladder/tumor health status of the MOCA workers as of June 1988.

Every effort was made to identify all workers who had the potential for MOCA exposure anytime during the period MOCA was handled at Du Pont (1954-1980). The following sources were utilized:

- Sign-in /sign-out sheets - used from 1973-1980
- Word of mouth
- Old work rosters
- Talking with people - both active employees and pensioners
- Medical records

An announcement of the study was communicated to the employees and letters sent to pensioners. All were asked to complete a health questionnaire, and to participate in a special MOCA surveillance program designed to detect genitourinary disorders, specifically bladder cancer.

A central person with long-term involvement with the MOCA program, coordinated data collection, collation, and question resolution aspects of the survey. These activities involved visiting the various sites, reviewing site and corporate records and talking with current and former employees. Everyone who volunteered to participate in the survey was included in our database.

Since hematuria and abnormal cytology are recognized as sentinels of underlying bladder cancer disease[3], the surveillance program consisted of microscopic analysis of the urine for the presence of red blood cells (RBCs) or white blood cells (WBCs) as well as urinary cytology. Any worker found to have positive findings, RBCs, WBCs or Class III or IV cytologies were referred for further diagnostic evaluation - IVP, cytoscopic examination, and the like.

RESULTS

Of the 57 non-participants, 17 were active or pensioned employees who elected not to participate, 1 was deceased, and 39 were employees who either resigned or were terminated after a short time and no longer have ties with the company. Of the 39 resigned/terminated employees, we had company service information on 22, which showed that 60% left the company after less than 3 years.

Table 1 gives the demographics and work status for both participants and non-participants.

TABLE 1: DEMOGRAPHICS AND STATUS OF PARTICIPANTS AND NON-PARTICIPANTS

	Participants (435)		Non-Participants (57)	
Sex	**Number**	**Percent**	**Number**	**Percent**
Female	10	2.3	3	5.3
Male	425	97.7	54	94.7
Race				
Black	24	5.5	2	3.5
Unknown	10	2.3	26	45.6
White	399	91.7	29	50.9
Other	2	0.5	0	0
Status				
Active	285	65.6	8	14.0
Died	4	0.9	1*	1.8
Pensioned	146	33.6	9	15.8
Resigned	0	0	39	68.4

*Malignant Melanoma

The median age of the participants was 54.5 years with a range of 32 to 86.5. Table 2 shows the age distribution of participants by quartiles.

TABLE 2: AGE DISTRIBUTION OF SURVEY PARTICIPANTS (BY QUARTILES)

Mean	Minimum	Maximum
40.6	31.9	46.5
50.1	46.5	54.5
58.0	54.5	62.0
69.4	62.2	86.5

The tumor history for the participants showed 7 tumors of which 3 were bladder (Table 3). The 3 bladder tumors involved workers who had long term exposure to other known bladder carcinogens (i.e. benzidine and/or beta-naphthylamine) and short term MOCA exposure. Work histories for the 3 bladder tumor cases (Cases A, B, and C) appear in Appendix A.

TABLE 3: TUMOR HISTORY BY PRIMARY SITE

Primary Site	Frequency	Percent
Breast	1	0.2
Colon	1	0.2
None	428	98.4
Prostate	1	0.2
Rectal polyps	1	0.2
Bladder	3	0.7

Since the June 1988 survey cut off date, 3 additional bladder cancer cases have been reported. Reports on these cases (Cases D, E, and F) appear in Appendix A. Case D worked for 34 years in the color areas where he had the potential for exposure to beta-naphthylamine and/or benzidine and had the potential for MOCA exposure during a two month period. Case E worked for 19 years in the colors area where he had the potential for exposure to beta-naphthylamine and/or benzidine and had the potential for MOCA exposure during a two month period. Case F worked in the colors area for 18 years where he had the potential for exposure to beta-naphthylamine and/or benzidine and worked in the MOCA area as foreman for 15 years where he had the potential for moderate MOCA exposure.

Fourteen percent of the MOCA workers had microscopic hematuria and 6% gross hematuria (Table 4). Previous investigators have found microscopic hematuria to range from 4% in the young[4] to 19% in men over 50 years of age[5]. Thus, our findings are not unexpected.

TABLE 4: URINALYSIS RESULTS

	Gross hematuria		Microscopic hematuria		Pyuria (white blood cells)	
Result	No. Subjects	%	No. Subjects	%	No. Subjects	%
Positive	28	6.4	59	13.6	44	10.1
Negative	399	91.7	368	84.6	383	88.0
Not screened	8	1.8	8	1.8	8	1.8

Three of 262 (1%) urine cytologies (Table 5) were abnormal Class III or greater. Upon further investigation, one abnormal cytology was related to prostatic disease and one reverted to normal without any underlying disease detected. One individual was later found to have transitional cell carcinoma, Grade II-III.

TABLE 5: CYTOLOGY RESULTS

Result	No. Subjects	%
Not screened	173	39.2
Screened	262	60.2
Normal (Class I/II)	259	98.9
Abnormal (Class III)	3	1.1

Table 6 enumerates the individuals evaluated by cystoscopic and IVP screening.

TABLE 6: CYSTOSCOPIC AND IVP SCREENING

	Cystoscopic		IVP	
Result	No. Subjects	%	No. Subjects	%
Not screened	382	87.8	388	89.2
Screened	53	12.2	47	10.8

The final diagnosis for each abnormal screening test result is given in Table 7.

TABLE 7: FINAL DIAGNOSIS BY SCREENING TEST

	Subjects tested by:		Subjects with:	
	IVP	Cystoscopic examination	Micro and/or gross hematuria	Abnormal cytology
Final diagnosis				
Bladder cancer	2	3	3	1
Prostate condition	4	7	-	1
Urinary tract infection	2	8	10	-
Kidney condition	17	9	15	-
Diagnosis unknown	7	-	-	-
Normal	15	26	27	1
Misc. urinary problem	-	-	6*	-
Total	47	53	61	3

*Prostate, medicine, congenital defect, mechanical problem, diverticulitis, glomerulonephritis

DISCUSSION AND CONCLUSIONS

In 1986-87 we became aware of several bladder cancer cases at another company's facilities that handled MOCA. Although these were among workers who had the potential for exposure to multiple chemicals, we decided to review our MOCA medical surveillance program to reaffirm that our employees were

not manifesting bladder health effects from MOCA exposure. Starting in September 1987, we re-emphasized our MOCA medical surveillance program and aggressively sought out all MOCA workers, both active and retired. These workers were encouraged to have urine cytology testing, and medical completed a brief form relating to these employee's tumor histories and the results of urine testing. This effort was very successful in tracking down ex-MOCA workers, getting them in for testing and accumulating the information. Data quality and participation rates were greatly enhanced by the program coordinator, a centralized person with long-term involvement with the MOCA program. With the help of the medical departments and site personnel the coordinator resolved all questions, double checked the replies and results at each site, and contacted employees whenever necessary. This survey was cross-sectional in design, a "snapshot in time" of the MOCA workers' bladder health status as of June 1988. The duration, intensity and frequency of potential MOCA exposure was only addressed for those individuals who had bladder tumors. Included in this survey are all of those employees originally present in the Linch MOCA cohort[6].

In this survey no bladder tumors associated with MOCA exposure alone were found, although there were several bladder tumor cases involving workers with long-term exposure to other known bladder carcinogens (e.g., benzidine and/or beta-naphthylamine) and short-term exposure to MOCA. Urinalysis results were typical of those found in other surveys.

A large case-control bladder cancer study of Du Pont Chambers Works/Repauno employees is in progress and scheduled for completion in 1993.

That study involves about 1000 cases and controls, many of whom were included in the present MOCA bladder health survey.

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APPENDIX A: BLADDER CANCER CASES

CASE A

72 YEAR OLD WHITE MALE CHEMICAL OPERATOR

EMPLOYED: 1936

PENSIONED: 1972

Risks	-	Possibility of exposure to Benzidine 1936-1967
		Possibility of exposure to beta-naphthylamine 1936-1956
		Possibility of exposure to MOCA 1962-1972
		Cigarette smoker 40 years 1 pack/day
Symptoms	-	Dysuria - 1975
		Normal urinalysis (no hematuria)
		Normal cytologies
		Normal pre-placement cystoscopy - 1947
Diagnosis	-	Infiltrating Grade III transitional cell carcinoma (1975)
Treatment	-	Cystoprostatectomy/uretero sigmoidoscopy
Status	-	Cancer free - 1992

Worked as chemical operator ir the colors areas from 1936-1956 with potential for benzidine and/or beta-naphthylamine exposure. Served as a foreman in the MOCA operation as well as many other operations from 1962-1972. Potential for MOCA exposure was average.

APPENDIX A: BLADDER CANCER CASES (continued)

CASE B

42 YEAR OLD WHITE MALE CHEMICAL OPERATOR

EMPLOYED: 1962

DISABILITY PENSIONED 1986

DECEASED: 1987

Risks	-	Possibility of exposure to Benzidine 1962-1972
		Possibility of exposure to MOCA for 2 months in 1962
		Cigarette smoked 5 years 1/2 PPD
Symptoms	-	Gross Hematuria 1984
		No cytology exams
Diagnosis	-	Epidermoid carcinoma of the bladder; metastatic
Treatment	-	Radical Cystoprostatectomy;
		Chemotherapy
Status	-	Died in 1987 of bladder cancer metastases

Worked as chemical operator in color areas (1962-1972) with potential for Benzidine exposure. During 1961-1962 there was a 2 month period during which MOCA was handled in the colors area. He could have had the potential for MOCA exposure during this two month period.

APPENDIX A: BLADDER CANCER CASES (continued)

CASE C

60 YEAR OLD WHITE MALE CHEMICAL ENGINEER

EMPLOYED: 1950

PENSIONED: 1985

Risks	-	Possibility of exposure to beta-naphthylamine (1950-1956)	
		Possibility of exposure to Benzidine (1950-1967)	
		Possibility of exposure to MOCA for 8 months (1955)	
		Non-smoker	
Symptoms	-	Microscopic urinalysis:	Intermittent 1979-1980
		Cytology:	Class III - 1969
			Class II - 1970
		Gross Hematuria:	April 1986
Diagnosis	-	Papillary transitional cell carcinoma, Grade II-III (3/3/86)	
Treatment	-	TUR (3/3/86)	
		Theotepa installation x 6 weeks (1986)	
Status	-	No reoccurrence (1992)	

Worked as an engineer in the colors areas from 1950-1967 with the potential for benzidine and/or beta-naphthylamine exposure. Worked as an engineer during early stages of MOCA lab development and pilot plant studies. Potential for MOCA exposure was low and of short duration (8 months).

APPENDIX A: BLADDER CANCER CASES (continued)

CASE D

76 YEAR OLD WHITE MALE CHEMICAL OPERATOR

EMPLOYED: 1933

PENSIONED: 1971

Risks	-	Possibility of exposure to beta-naphthylamine (1933-1956)
		Possibility of exposure to Benzidine (1933-1967)
		Possibility of exposure to MOCA for 2 months in 1961-1962
		Cigarette smoker - 30 years, 1 PPD
		Familial - son with no occup. exposure developed bladder cancer
Symptoms	-	Normal pre-employment cystoscopy-1947
		Intermittent microscopic hematuria
		Intermittent abnormal cytologies
		Gross Hematuria (1988)
Diagnosis	-	Grade III-IV transitional cell carcinoma 1988
Treatment	-	Total Cystectomy 1989
Status	-	Cancer free 1992

Worked as chemical operator in colors areas from 1933 to 1971 with the potential for exposure to beta-naphthylamine and/or benzidine. During 1961-1962 there was a 2 month period during which MOCA was handled in this area. He could have had the potential for MOCA exposure during this two month period.

APPENDIX A: BLADDER CANCER CASES(continued)

CASE E:

63 YEAR OLD WHITE MALE CHEMICAL OPERATOR

EMPLOYED: 1948

PENSIONED: 1979

Risks	-	Possibility of exposure to beta-naphthylamine (1948-1956)
		Possibility of exposure to benzidine (1948-1967)
		Possibility of exposure to MOCA (1961-1962 for 2 month period)
		Cigarette smoker, 10 years - 1 PPD
Symptoms	-	Normal cytologies
		Normal urine (no hematuria)
		Urinary Symptoms - urgency/frequency 1990-1991
Diagnosis	-	Papillary transitional cell carcinoma Grade I-II (1991)
Treatment	-	TUR 1991
		BCG treatment 1992
Status	-	Reoccurrence of tumors 1991 (tumors removed)
		Guarded (1992)

Worked as a chemical operator in colors areas from 1948 to 1979 with the potential for exposure to beta-naphthylamine and/or benzidine. During 1961-1962 there was a two month period during which MOCA was handled in this area. He could have had the potential for MOCA exposure during this two month period.

APPENDIX A: BLADDER CANCER CASES (continued)

CASE F:

75 YEAR OLD WHITE MALE FOREMAN

EMPLOYED: 1939

PENSIONED: 1977

Risks	-	Possibility of exposure to beta-naphthylamine (1939-1956)
		Possibility of exposure to benzidine (1939-1957)
		Possibility of exposure to MOCA (1962-1977)
		Cigarette smoker, 15 years - 1 PPD
Symptoms	-	Normal urinalysis (no hematuria)
		Class III & IV cytology 6/92
Diagnosis	-	Transitional cell carcinoma, Grade IV (6/24/92)
Treatment	-	Total cystectomy (7/8/92)
Status	-	Guarded - no known reoccurrence (1992)

Worked as foreman in MOCA operation during the period 1962-1977. Potential for MOCA exposure was average. Also worked in colors area as operator from 1939-1957 where he had potential for beta-naphthylamine and/or benzidine exposure.

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