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# CARCINOGEN ASSESSMENT GROUP'S ASSESSMENT OF CARCINOGENIC RISK FROM POPULATION EXPOSURE TO CADMIUM IN THE AMBIENT AIR

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The Carcinogen Assessment Group's

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# Assessment of Carcinogenic Risk from Population Exposure to Cadmium in the Ambient Air.

This document is being released by EPA for external review.

MAY 19 1978

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## I. SUMMARY AND CONCLUSIONS

Cadmium compounds have been shown to produce adverse effect in experimental animals, and studies in man link cadmium exposures with several clinical disease states. Body concentrations of cadmium increase with age, at least up to middle age, due to the poor renal excretion of the compound; thus, each source of exposure to cadmium adds an increment to the body burden.

Injection of cadmium in experimental animals results in the development of malignant tumors (sarcomas) at the site of injection. In addition, following subcutaneous injection of soluble cadmium salts, a significant increase in tumors at a distant site, namely interstital cell tumors of the testis, was found in treated rats and mice.

Orally administered cadmium has not produced a significant increase in tumors in experimental animals, but the three available studies have deficiencies which preclude accepting them as negative studies.

Cadmium salts increase the frequency of point and chromosomal mutations. They induce *in vitro* mammalian cellular transformation and enhance transformation of virus-infected mammalian cells. The outcome of these tests is known to be highly correlated with oncogenicity.

Occupational epidemiology studies at three independent locations with known exposure to cadmium have reported associations between cadmium exposure and excess rates of prostate cancer. At an alkaline battery plant a proportionate mortality study reported a high frequency of prostatic cancer amongst deaths in workers exposed to cadmium for at least 10 years. Another study at the same plant involving a follow up of the population of workers who were exposed at least one year to cadmium showed a statistically significant increase in the incidence of prostatic cancer. At a cadmium smelter a retrospective cohort study of workers exposed to cadmium for at least two years reported a significant increase in cancer deaths, mainly due to respiratory cancer. A statistically significant excess prostate cancer was found only in workers exposeed for more than 20 years. In a survey of four rubber producing plants the authors found that one of the four job catergories that was associated with workers dying of prostrate cancer involved exposure to cadmium and other metal oxides.

When all of this information is considered together it is possible that cadmium is a human carcinogen, although the evidence is not decisive.

A very crude quantitative assessment of population risks of prostrate cancer due to cadmium in the ambient air can be done on the basis of the prostate cancer data on alkaline battery and smelter workers together with EPA estimates of ambient concentrations and number of people exposed. The conclusion is that a lifetime exposure to atomospheric cadmium from any of the individual sources results in a lifetime risk of less than $2 \times 10^{-5}$ and the total number of prostate cancer deaths in the United States population exposed to ambient airborne cadmium is less than about 5 deaths per year. Since the daily cadmium retention from ambient air is only about 1/20 of the retention from food and about 1/3 of the intake from smoking a half-pack of cigarettes per day, this report deals with a relatively small part of the total problem of cadmium contamination

## II. INTRODUCTION

Environmental exposure to cadmium occurs by several routes. It is estimated that the exposure to an individual in food is about 50 ug per day; water, 2 ug per day; and air, less than 1 ug per day. The major sources of cadmium in the ambient air are non-ferrous metal smelters, iron and steel mills and municipal incinerators. In addition sources of cadmium exposure are wide ranging. For example it is present in cigarettes at relatively high levels and is used as a pesticide, largely on turf grasses.

## III. METABOLISM

This section is based on literature reviews by Friberg et al., (1971) and the International Agency for Research on Cancer (1976).

The two primary routes of cadmium absorption in man are the respiratory and gastrointestinal tract. The extent of absorption varies with the route of exposre.

In acute and chronic inhalation studies of mice, dogs and rabbits about 10 to 40% of the inhaled dose was absorbed. Salts tested were cadmium chloride, oxide, sulfide and cadmium iron dust. It is possible that absorption differs with the form of cadmium; however, these studies were not adequate to determine this.

There is markedly less absorption from oral dosing of cadmium salts than by inhalation. The average absorption by mice, rats and goats was only a few percent of the dose (range: 0.5 to 8%). Compounds tested were cadmium chloride and cadmium nitrate. Dietary factors have also been shown to influence absorption.

Low calcium and low iron diets have increased cadmium absorption in mice and rats. Vitamin D has been reported to increase intestinal absorption in chickens.

Skog and Wahlberg (1964) studied the absorption of cadmium chloride from the guinea pig skin. Absorption was determined by "disappearance measurements" using a scintillator to measure radioactive skin deposits. Six molar concentrations ranging from 0.005 to 4.87 were tested. Dermal absorption of cadmium was very low. It increased with increasing molar concentrations to a maximum at 0.239 M when the mean absorption was 1.8%/5 hours. At other concentrations mean absorption values were less than 1.0%/5 hours.

Cadmium steadily accumulates in the body with normal exposure, reaching a peak level at age 50. The background level of a newborn baby is about 1ug total; the body burden of a 50-year-old American man is about 30 mg. Friberg estimates that daily cadmium intake from food in the United States is in the upper portion of the 20 to 50 ug range and calculates that cadmium retention would have to be 3 to 8% to account for the 30 mg accumulation. This does not account for intake from sources other than food and assumes a linear accumulation with negligible excretion.

In both animal and human studies, very small amounts of cadmium were excreted in the urine. In humans, urinary levels have been less than 5 ug/day; generally excretion is 1 to 2 ug/day. Smokers excrete more cadmium than nonsmokers; cigarettes contribute to smokers increase in cadmium body burden and excretion as compared with nonsmokers. Excretion also increases in persons with renal tubular dysfunction, a condition which can be produced by prolonged

cadmium exposure. Cadmium has a long biological half-life. In humans it is estimated to be 10 to 30 years, and in other species it usually has been found to be at least 200 days.

About one third of the total body burden of cadmium in man is in the kidneys; together the kidneys and liver store about 50% of the burden. Renal concentrations of cadmium have generally been 5 to 100% higher in smokers than nonsmokers.

Cadmium has also been found in significant amounts in the pancreas. After a single intravenous injection of 109 Cd-Chloride, mice were found to accumulate cadmium in bone marrow, periostium, testes and hypophysis. The latter two sites are of interest in light of the tumors observed in Cd-injected animals.

The metabolism of cadmium is closely associated with zinc metabolism. Added zinc can protect animals from some cadmium-induced toxic effects. Metallothionein, a low molecular weight cadmium and zinc-binding protein, is believed to transport cadmium. Some evidence suggest that low cadmium exposures are nontoxic because the metal is bound to the protein. When all metallothionein sites are bound to cadmium, any additional cadmium is free to produce toxic effects.

## IV. MUTAGENICITY AND OTHER RELEVANT TESTS

Three secondary as well as several primary sources were consulted in the preparation of this section. The secondary sources were Sandhu, 1977; Pertel, 1977 and FDA, 1977; all primary references are cited in those three sources.

| Organism | Reported Mutagenicity | Comments | Authors |
|---|---|---|---|
| 1. Point Mutations | | | |
| Sacchromyces | (+) | | Takahashi, 1975 |
| Drosophila | (-) | Sex linked lethals; low power of test | Friberg et al., 1974 |
| Chinese hamster cells in culture | (+) | 8-azaguanine resistance | Costa, 1976 |
| 2. Chromosome Mutations | | | |
| a. Mammalian cells, in vitro | | | |
| Human leukocytes | (+) | | Shirashi et al., 1972 |
| Chinese hamster line | (+) | | Rohr & Bauchinger, 1976 |
| Human leukocytes & fibroblast line | (-) | | Paton & Allison, 1972 |
| b. Mammals, in vivo | | | |
| Sheep leukocytes | (+) | Numerical not structural aberrations | Doyle et al., 1974 |
| Mouse oocytes | (+) | | Shimada et al., 1976 |
| Human leukocytes | (+) | Itai-itai patients | Shirashi & Yosida, 1972 |
| | (-) | Itai-itai patients and Cd workers | Bui et al., 1975 |
| | (+) | Workers exposed to Cd & Pb | Deknudt & Leonard, 1975 |
| | (+) | Workers exposed to Cd, Pb and Zn | Bauchinger et al., 1976 |

| Organism | Reported Mutagenicity | Comments | Authors |
|---|---|---|---|
| Dominant lethal | (-) | Mouse | Epstein et al., 1972 |
| | (-) | Mouse | Gilliavod & Leonard, 1975 |

| Other Tests | Reported Effect | | |
|---|---|---|---|
| B. subtilis | (+) | for Cl but $NO_3$ salt in "rec" assay | Nishioka, 1975 |
| S. cerevisiae | (+) | for mitotic segregation | Takahashi, 1972 |
| Syrian hamster cells | (+) | for alteration in DNA sedimentation in $C_sCl_3$ gradients | Costa, 1976 |
| | (-) | for unscheduled DNA synthesis | Costa, 1976 |
| | (+) | for in vitro transformation | Costa, 1976 |
| | (+) | for enhancement of SA7 viral transformation, in vitro | Costa, 1976 |

In summary, cadmium salts have been reported to increase the frequency of point mutations and somatic chromosome aberrations and to interact with and break DNA. In addition, cadmium appears to induce in vitro mammalian cell transformation and enhance viral transformation of mammalian cells. The ability to induce mutations and in vitro mammalian cell transformation are correlated with the ability to induce carcinogenic effects.

## V. TOXIC EFFECTS

Chronic occupational exposure to excessive cadmium in the air produces emphysema after an exposure period of about 20 years. Kidney malfunction also occurs in these workers, manifested by glucosuria, proteinuria, excess cadmium excretion, and increased incidence of renal stones. In rats, many studies have shown that cadmium affects the testis, causing vascular degeneration and testicular atrophy. In addition it causes hypertension and kidney damage in experimental animals. Itai-itai disease, due to chronic ingestion of cadmium-contaminated rice, was characterized by multiple bone fractures mainly in multiparous post menopausal women (Friberg, 1971).

## VI. CARCINOGENICITY

### A. Human Studies

The epidemiology studies reviewed here include four studies of workers occupationally exposed to cadmium, two of them with overlapping samples. Two additional studies analyze cancer mortality in relation to metals in drinking water.

#### 1. Occupational Exposure

##### a. Potts Study (1965)

This article reports the health status of current and past employees of a British alkaline battery factory who were exposed to cadmium oxide dust for at least 10 years. The plant had been in operation since 1920, and in 1946 it was moved to a new location in the same town. Before 1950, when an extensive exhaust ventilation system was installed, cadmium concentrations of 236 $mg/m^3$ and 0.6 to 2.8 $mg/m^3$, were measured.

in two separate areas of the plant. Between 1950 and 1956 the levels were less than 0.5 $mg/m^3$ in most parts of the factory but some regions were well above this. After 1956, when further improvements were made, most areas had levels below 0.1 $mg/m^3$, and the operating policy since then has been to take special action when the level exceeds 0.5 $mg/m^3$.

The health survey covered workers employed by the plant since 1920. In 70 employees working over 10 years, 44% had protein in their urine. The protein had the same characteristics as that observed in workers at another factory who were exposed to cadmium fumes. Kidney function tests were not done routinely but four case reports of workers with proteinuria revealed no kidney damage.

Potts reports that "careful search" showed a total of 74 men had been exposed to cadmium for more than 10 years, and eight of those workers had died. He leaves the impression that he succeeded in determining the vital status of all 74 men without indicating the source of his mortality figures or cause-specific death data. Of the eight deaths he reports, five were from cancer and three of these were cancer of the prostate. The data from Potts paper are summarized below.

Mortality Data for Cadmium Workers Exposed for More Than Ten Years

| Year of Death | Age | Length of Cadmium Exposure (Years) | Cause of Death |
|---|---|---|---|
| 1960 | 65 | 31 | Auricular Fibrillation |
| 1960 | 75 | 14 | Carcinoma of Prostate |
| 1961 | 65 | 37 | Carcinoma of Prostate |
| 1962 | 63 | 34 | Bronchitis and Atheroma |
| 1962 | 78 | 18 | Bronchitis |
| 1963 | 53 | 35 | Carcinoma of Bronchus |
| 1964 | 65 | 38 | Carcinoma of Prostate |
| 1964 | 59 | 24 | Carcinomatosis |

All of these people were exposed to the high cadmium concentrations that existed before 1950; two of the prostate cases were thus exposed for at least 24 years and the third for at least 4 years. The exact time of the start of exposure was not stated and the cadmium concentrations in the earlier period are known only in 1949, when the decision was made to improve conditions at the new plant. No report was made of workers exposed less than 10 years.

While Pott's cancer mortality findings are striking, it is impossible to make a meaningful comparison of rates with the general population since the age structure of the exposed population is not reported.

b. Kipling and Waterhouse Study (1967)

In a letter to the editor of Lancet, Kipling and Waterhouse report on a survey of 248 British workers occupationally exposed to cadmium oxide. This work was conducted on the same population as Potts' study, however, Kipling and Waterhouse examined incidence of prostate cancer and included workers with at least one year of exposure to cadmium.

The rate of cancer for all sites as well as for cancer of the prostate, bronchus, bladder, and testes was determined, using an analysis based on total time-to-tumor, and compared with the expected rate for "such a group of men of known age". No other description of the control group was provided. The results are shown in the table below. There were 4 cases of prostate cancer compared to the expected number of 0.58, a significant increase at the .003 level. Three of these cases are the same as Pott's prostate mortality cases, according to a personal communication from Kipling reported in IARC (1976). There was no report of the age distribution of the cancer cases or the level or duration of exposure to cadmium.

Cancer Incidence In 248 Workers Exposed To Cadmium Oxide For More Than 1 Year

| Site of Cancer | No. of cases Expected | Observed | Probability of occurrence |
|---|---|---|---|
| All sites — — | 13.13 | 12 | 0.660 |
| Bronchus — — | 4.40 | 5 | 0.449 |
| Bladder — — | 0.51 | 1 | 0.398 |
| Prostate — — | 0.58 | 4 | 0.003 |
| Testis — — | 0.11 | 0 | 0.898 |

c. Lemen et al., Study (1976)

These investigators did a retrospective cohort study of workers at a cadmium smelter at which cadmium metal powder, cadmium oxide and cadmium sulfide were present. The smelter has been producing cadmium since 1925. Cadmium concentrations were measured on two occasions. In 1947 the average concentration of cadmium fumes ranged from 0.04 to 6.59 $mg/m^3$ and of cadmium dust was 17.23 $mg/m^3$, with most plant operations below 1.5 $mg/m^3$. In 1973, another measurement showed average air concentrations ranging below 1 $mg/m^3$ on an 8-hour time-weighted average basis, with excursions up to 24 $mg/m^3$ during infrequent operations. The authors reported that in 1973 a respirator program was in use at the plant which reduced exposures by a factor of about 10. No information was given about how long before 1973 the respirator program had been in operation or whether the respirators were routinely used by workers in all sections of the plant. In two sections of the plant concentrations of 75 to 90 $ug/m^3$ were measured in 1973. The arsenic air concentrations were generally less than about 1/100 of the cadmium levels. The ratios of zinc and arsenic to cadmium in the ores which are processed are about 1/10 and 1/200, respectively, and the authors concluded that exposure to metals other than cadmium were insignificant.

The study included 292 white male workers who worked at the plant between 1940 and 1969 and who were employed for at least two years. The vital status of these workers was determined as of 1974, and it was found that 92 had died, 180 were still alive and 20 were not accounted for; the latter were assumed to be alive in the analysis of the data. Person-years at risk of dying were computed and observed cancer rates were compared to age-adjusted rates for the total U.S. white male population.

A significant increase in cancer mortality among the exposed group was observed; most of this excessive risk was accounted for by neoplasms of the respiratory system which was significant at the .05 level. Of the 12 malignant respiratory disease cases, the cell type of eight was known. Three of these eight were squamous cell carcinomas, the type most commonly associated with cigarette smoking. No smoking histories for the groups were included. An association between respiratory cancer and cadmium has not been observed in other studies. In one dog study, the cause of death for cadmium-exposed animals was non-neoplastic respiratory problems (personal communication, Dr. Richard Lemen, 8/10/77).

Because of previous reports of increased prostate cancer in workers exposed to cadmium, the prostate cancer mortality of the cohort was also studied. The results are given in the table below:

Prostate Cancer Deaths Among Cadmium Smelter Workers with More Than 2 Years Exposure

| Case | Age | Exposure | Latency | Date of Death |
|---|---|---|---|---|
| 1 | 71 | 4 | 32 | 2/26/72 |
| 2 | 77 | 13 | 25 | 3/19/68 |
| 3 | 79 | 18 | 31 | 12/10/60 |
| 4 | 64 | 17 | 26 | 4/3/51 |

The four deaths from prostate cancer were not significantly higher than the 1.15 expected to occur in the full cohort. However, an increased risk was found (4 cases compared to 0.88 expected) at the .05 level among workers with a 20 year latency period since initial cadmium exposure.

d. McMichael et al. (1976)

These investigators identified cohorts of active and retired workers, aged 40 to 84, at four rubber-producing plants and followed their mortality experience for 10 years.

The mortality experience was determined from group life insurance records and confirmed with internal companny records. In the case of one cohort, a random sample of apparent survivors was checked against Internal Revenue Service records to verify that they were still alive.

It is important to note that rubber workers are potentially exposed to numerous organic and inorganic chemicals, some of them known or suspected carcinogens. While cadmium is present in these factories, mortality rates and cause-specific deaths in this study, which is not controlled for type of exposure, can not be attributed to cadmium alone.

A total of 18,903 male workers from the four facctories were included. About 1% of this group--active workers who switched jobs during the course of the study-- was lost to follow-up. Death certificates were obtained from 98% of the remaining cohort members who had died.

For the entire group 18,903 men, 98% had worked at the plant for at least 10 years. The study did not include former workers who had transferred to another place of employment or had died as of the date the cohort was identified. As a result, the sample could have selected for the stronger workers who survived and could have

excluded some who might have died due to occupational exposure. While such a study might show an excess mortality in the worker population, the effects of the work environment could be underestimated or overlooked.

The mortality data for the workers was compared to mortality figures for the 1968 U.S. male population. The analysis was made using standardized Mortality Ratios (SMR), controlling for race and using age categories of 40-64, 65-84, and 40-84. A SMR of 100 indicates no difference between the study group and the standard populaton. An SMR greater than 100 indicates an excess of deaths in the test group. However, since worker populations are generally healthier than the general population, in a non-hazardous work environment the SMR is expected to be slightly less than 100.

The total number of deaths from all causes was 5,106, with 1,014 due to cancer. The SMR for deaths from all causes for the full cohort was 94, it was relatively higher in the older group than in the younger workers. The SMR for all cancer sites showed similar trends, with a value of 100 for all ages and companies combined, 104 for the older group and 92 for the younger group. When specific sites were examined, SMR's for all companies combined were considerably higher than 100 for stomach (148), rectum (116), prostate (119), all leukemias (130), lymphatic leukemia (15), and lymphosarcoma and Hodgkin's disease (129). No striking excesses were seen in the combined-company SMR's

for cancers of the rectum, pancreas, respiratory system, bladder, and brain.

These figures reflect exposure to a variety of substances in the workplace. In an attempt to correlate cancer sites with specific job exposures, an exploratory study was made of the job classifications of workers with stomach, prostate and bladder cancer and lymphosarcoma and Hodgkin's disease. The work histories of men dying from each of these causes was compared to an age-stratified random sample of 23% of the full cohort (n=1476) to see whether differences existed in the porportion of men who had worked for at least two years in any job category.

Four jobs, compounding and mixing, cement mixing, janitoring and trucking, were assocciated with prostate cancer. The compounding and mixing association is of interest because these workers are exposed to cadmium oxides and other metal oxides that are used as vulcanization accelerators. The exposure levels are not reported. While this is of interest as a basis for future investigations, it is clearly insufficient as a basis for associating cadmium with prostate cancer since the worker's exposure to other substances and the extent of cadmium exposure have not been anaylsed.

e. Summary of Occupational Epidemiology Reports

Four occupational epidemiology studies have been reviewed. In all of them an association between prostate cancer and cadmium is suggested. In one study (Kipling & Waterhouse, 1967) an excess number of cases of prostate cancer occurred in exposed workers. Another study on the same population shows a high death rate from prostate cancer (Potts, 1965). Excess mortality from prostate cancer among workers whose initial cadmium exposure had been at least 20 years before the study was observed in a third paper (Lemen et al., 1976). Although it was not a controlled study, a fourth report (McMichael et al., 1976) suggested a possible correlation between excess prostate cancer mortality and possible exposure to cadmium.

All of these studies involved small numbers which makes the estimation of risk difficult. However, because of the consistency of the findings, together they raise a serious question as to a possibility of a relationship between cadmium and prostate cancer.

f. Non-occupational Epidemiology Studies

Correlations between cancer mortality and cadmium in drinking water have been studied by Berg and Burbank (1972) and by Zyka (1973). In Berg and Burbank's study, the drinking water concentrations of eight metals, including cadmium, were determined in 15 water basins of the United States. Death rates for 34 types of cancer were also determined for the regions corresponding to the same water basins. The water basins were then ranked with respect to each metal and each cancer site, and rank correlation coefficients were calculated.

For cadimum 10 positive (statistically significant) correlations were observed. No correlation was noted for testicular cancer, which might be expected from animal experiments. The authors did not report looking for prostate cancer correlations. Positive associations were observed for intestinal cancer and "smokers cancer" of the mouth, escphagus, larynx, lung, and bladder. The authors were unable to separate the effects of tobacco from possible effects of cadmium in the "smokers cancer". Cigarettes contain cadmium, and smokers have excess body burdens of cadmium; this could account for the correlation. Other studies cited by the authors have found no correlation between cadmium levels and intestinal cancer.

The authors note that, depending how cadmium is measured, rank orders of cadmium levels can be vastly different from one another. Berg and Burbank report that their results "are based on less than perfect analytical results and sampling." In light of this study's limitations, no conclusions can be drawn about cadmium's relationship to cancer mortality. It does suggest areas for further investigation.

Zyka (1973) chemically analyzed current and past drinking water sources in districts of the city of Kutna Hora, near Prague, Czecholslovakia and correlated metal concentrations with cancer mortality rates. Considerable disparity existed in cancer mortality rates among the several districts of the city, and Zyka reported that the source of drinking water was the only environmental factor that varied.

He found that the water from the Havirna mine, the water source for the area with the highest cancer mortality, had high levels of Cd, Zn, As, Cu, Al, Fe and Se. In contrast, in the districts with the lowest cancer mortality, the only drinking water contaminants found were $NO_3$ and low levels of Pb, Zn, As and Hg.

There was apparently no attempt to control for other factors possibly associated with the variation in mortality rates (e.g. age structure of the population), and the effect of cadmium independent of other trace metals was not identified. High concentrations in drinking water of several of the trace metals found in the Havirna water have been associated with cancer in previous studies. The effect of this study is to suggest a possible relationship between high concentrations of trace metals in drinking water and excess cancer mortality without specifically implicating cadmium.

B. Chronic Animal Studies

1. Injection Studies

In 14 chronic studies on rats reviewed by a working group for the International Agency for Research on Cancer (IARC) (1976), malignant tumors at the injection site wer reported in 10. Tumors followed administration of soluble cadmium salts (chloride and sulfate), insoluble salts (sulfide and oxide) and finely divided cadmium metal. Rats receiving injections at four sites (0.04 or 0.08 mg/site) developed local tumors in areas originating from mesenchymal mesoderm (subcutaneous, intramuscular, subperiostial) but not from those originating from ectodermal (intracutaneous), endodermal (liver, ventral prostate, salivary gland) or epithelial mesoderm (kidney) (Gunn et al., 1967).

In several studies, subcutaneous injection of soluble cadmium salts has resulted in the development of interstitial cell tumors of the testis in rats and mice (IARC, 1976). Injection of cadmium produces degeneration of seminiferous tubules followed by proliferation of interstitial cells and finally tumors. A summary of the findings is given on the next page.

2. Oral Studies

a. Schroeder et al. (1965) Rat Study

In a laboratory designed for low trace-metal animal experiments Long-Evans rats were fed a low-metal diet supplemented with 5 ppm of cadmium, lead, or chromium (III) as acetate salts in drinking water. This treatment was continued from weaning until death of the animals. Initially there were 69 males and 58 females; but high early mortality (before 3 months) occurred in treated animals; and the groups were replenished before 3 months so that each group had more than 52 animals. Further

TESTICULAR INTERSTITIAL CELL TUMORS IN ANIMALS

GIVEN CADMIUM BY SUBCUTANEOUS INJECTION

| Strain | $CdCl_2$ a/ Dose(mg/kg) | Tumor Bearing Animals Treated | Control | Observation Time(mo.) | References |
|---|---|---|---|---|---|
| Mouse | | | | | |
| Charles River | 5.5 | 20/26 | 0/25 b/ | 14 | Gunn et al., 1963 c/ |
| Rat | | | | | |
| Wistar | 5.5 | 17/25 | 0/20 b/ | 11 | Gunn et al., 1963 c/ |
| Albino CB | 0.5mg/rat | 10/18 | 0/16 b/ | 20 | Roe et al., 1964 c/ |
| Wistar | 5.5 | 10/25 | - | 23 | Knorre, 1971 |
| Wistar | 3.7 to 5.5 | 13/13 | - | 11 | Lucis et al.,1972 |
| Fischer 344 | 5.5 | 16/20 | 0/10 b/ | 12 | Reddy et al., 1973 |

a/ Single S.C. injection except Roe et al., who used 10 weekly injections of $CdSO_4$

b/ Difference significant at $p<.001$.

c/ Reviewed by IARC (1976); original papers not received in time to be reviewed by CAG.

mortality occurred because of a pneumonia epidemic during weeks 107 to 117, reducing the effective size of the groups to 42 males and 44 females in controls and 50 males and 46 females in treated groups. In the cadmium group there was significantly higher mortality as compared with controls during the first 33 months of observation. (Animals survived up to 42 months).

The major gross causes of death were pneumonia and tumors. Hypertension contributed to the progressive mortality of males, especially since treated animals had enlarged hearts and thickened left ventricles, and the authors had previously reported hypertension in rats. Of the animals which were autopsied, gross tumors were the cause of death in 13/48 treated males compared to 9/35 control males. For females the corresponding observations were 15/36 in treated versus 15/35 in controls. The differences are not statistically significant. No microscopic examination of the tumors was reported. All but one animal with tumors died after 86 weeks. Sixteen of 20 cadmium-fed rats examined (80%) had cirrhosis of the liver as did 13 of 21 control rats (62%). The high frequency of cirrhosis in controls is unusual and makes one wonder what accounted for this finding. Other adverse effects of the cadmium treatment include arteriolarsclerosis in the kidney and enlarged hearts. Cadmium accumulated in livers and kidneys of young rats, but not in animals older than 2 years.

b. Levy and Clack (1975) Rat Study

These investigators administered cadmium sulfate in distilled water to male specific pathogen-free CB hooded rats. Doses of 0.35, 0.18, and 0.087 mg/kg/week in distilled water were administerd by stomach tube for 2 years. Initially there were 30 animals in each treated group and 90

animals in the control group. All sick and moribund animals as well as those surviving for the 2-year period were examined grossly. Microscope preparations were made of all tissues of ten high-dose and ten control animals randomly selected from the animals killed at termination of the experiment. In addition, sections of all testes and any abnormal tissue or organ were examined. The survival at 100 weeks for controls, low, medium, and high dose groups were 67%, 53%, 67%, and 57%, respectively, with some early deaths from mechanical injury during passage of the stomach tube.

The incidence of interstitial-cell testicular tumors was 75% in controls; in the treated rat it was not significantly different. Careful observation of prostate glands showed no gross abnormalities, but foci of slight hyperplasia, inflammation and desquamation of epithelial cells were observed in high-dose and control groups. These changes were not interpreted as metaplastic or pre-neoplastic. Tumors of other organs were observed as follows (number of tumors observed/number of animals in the initial group): controls, 10/90; low dose, 4/30; medium dose, 3/30; high dose, 8/30. All tumors were benign except one basal-cell skin carcinoma in the high-dose group and two sarcomas in the control group.

The number of liver adenomas in the four dose groups was: controls, 1; low dose, 2; medium dose, 0; high dose, 3. The paper did not report which of the tumors were identified on gross examination and which by random selection, making it impossible to determine statistical significance. The Cancer Assessment Group is seeking additional information in this area.

It is difficult to draw conclusions from this report because: (1) only 10 animals randomly selected from the high dose and control group were microscopically examined, rather than all animals from all dose groups; and (2) because of the higher mortality in the high-dose group compared to controls, a correction of the tumor incidence data is necessary. This correction cannot be done without data for the time when the tumors occur in individual animals.

c. Levy et al. (1975) Mouse Study

Groups of specific pathogen-free male Swiss mice were given cadmium sulphate once per week for a period of 18 months. Three treated groups of 50 animals each were given 1.75, 0.88, and 0.44 mg/kg/week by stomach tube and the control group of 150 animals received distilled water alone.

All sick and moribund animals as well as those surviving for the 18 month period were examined grossly. Tissue sections of 20 animals from the high-dose group and 20 from the control group were examined microscopically. These animals were selected randomly from animals with no gross lesions that had survived until termination of the experiment. In addition, sections were examined microscopically from all tissues appearing abnormal grossly. The fraction of animals surviving at the time of terminal sacrifice in the control, low, medium, and high-dose groups were 83%, 94%, 84%, and 84%, respectively.

No gross abnormalities were observed in prostate, bladder, kidney, or testis. A small number of animals in each group had over-distension of seminal vesicles and several showed lesions of the lung and/or liver. From the microscopic sections examined occasional slight epithelial hyperplasia or desquamation was seen in the prostate of both high-dose and control animals. The testes were either normal or had slight atrophy of isolated

seminiferous tubules, occuring with equal frequency in control and high-dose groups. No treatment-related differences in tumor frequency were observed for kidney, lung, or liver tumors.

It is difficult to make quantitative conclusions from this experiment because (1) not all animals were examined histologically and therefore it is possible that small tumors not noticed in gross examination remain undetected; (2) the results of the microscopic examination were only qualitatively stated. However, there is no firm reason to reject the authors' conclusion that this treatment caused no carcinogenic effect.

3. Summary of Animal Experiments

Although direct injection of cadmium salts intramuscularly and subcutaneously usually produces malignant tumors at the injection site and interstitial-cell tumors in the testes, no carcinogenic effect has been clearly seen in rats or mice following oral administration. A plausible explanation for the difference in response is that only about 0.3 to 1% of the orally-administered cadmium dose is absorbed in chronic studies, (Fleischer, et al., 1974). The tumors observed in typical injection experiments are produced by single doses of 4 to 5 mg/kg or repeated doses of 1.7 mg/kg/week. The highest oral dose tested by Levy was 1.75 mg/kg/week in mice and 0.35 mg/kg/week in rats, and the oral dose used by Schroeder in rats was 2.6 mg/kg/week. If only 1% of this oral dose is absorbed, the actual exposure of the animals in the oral experiments is only about 1% of the dose administered in the injection experiments. Therefore, the oral dose might be too small to produce observable effects. In keeping with this only in the Schroeder study was there any indication of a treatment effect as to weight or survival.

# VII. RISK ASSESSMENT

## Introduction and Summary

It was noted in section IV, part 8, that cadmium is carcinogenic in experimental animals by subcutaneous injection. In the case of human exposure to atmospheric cadmium, epidemiological evidence is accumulating from several small-scale studies which suggests an increase in the prostate cancer rate where workers were exposed to high levels of cadmium dust and/or fumes.

Two of these studies, Potts (1965) and Lemen et al. (1976), contain enough exposure information that crude dose-response relationships can be established between lifetime exposure levels and prostate cancer death rates. It was estimated that the percentage increase in the prostate cancer rate per increase of 1 $\mu gm/m^3$ of atmospheric cadmium was 10.1% based on the Potts study and 9.4% based on the Lemen et al. study. The consistencies of these estimates should be viewed as merely coincidental. Considering the crudeness of the exposure data and the small sample sizes of the study cohorts, it would not have been surprising to find a difference of a full order of magnitude, even assuming an identical effect in the two exposed populations.

Using the Potts rate estimate of 10.1% and a 1978 exposure document prepared by Energy and Environmental Analysis, Inc. (EEAI), for EPA, it was calculated that a population of about $34 \times 10^6$ males was exposed to atmospheric cadmium from point sources in sufficient amounts to increase their lifetime probability of death due to prostate cancer by

more than $10^{-5}$. This total exposure resulted in an estimate of about 5 expected deaths per year, which amounts to approximately .03% of the total prostate cancer deaths in the United States.

## Epidemiological Studies with Pertinent Exposure Information

### Potts (1965)

Potts describes the observed mortality in a cohort of men exposed, for at least ten years, to cadmium oxide dust in the manufacture of alkaline batteries. Unfortunately, neither the age structure of the worker population nor the duration of its exposure is given in the paper. As a result, it is not possible to calculate age-exposure-specific mortality rates from the supplied information.

However, three deaths due to prostate cancer were noted in the eight observed deaths in the cohort. If a sample of eight deaths age-matched to the eight deaths in Potts' cohort were taken from the United States population, the probability of three or more prostate-cancer-caused deaths occurring by pure chance in the sample is calculated, based on 1973 U.S. vital statistics, to be $2.16 \times 10^{-4}$. The derivation of this result is shown in appendix I. Since this strongly suggests a cadmium-caused elevation in prostate cancer, we decided to base part of our risk analysis on the proportional mortality of the deceased workers in Potts' cohort.

Based on results of efforts at monitoring industrial plant hygiene dating from 1949 and on worker records, it was possible to make a crude estimate of the lifetime average exposure to atmospheric cadmium for each of the deceased. The bases for these estimates are shown in

table 1. The marked decrease in the average level of exposure over time is due primarily to major plant hygiene improvements in 1950 and 1956. The exposure in the early time period is taken as the geometric mean of the quoted measured levels.

In table 2 the proportional mortality ratio of prostate cancer to total deaths on an age-specific basis is shown for Potts' cohort, as well as U.S. male death rates based on 1973 vital statistics. Under the following assumptions it is possible to utilize the data contained in table 2 to estimate the increase in the U.S. prostate cancer rate per change in each μgm of cadmium in the atmosphere.

1. Given the same exposure, x, the age-specific proportional mortality ratio, $\rho_j$, is the same for Potts' cohort as for the U.S. male population.

2. The increase in the age-specific U.S. prostate cancer rate is a linear function of the exposure x.

From these assumptions it follows that:

$$\rho_j \quad \frac{\alpha_{2j}(1 + \beta x_j)}{\alpha_j + \alpha_{2j}\beta x_j}$$

where $\alpha_{2j}$ = the U.S. prostate age-specific death rate for the jth interval

$\alpha_j$ = the total U.S. age-specific death rate for the jth age interval

$x_j$ average lifetime exposure for those in the jth age interval

$\beta$ = unknown increase in prostate cancer rate in percent per change of one $\mu gm/m^3$ of atmospheric cadmium.

Solving for $\beta x_j$, we have that

$$\beta x_j = \left(\frac{1}{1 - \rho_j}\right)\left(\frac{\rho_j \alpha_j}{\alpha_{2j}} - 1\right) = Y_j$$

so that $\beta$ may be estimated given $Y_j$, $x_j$, $\alpha_j$, $\alpha_{2j}$ by means of fitting a least squares linear equation through the origin. If we weight each point by the value $W_j$, which in this case is the number of deaths in the age interval, we have that $\hat{\beta} = .5024$ (the data utilized to compute $\hat{\beta}$ is shown in table 3). The goodness of fit in a $\chi^2$ sense is shown in table 4, where we note that the variation is reduced to less than half that observed assuming that age or exposure has no effect on the prostate cancer rates.

At the usual levels of environmental exposures, x, it is generally the case that $\alpha_j >> \beta\alpha_{2j}x$. If x is continuous over time, a very close approximation to the increase in the lifetime probability of prostate cancer due to a lifetime exposure x is $P \sim P_0\hat{\beta}x$, where $P_0$ is the lifetime probability of prostate cancer in the U.S. population. From 1973 vital statistics we calculate that $P_0 = .0187$, so that our predictor equation for lifetime probability for low-level atmospheric exposures is

$$P_x \sim .0187 \times .1005 = 1.879 \times 10^{-3}x,$$

where x is lifetime average exposure in $\mu gm/m^3$.

Lemen et al. (1976)

The mortality observed in a cohort of 292 white males engaged in the production of cadmium metal and cadmium compounds for at least two years is discussed in Lemen's paper. These workers were exposed to cadmium fumes and dust during normal smelter operations.

Ideally the entire exposure pattern for each of the workers, in conjunction with age-specific expected and observed death rates, would be utilized for a complete analysis. Unfortunately, the only data available from the paper regarding exposure durations are for four individuals who died from prostate cancer. Under the assumption that this is a random sample from the entire cohort we calculate the lifetime average exposure as indicated in table 5. The air exposure levels in each of the time periods is approximated by utilizing information obtained from industrial hygiene studies conducted in 1947 and 1973.

It was found that the cohort with 20 or more years since first exposure had 4 observed prostate deaths where only .88 would be expected. However, two biasing factors exist that tend to make the expected number larger than its best estimate:

(1) A U.S. white male death rate was used, while it is well known that factory workers in demanding jobs tend to have death rates lower than the U.S. average. To correct for this factor, we note that our observed-to-expected ratio in this cohort for total nonmalignant neoplasm deaths is f 65/81.8. = .79, which, assuming the same ratio of general health regarding prostate cancer, would give a 21% reduction in the .88 expected cases.

(2) A total of 20, or 8% of the cohort, whose vital status was not known were assumed by Lemen to be alive and were included in the calculations of the expected deaths. Since they could not contribute to observed deaths, they can be eliminated by assuming they were of the same age structure as the rest of the cohort. This would result in a reduction of 8% in the expected number of cases.

Accounting for these two factors we calculate that an unbiased estimate of the standard mortality ratio, R, is

$$R \quad 4/(.88 \times .79 \times .92) = 6.254 \ .$$

Under the assumptions of a linear dose response and equivalence of part and total lifetime risk, it can be shown that an estimate of the percentage change in the lifetime probability of contracting a disease is approximately

$$(\beta/\alpha) = (R - 1)/x$$

per change in one $\mu gm/m^3$ of lifetime exposure, where x is the average lifetime exposure in $\mu gm/m^3$. In this case

$$(\beta/\alpha) = (6.254 - 1)/56.1 = .0937, \text{ or } 9.4\%.$$

The predictor equation in this case for the lifetime probability of prostate cancer is

$$P_x \sim .0187 \times .0937x = 1.752 \times 10^{-3}x,$$

where x is the lifetime average exposure to atmospheric cadmium in $\mu gm/m^3$.

## Risk to U.S. Population from Different Sources Releasing Cadmium into the Atmosphere

The 1978 EEAI document prepared for EPA estimated the human exposure to cadmium for selected major emission sources. These data were summarized in table 1 of that document, which listed average exposures from different emission sources and the number of people exposed from each source.

In table 6 this data is shown along with the average lifetime probabilities of prostate cancer by source and the expected number of cases per year calculated from the equations:

$$P_x = 1.879 \times 10^{-6}x$$

and

$$E(D) \sim [1.879 \times 10^{-6} \div 70.9]xN = 2.65 \times 10^{-8}xN$$

where, to correspond to the units of exposure given, x is lifetime average exposure in $\eta gm/m^3$, and N is the number of males exposed. Based on 1973 vital statistics, males make up 48.7% of the U.S. population. Assuming that exposure is independent of sex, multiplying EEAI's estimate of total people exposed by .487 gives the number of males exposed.

It is estimated that about 5 cases of prostate cancer would be caused by atmospheric cadmium each year, with about 87% of that total due to municipal incinerators. This amounts to approximately .03% of the total yearly deaths due to prostate cancer, based on 1973 vital statistics. To place this risk in perspective, a comparison using EEAI's Sources of Atmospheric Cadmium (p. 16) can be developed: based on a retention rate of .07 μgm of cadmium per cigarette smoked, the average risk to a person exposed to cadmium from municipal incinerators is equivalent to smoking 1 cigarette every other day.

If we had used the estimates derived from Lemen's data rather than Potts', all the calculated probabilities and expected numbers of deaths would have been reduced by a factor of only 1.07.

TABLE 1

EXPOSURES OVER TIME AND CALCULATION OF
LIFETIME AVERAGE EXPOSURE TO CADMIUM

| Age Interval | Individual's Age at Death | Working Years of Exposure to Cadmium | | | Lifetime Average Exposure[a] in $\mu gm/m^3$ |
|---|---|---|---|---|---|
| | | 1920-1949 (Average Exposure Level: 7.4 $mg/m^3$) | 1950-1955 (Average Exposure Level: .5 $mg/m^3$) | 1956-1964 (Average Exposure Level: .1 $mg/m^3$) | |
| 50-54 | 53 | 21 | 6 | 8 | 660.8[b] |
| 55-59 | 59 | 19 | 6 | 9 | 262.9 |
| 60-64 | 63 | 21 | 6 | 7 | 555.6 |
| 65-70 | 65 | 20 | 6 | 5 | 512.8 |
| | 65 | 25 | 6 | 6 | 638.3 |
| | 65 | 23 | 6 | 9 | 589.3 |
| | | | | | $\bar{x}$ = 580.1 |
| 75-80 | 75 | 14 | 0 | 0 | 303.8 |
| | 78 | 18 | 0 | 0 | 375.7 |
| | | | | | $\bar{x}$ = 339.8 |

[a]Average exposure weighted by number of years exposed × (fraction of working year exposed = .22) ÷ age at death × $10^3$ = lifetime average exposure in $\mu gm/m^3$.

[b]Example: $660.8 = (7.4 \times 21 + .5 \times 6 + .1 \times 8) \times .22 \div 53 \times 10^3$.

TABLE 2

DATA USED TO ESTIMATE EFFECT OF CADMIUM EXPOSURE ON INCREASE IN U.S. PROSTATE CANCER

| Age Interval | Potts' Data | | | 1973 U.S. Male Death Rates × $10^5$ | |
|---|---|---|---|---|---|
| | Total Deaths | Deaths Due to Prostate Cancer | $\rho_j$ = Proportional Mortality Ratio | $\alpha_j$ Total | $\alpha_{2j}$ Prostate Cancer[a] |
| 50-54 | 1 | 0 | 0 | 1,103.0 | 5.1 |
| 55-59 | 1 | 0 | 0 | 1,779.0 | 13.6 |
| 60-64 | 1 | 0 | 0 | 2,695.5 | 33.7 |
| 65-69 | 3 | 2 | .6667 | 3,933.5 | 72.0 |
| 75-79 | 2 | 1 | .5000 | 8,813.5 | 246.0 |

[a]ICD 180-187, malignant neoplasms of genital organs, × .942, where

$$.942 = \frac{18,830}{19,864}$$

is the fraction of total number of deaths classified 180-187 which are attributed to ICD 185, malignant neoplasm of prostate, based on 1973 U.S. mortality data.

TABLE 3

DATA UTILIZED TO COMPUTE SLOPE OF
DOSE RESPONSE CURVE $\beta$

| Age Interval | Number of Deaths in Interval = $W_j$ | Lifetime Average Exposure = $x_j$ | $Y_j$ |
|---|---|---|---|
| 50-54 | 1 | 660.8 | -1. |
| 55-59 | 1 | 262.9 | -1. |
| 60-64 | 1 | 555.6 | -1. |
| 65-69 | 3 | 580.1 | 106.3 |
| 75-79 | 2 | 339.8 | 33.8 |

$$\text{RESULT:} \quad \beta = \frac{\sum W_j x_j Y_j}{\sum W_j x_j^2} = \frac{206,485.1}{2,054,940.5} = .1005$$

TABLE 4

GOODNESS OF FIT IN $\chi^2$ SENSE OF MODEL

| Age Interval | Observed Prostate Cancer Deaths | Under Assumed Model† | | Under No-Effect-of-Exposure Assumption†† | |
|---|---|---|---|---|---|
| | | Expected Prostate Cancer Deaths | $\chi^2$ Deviation | Expected Prostate Cancer Deaths | $\chi^2$ Deviation |
| 50-54 | 0 | .238 | .238 | .375 | .375 |
| 55-59 | 0 | .174 | .174 | .375 | .375 |
| 60-64 | 0 | .418 | .418 | .375 | .375 |
| 65-69 | 2 | 1.575 | .115 | 1.125 | .7777 |
| 75-79 | 1 | 1.005 | .000 | .75 | .08333 |
| Total | 3 | | .945 | 3 | 1.986 |

† $\varepsilon = n\hat{\rho} = \dfrac{n\alpha_{2j}(1 + .1005x_j)}{\alpha_j + .1005\alpha_{2j}x_j}$

†† $\varepsilon = n \times 3/8$

RESULT: % reduction in $\chi^2$ is $\dfrac{1.986 - .945}{1.986} = 52.42\%$

TABLE 5

EXPOSURES OVER TIME AND CALCULATION OF LIFETIME AVERAGE EXPOSURE TO CADMIUM

| Individual's Age at Death | Working Years of Exposure to Cadmium[a] | | Lifetime Average Exposure[b] in $\mu gm/m^3$ |
|---|---|---|---|
| | 1925-1947 (Average Exposure Level: 1.5 $mg/m^3$) | 1948-1973 (Average Exposure Level: 1.0 $mg/m^3$) | |
| 71 | 4 | 0 | 18.6 |
| 77 | 5 | 8 | 44.3[c] |
| 79 | 17 | 1 | 73.8 |
| 64 | 17 | 0 | 87.7 |
| | | Average = 56.1 | |

[a]Based on Lemen et al., table 4.

[b]Average exposure weighted by number of years exposed × (fraction of working year exposed = .22) ÷ age at death × $10^{-3}$ = lifetime average exposure in $\mu gm/m^3$.

[c]Example: $44.3 = (5 \times 1.5 + 8 \times 1.0) \times .22 \div 77 \times 10^3$.

TABLE 6

EXPECTED NUMBER OF PROSTATE CANCER CASES PER YEAR DUE TO DIFFERENT SOURCES OF ATMOSPHERIC CADMIUM EXPOSURE

| Source | Average Exposure ngm/$m^3$ | Lifetime Probability of Prostate Cancer due to Cadmium | Expected Number of Prostate Cancer Deaths per Year due to Cadmium |
|---|---|---|---|
| Secondary Copper | 1.54 | $2.90 \times 10^{-6}$ | .20 |
| Secondary Zinc | .47 | $8.84 \times 10^{-7}$ | - |
| Municipal Incinerators | 7.16 | $1.35 \times 10^{-5}$ | 4.53 |
| Primary Zinc | 10. | $1.88 \times 10^{-5}$ | .01 |
| Primary Lead | 10. | $1.88 \times 10^{-5}$ | - |
| Primary Copper | 10. | $1.88 \times 10^{-5}$ | .01 |
| Primary Cadmium | 10. | $1.88 \times 10^{-5}$ | - |
| Iron and Steel | 1.9 | $3.58 \times 10^{-6}$ | .49 |
| Total | | | 5.24 |

## APPENDIX I

### DERIVATION OF PROBABILITY OF THREE OR MORE PROSTATE CANCER DEATHS IN U.S. AGE-MATCHED SAMPLE

In general, if we wish to calculate the probability of k or more deaths of a specific type from a series of deaths from m different age groups, we proceed as follows:

Let $N_j$ = Number of deaths in jth age group

$N = \sum_{j=1}^{m} N_j$ = Total number of deaths in population of interest

$r_j$ = Number of deaths in jth age group of type of interest

$r = \sum_{j=1}^{m} r_j$ = Total number of deaths of type of interest

$\alpha_j$ = Age-specific death rate for jth age group

$\alpha_{2j}$ = Age-specific death rate for jth age group for cause of interest

$P_j = \alpha_{2j}/\alpha_j$ = Probability, given that an individual in the jth age group died, that death was due to the cause of interest.

Then

$$\phi(\nu,r) = \sum_{\text{all } \nu} \prod_{j=1}^{m} \binom{N_j}{r_j} P_j^{\,r_j} (1 - P_j)^{N_j - r_j}$$

equals the probability of exactly r deaths in the entire population due

to the cause of interest, where $\nu$ is all possible combinations of the $r_j$ that sum to r. It follows that

$$P(r \geq k) = \sum_{r=k}^{N} \phi(\nu,r) = 1 - \sum_{r=0}^{k-1} \phi(\nu,r)$$

equals the probability of k or more deaths due to the cause of interest.

From section VI, table 2, we calculate the $P_j$ for prostate death rates and show them in appendix table 1, along with all the possible combinations that could result in two or less prostate cancer deaths. For each combination, $\phi(\nu,r)$ r = 0,1,2 is calculated where $\nu$ = 18. The probability of $r \geq 3$ is simply 1 minus the sum of all these probabilities, or $P(r \geq 3) = 1 - (.872032 + .120665 + .007087) = .000216$.

APPENDIX TABLE 1

PROBABILITY OF THREE OR MORE PROSTATE CANCER DEATHS
OUT OF EIGHT DEATHS IN SPECIFIED AGE GROUPS
BASED ON 1973 U.S. DEATH RATES

| Age Interval | Number of Deaths $N_j$ | Probability Death Was Due to Prostate Cancer $P_j$ | All Possible Combinations That Result in Two or Less Prostate Cancer Deaths $r_j$ | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | r=0 | r=1 | | | | | r=2 | | | | | | | | | | | | | | |
| 50-54 | 1 | .004624 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| 55-59 | 1 | .007645 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | | | |
| 60-64 | 1 | .012502 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | | | |
| 65-69 | 3 | .018304 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 2 | 0 | | | |
| 75-79 | 2 | .027912 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 2 | | | |
| | | | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | | | |
| Total Prostate Cancer Deaths r = | | | 0 | 1 | | | | | 2 | | | | | | | | | | | | | r | |
| | | | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | | | Probability of Specified Outcome |
| | | | ↓ .872032 | ↓ .004051 | ↓ .006718 | ↓ .011040 | ↓ .048778 | ↓ .050078 | ↓ .000031 | ↓ .000051 | ↓ .000227 | ↓ .000233 | ↓ .000085 | ↓ .000376 | ↓ .000386 | ↓ .000618 | ↓ .000634 | ↓ .002801 | ↓ .000926 | ↓ .000719 | | | |
| | | | } .872032 | .120665 | | | | | .007087 | | | | | | | | | | | | | | Probability of Exactly r Prostate Cancer Deaths |

RESULT:

$P(r \geq 3) = 1 - (.872032 + .120665 + .007087)$

$= .000216$

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