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Dear Sir or Madam:

Enclosed is a report entitled "Mortality Study of Employees Engaged in the Manufacture and Use of Hydroquinone". This report is being submitted as a follow-up to our original submission on hydroquinone of April 2, 1991 (EPA Document Control Number [redacted])

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Sincerely,

R. Hays Bell  
(716) 722-5036

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R. Hays Bell, Ph.D., Vice-President and Director, Corporate Health, Safety, and Environment  
Eastman Kodak Company, Rochester, NY 14652-6256



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**MORTALITY STUDY OF EMPLOYEES ENGAGED IN THE  
MANUFACTURE AND USE OF HYDROQUINONE**

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May 1994

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## SUMMARY

Mortality in a 1942-1990 cohort of 858 men and 21 women employed in the manufacture and use of hydroquinone was evaluated through 1991. Average exposure concentrations, 1949-1990, ranged from 0.1 to 6.0 mg/m<sup>3</sup> for hydroquinone dust and from less than 0.1 to 0.3 for quinone vapor (estimated eight-hour time-weighted averages). Compared with general population and occupational referents, there were statistically significant deficits in total mortality and deaths due to cancer. No significant excesses were observed for such hypothesized causes as kidney cancer (2 observed vs. 1.3 expected [both control groups],  $p \sim 0.39$ ), liver cancer (0 vs. 0.8, 1.3), and leukemia (0 vs. 2.3, 2.7). Dose-response analyses of selected causes of death, including renal carcinoma, demonstrated no statistically significant heterogeneities or linear trends according to estimated career hydroquinone exposure (mg/m<sup>3</sup>-years) or time-from-first-exposure.

## INTRODUCTION

Hydroquinone (HQ; 1,4-benzenediol) is a white crystalline compound used extensively as a developer for black-and-white photography, medical and industrial x-ray films, and graphic arts films. Major nonphotographic applications include use as an antioxidant and antiozonant for rubber, a polymerization inhibitor for acrylic and vinyl acetate monomers, and an intermediate for agrochemicals, performance plastics, and dyes. HQ is also an ingredient of dermatologic preparations used to lighten hyperpigmented areas. Quinone (BQ; *p*-benzoquinone), a yellowish crystalline solid which readily sublimates, is utilized primarily as an intermediate in agrochemical manufacturing. It is also used in the dye, textile, and chemical tanning industries and for the production of unsaturated polyesters. In addition to being an intermediate for the HQ aniline oxidation process, BQ is an *in vivo* metabolite of HQ.

Case reports and clinical studies have described ocular effects in HQ production workers. Exposure to relatively high concentrations of HQ dust and BQ vapor in older manufacturing operations has been associated with both temporary and permanent eye effects, including irritation, conjunctival and corneal pigmentation, and corneal opacities and structural irregularities (e.g., erosion of the epithelium and changes in the thickness and curvature of the cornea) which resulted in loss of visual acuity in a few severe cases.<sup>1,2</sup> The earliest report of conjunctival staining was observed after only four months of exposure; no cases of corneal involvement occurred in less than five years.<sup>3</sup> There was evidence of greater severity of response with increasing duration of employment, albeit there was considerable individual variability. Although BQ vapor was hypothesized as the major etiologic factor, HQ dust was considered a contributory cause.

A few cases of a vitiligo-like depigmentation have been described among film processing workers handling developing solutions containing HQ.<sup>4-7</sup> In addition, Choudat et al.<sup>8</sup> reported respiratory effects in a group of employees exposed simultaneously to a number of chemicals, including HQ and its derivatives.

In 1990, the National Toxicology Program published the results of a two-year

gavage study of HQ which showed "some evidence of carcinogenic activity" for kidney adenomas in male rats, for mononuclear cell leukemia in female rats, and for liver neoplasms, mainly adenomas, in female mice.<sup>9</sup> A recently conducted animal bioassay reported a statistically significant excess of renal adenomas in male rats and hepatocellular adenomas in male mice administered HQ in the diet for two years.<sup>10</sup> The incidence of kidney and liver carcinomas was not significantly different between the treated rodents and controls of either sex. The results of these bioassays have raised questions concerning the potential carcinogenicity of HQ and its metabolite, BQ, in humans.

Epidemiologic studies of HQ-exposed populations have not reported adverse health effects. Friedlander *et al.*<sup>11</sup> found no evidence of an increased risk of cancer or other chronic diseases in a group of photographic processors with limited exposure to HQ. In a cohort mortality study of men at a large chemical plant, Pifer *et al.*<sup>12</sup> reported a statistically significantly decreased Standardized Mortality Ratio (SMR) of 50 from all causes among employees of the organic chemicals division, where HQ is produced. The numbers of deaths due to all cancers (SMR 56), lung tumors (SMR 60), and nonmalignant respiratory diseases (SMR 24) were all lower, although not statistically significantly, than expected among the general population referents.

The present epidemiologic study, which was based on data collected at the Tennessee Eastman Division (TED) of Eastman Chemical Company, was designed to (1) evaluate the mortality experience of a cohort of men and women employed in HQ manufacturing and related activities, (2) test hypotheses for deaths due to renal and hepatic tumors and leukemia, and (3) assess dose-response relationships for these hypothesized cancer sites according to estimated career HQ exposure and time-from-first-exposure (latency).

## BACKGROUND

TED, Eastman Chemical Company's largest facility, was established in Kingsport, Tennessee in 1920 to produce wood alcohol for photographic film base

manufacturing. It currently produces a wide variety of chemicals, fibers, and plastics, including filter tow, textile dyes, photographic chemicals, cellulosic plastics, various other specialty chemicals, and polymers for beverage bottles. HQ has been manufactured at TED since 1930.

In 1941, a Kingsport ophthalmologist reported that a HQ worker had developed an unusual staining of the conjunctiva. Shortly thereafter, two other cases were observed, including one diagnosed by a Duke University ophthalmologist who subsequently conducted periodic eye evaluations of all TED employees with exposure to HQ and BQ. Follow-up examinations were performed at 1-, 3-, or 5-year intervals based on the extent of exposure and physical findings. In the mid-1980's, surveillance of HQ-exposed personnel, including retirees, was transferred from Duke University eye specialists to TED physicians. Clinical results were reported in 1947,<sup>1,13</sup> 1958,<sup>2</sup> 1973,<sup>3</sup> and 1976.<sup>14</sup>

#### **METHODS**

The study population, which was identified from eye examination lists and medical records (1942-1975) and from computer files (1967-1990), included 858 men and 21 women who worked at least six months between January 1930 and December 1990 in HQ manufacturing and other areas in which HQ was used.

The vital status of the study subjects was obtained from both internal (TED mortality data base) and external (Social Security Administration) sources. Death certificates, required for the processing of life insurance claims, have been routinely collected at TED since the 1940's. In addition, the social security numbers of the study subjects were matched against the Social Security Administration's Death Master File through 1990. The underlying cause of death was coded by a nosologist consultant according to the Ninth version of the International Classification of Diseases (ICD-9).<sup>15</sup>

Person-years of risk, initiated after the employee had completed six months of service, were accumulated for the study subjects by five-year age group, sex, and calendar year category beginning January 1942, when the first eye examinations were

conducted (if employed prior to 1942), or on the date hired (between 1942 and 1990) and ending at death, the date of termination, or December 31, 1991.

The mortality experience of the study subjects was compared with vital statistics from both general population (State of Tennessee) and occupational (Eastman Kodak employees in Rochester, N.Y.) referents. For the state comparison, the expected number of deaths by cause was calculated by applying quinquennial age-sex-cause-specific death rates, 1950 to 1990, to the appropriate survival-years of follow-up in the study population. A similar procedure was used for more than 30,000 hourly-wage personnel (few of whom had potential HQ exposure) employed at Kodak Rochester facilities from 1964 to 1992.

The statistical significance of observed-to-expected differences was tested according to two sets of criteria depending on whether the cause of death was hypothesized or nonhypothesized. Based on the results of animal bioassays, a priori hypotheses for deaths due to kidney and liver cancer and leukemia were evaluated using  $p \leq 0.05$  (one-tailed test); all other causes were assessed using  $p \leq 0.05$  (two-tailed test). The Poisson probability distribution was applied to test statistical significance.

### OCCUPATIONAL STANDARDS

The Threshold Limit Value (TLV<sup>®</sup>) for HQ of 2 mg/m<sup>3</sup> as an eight-hour time-weighted average (TWA) has remained unchanged since it was adopted by the American Conference of Governmental Industrial Hygienists (ACGIH)<sup>16</sup> in 1956. In 1971, the U.S. Occupational Safety and Health Administration (OSHA) adopted the TLV level for its permissible exposure limit (PEL).<sup>17</sup> The current TLV and OSHA PEL for BQ, which were promulgated in 1961 and 1971, respectively, are 0.1 ppm as an eight-hour TWA.<sup>16,17</sup>

### PRODUCTION TECHNIQUES

Table 1 identifies HQ manufacturing operations and other areas in which HQ was used at TED, describes job assignments, and provides estimates of the number of

employees and statistics describing average annual HQ exposure levels. From approximately 1930 through June 1986, HQ was manufactured by the aniline oxidation process in which aniline sulfate reacts with manganese dioxide ore in the presence of sulfuric acid and water to produce BQ. After part of the excess sulfuric acid is neutralized with hydrated lime, the BQ is steam distilled from the oxidation solution for final processing. To produce HQ, this mixture is reduced with an aqueous suspension of iron and sulfuric acid. The iron oxide is then filtered to isolate the HQ. After crystallization, centrifuging, drying, and packaging operations, the technical-grade HQ at TED is dissolved in demineralized water, treated with activated charcoal to remove impurities, centrifuged, and dried to produce photographic-grade HQ. From 1936 to 1987, a byproduct, manganese-ammonium sulfate, was sold as a fertilizer and animal feed additive.

In July 1986, TED began manufacturing HQ through a process involving the air oxidation of *p*-diisopropylbenzene (DIPB) to its dihydroperoxide (DHP), followed by cleavage of DHP to acetone and HQ. After separation as an aqueous solution, the HQ is processed through the recovery operations outlined above, viz., crystallization, centrifuging, drying, and packaging, which yields photographic-grade HQ without further purification. At present, HQ is manufactured by approximately 70 production and supervisory personnel who maintain two 12-hour shifts seven days a week.

Table 1 shows that, in addition to HQ production and support personnel who represented about half of the cohort, the study population included employees who received limited HQ exposure during the manufacture of specialized chemical compounds.

#### **HISTORICAL WORK PRACTICES**

Two papers published in 1947 describe early HQ production at TED.<sup>13,18</sup> Prior to 1942, when the first evidence of ocular effects was reported, "practically all operations were conducted in open tanks", and "the accepted criterion for regulating the concentration of quinone vapor ... was the discomfort of the workman as judged by

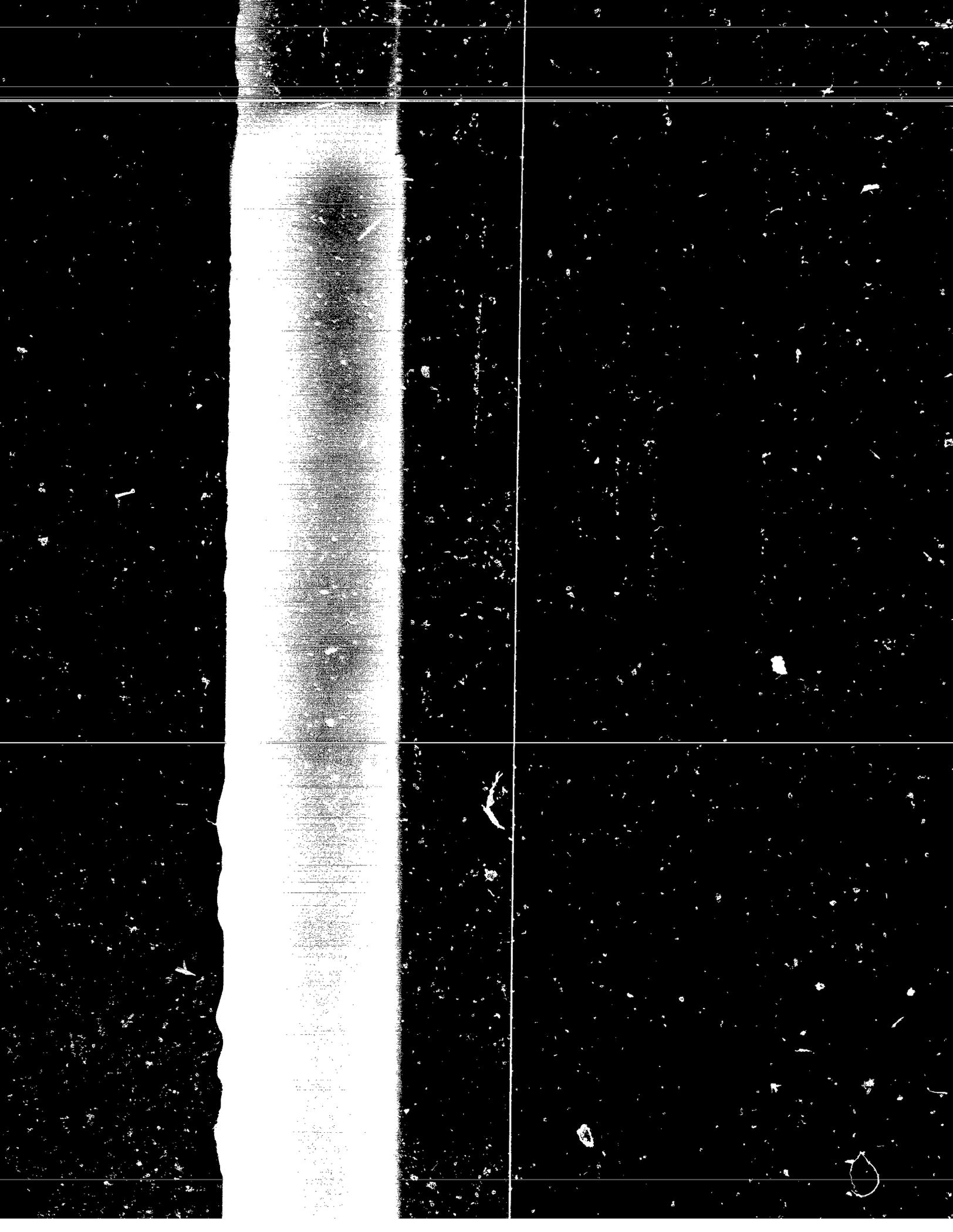
the signs and symptoms of continued eye irritation ...<sup>13</sup> Efforts to minimize high-exposure operations during the 1940's included engineering controls such as isolating the filter presses from the mixing tanks, installing exhaust ventilation in the oxidation and centrifugation areas, and redesigning the HQ packaging machinery where "concentrations ... were of the order of 20-35 mg/m<sup>3</sup>."<sup>18</sup> In addition, filter press cleaning jobs were shared among the operators who were provided with respiratory protective devices, "few of (which) were the full face-piece type, and excepting on unusual occasions their use was not enforced."<sup>13</sup>

During the 1940's, training programs were started to educate employees about the potential for ocular damage, work practices were changed to limit exposures, and operating system improvements were introduced to control emissions. However, as a result of a four-fold higher rate of HQ production in the 1950's, airborne concentrations increased above the levels recommended in 1947 (viz., 2-3 mg/m<sup>3</sup> HQ and 0.1 ppm BQ)<sup>18</sup> for preventing eye injury.

The improvements in HQ manufacturing techniques during the past four decades, including the construction of an essentially closed system in the mid-1930's, have reduced exposure to HQ dust and BQ vapor to concentrations substantially below the current standards. To minimize potential exposure from skin contact, employees are required to wear gloves and protective clothing; coveralls are washed at a company laundry facility. Safety glasses (with side shields) and safety shoes are also prescribed equipment, and face masks and respirators are worn when necessary. Engineering controls such as local exhaust systems are located at packaging and drying sites where there is the possibility of HQ dust exposure. Finally, good housekeeping practices (i.e., washing floors and cleaning equipment) are performed on a regular basis, and workers are required to shower at the end of the shift.

#### AIR MONITORING PROCEDURES

Industrial hygiene surveys of airborne concentrations of HQ and BQ have been routinely conducted at TED since the late 1940's. Until 1984, when the analytic



techniques were changed, short-arm personal and area samples were collected in impingers containing isopropyl alcohol and analyzed colorimetrically.<sup>16</sup> With the exception of some general area samples, most of the data were collected for specific areas or tasks (viz., oxidizers, control room, filter presses, centrifuges, dryers, and packaging) where exposures were expected. Starting in approximately 1985, full-shift samples using filters and solid sorbent sampling tubes were assessed by liquid chromatography. With the advent of the DIPB process in 1986, sampling was generally limited to operations following isolation of HQ as an aqueous solution.

Annual estimates of HQ and BQ exposures, shown in Figure 1, were based on approximately 8000 breathing zone and area samples collected between 1949 and 1990. It has only been since 1985, however, that full-shift sampling representative of eight-hour TWAs has been conducted.

As noted, during early production operations, workers were potentially exposed to concentrations of HQ dust and BQ vapor, respectively, as high as 15 to 30 times the current TLVs.<sup>16</sup> Data collected during the past four decades show that HQ values have generally decreased from concentrations of more than 6.0 mg/m<sup>3</sup> in the mid-1950's to levels which are presently less than 0.1 mg/m<sup>3</sup> as an eight-hour TWA. Similarly, BQ levels have declined from approximately 0.27 ppm to less than 0.05 ppm currently.

### CAREER EXPOSURE ESTIMATES

Career HQ exposure estimates were derived from extensive air monitoring data and from job histories abstracted from company personnel records. Estimates of HQ exposure levels were prepared for five periods: 1930-1945, 5.0 mg/m<sup>3</sup>; 1946-1951, 2.5 mg/m<sup>3</sup>; 1952-1956, 6.0 mg/m<sup>3</sup>; 1957-1966, 2.0 mg/m<sup>3</sup>; and 1967-1990, 0.4 mg/m<sup>3</sup>. In addition, a data base was constructed containing the beginning and ending dates, department numbers, and job codes of all occupational assignments held by each study subject, starting in 1930 when HQ was first manufactured at TED. Jobs were assigned an exposure rating (High, Medium, Low) based on historical air sampling results. The HQ concentration for jobs classified as "High Exposure" was 100% of the estimated HQ

level for the specified time period. Included were such occupations as crude HQ operator, filter press cleaner, pilot plant operator, and refining operator as well as managerial positions in the HQ production department. Certain jobs in which HQ was used as a raw material in the manufacture of specialized chemicals were classified as having "Medium Exposure", which was defined as 25% of the estimated HQ level. Finally, the "Low Exposure" category, which included jobs in which there was minimal HQ exposure (e.g., loading drums of HQ to a reactor once during an eight-hour shift), was assigned a value which was 5% of the estimated HQ concentration. An index of career exposure ( $\text{mg}/\text{m}^3\text{-years}$ ) was developed for each subject by summing the products of estimated HQ exposure (concentration times exposure time) and duration of employment for all jobs held between 1930 and 1990.

## RESULTS

### Cohort Description and Follow-up

The 879 employees in the study contributed 22,895 person-years during the 50-year observation period, 2205 (10%) of which represented ages 65 and older. The distribution of cohort members according to year of first employment was: 1930-1939, 5%; 1940-1949, 15%; 1950-1959, 22%; 1960-1969, 21%; 1970-1979, 27%; and 1980-1990, 10%. The mean duration of tenure in a HQ environment was 13.7 years, and the mean follow-up from first exposure was 26.8 years. As of December 31, 1991, 46% of the subjects were on active status and 35% were on inactive status (22% retired, 3% disabled, and 10% terminated). One hundred and sixty-eight employees (19%) had died.

Follow-up was essentially complete. The 91 terminees were young (average age 28.8 years) and short tenured (average length of service 3.8 years). Death certificates were unavailable for three decedents.

### Mortality Findings

Table 2 shows the number of observed and expected deaths based on comparison with the general population (Tennessee) and occupational (Kodak

Rochester) referents for major causes of death and subcategories of cancer and circulatory disease. SMRs and 95% confidence intervals are presented for causes with more than one death. The 168 observed deaths compared with 256.7 expected deaths vs. Tennessee (SMR 65) and 204.3 expected deaths vs. Kodak Rochester (SMR 82); both SMRs were statistically significantly less than 100. Thirty-three employees died of cancer compared with 57.9 and 53.5 deaths expected based on Tennessee and Kodak Rochester death rates, respectively; the SMRs of 57 and 62 were statistically significant. Among hypothesized cancer sites, there were two renal tumors (vs. 1.3 expected, one-tailed  $p = 0.39$ , Tennessee comparison) and no deaths due to liver cancer (vs. 1.3 expected) or leukemia (vs. 2.3 expected). The number of malignant kidney neoplasm deaths expected relative to the mortality experience of Kodak Rochester hourly-wage employees was also 1.3 ( $p = 0.36$ , one-tailed). The expected numbers of liver cancer and leukemia deaths were, respectively, 0.8 and 2.7.

Other causes demonstrating statistically significant deficits compared with Tennessee vital statistics were respiratory system malignancies (14 observed vs. 24.5 expected), cardiovascular diseases (92 vs. 118.3), digestive diseases (3 vs. 9.1), and accidental fatalities (18 vs. 29.1). Digestive system cancer mortality was significantly below expectation vs. the Kodak Rochester controls (7 observed vs. 15.4 expected). There were no causes demonstrating statistically significant excesses.

To evaluate dose response, we analyzed the data in terms of career HQ exposure and time-from-first-exposure (TFFE). For the cumulative exposure analysis, three categories of HQ exposure ( $< 3$ , 3 to  $< 15$ , and  $\geq 15$   $\text{mg}/\text{m}^3\text{-years}$ ) were defined in order to achieve an approximately equal number of expected deaths in each dosage subgroup. Similarly, the assessment of mortality based on TFFE included persons with  $< 20$ , 20 to 34, and  $\geq 35$  years elapsing since initial employment in a HQ environment. In each case, person-years were apportioned to the appropriate career and TFFE categories as the employee advanced through his/her TED career. The number of deaths observed was compared with the number expected based on Tennessee and

Kodak Rochester death rates. Chi square tests were performed to assess homogeneity<sup>19</sup> and linear trend<sup>20</sup> for the SMRs across both career exposure and TFFE categories.

Table 3 shows that there was no evidence of a dose-related effect for any cause of death category, including all causes, cancer, and cardiovascular diseases. Based on comparison with Tennessee vital statistics, the total mortality SMRs for the lowest to the highest exposure groups were, respectively, 55, 75, and 66, all statistically significantly below 100. Similar results were reported for cancer mortality; SMRs were 35 (statistically significant), 77, and 50. There were no renal carcinoma deaths in the low exposure category and one each vs. 0.4 expected ( $p = 0.33$ , one-tailed) in the middle and high categories.

No consistent mortality pattern was observed for the analysis according to TFFE (Table 4). Total mortality SMRs vs. Tennessee death rates were 63 (< 20 years), 62 (20-34 years), and 70 ( $\geq 35$  years). The respective SMRs for the three TFFE categories were 53, 34, and 77 for cancer and 69, 90, and 72 for circulatory diseases. The two kidney cancer deaths occurred among employees in the longest TFFE category; the number of deaths expected based on Tennessee and Kodak Rochester death rates were, respectively, 0.6 ( $p = 0.12$ , one-tailed) and 0.5 ( $p = 0.16$ , one-tailed).

Table 5 summarizes the results according to career exposure and TFFE for the kidney cancer deaths and selected other causes. The renal tumor observed-expected ratios (internal comparisons) for the lowest to highest exposure categories were 0.0, 1.45, and 1.73; the  $p$  values for the tests of linear trend and equality of observed-expected ratios were, respectively, 0.30 and 0.56. Similar results were observed for the TFFE analysis: ratios 0.0, 0.0, and 1.33, and  $p$  values 0.43 (trend test) and 0.72 (difference test). With the exception of respiratory cancer deaths, for which there was statistically significant heterogeneity ( $p = 0.007$ ) but no evidence of a dose-response association, the results for the other causes of death were unremarkable.

## DISCUSSION

Concern about the carcinogenic and toxic potentials of HQ and BQ is based on several factors. The first is that HQ and BQ are metabolites of benzene, which has been classified as a carcinogen in rodents and a leukemogen in humans.<sup>21</sup> Chronic benzene exposure has also been associated with blood disorders, pancytopenia, and aplastic anemia in humans.<sup>22</sup> Concomitant administration of HQ and phenol by intraperitoneal injection in mice has been reported to reduce bone marrow cellularity, possibly due to phenol-induced stimulation of HQ metabolism to BQ.<sup>23</sup> HQ and other benzene metabolites given alone have not shown similar effects on the bone marrow.

A second factor is the tumorigenicity of HQ and BQ in experimental animals. When HQ was given to F344 rats and B6C3F<sub>1</sub> mice, it demonstrated some evidence of carcinogenicity as shown by increased incidences of benign tumors of the kidney (male rats) and liver (female mice), and mononuclear cell leukemia (female rats) in one study<sup>9</sup> and benign tumors of the kidney (male rats) and liver (male mice) in a second study.<sup>10</sup> Male F344 rats demonstrated a significant incidence of enhanced chronic progressive nephropathy when given HQ.<sup>9,10</sup> In addition, HQ was marginally effective in promoting esophageal tumors induced by methyl-N-amyl nitrosamine.<sup>24</sup>

Three toxicologic investigations provide very limited data suggestive of a carcinogenic effect for BQ.<sup>25-27</sup> In a study by Takizawa and Kanizawa,<sup>25</sup> Strain A mice exposed to BQ vapor were reported to have developed a higher rate of "malignant adenomas" of the lungs. Otsu<sup>26</sup> also exposed mice (A/HeMs F94 strain) to BQ vapor and observed an increased incidence of lung tumors. Finally, Umeda<sup>27</sup> observed that two of 17 rats injected subcutaneously with BQ in propylene glycol developed fibrosarcomas, while control rats developed none.

Lastly, HQ and BQ, when tested for genotoxicity using *in vitro* assays or parenteral routes of administration *in vivo*, have commonly demonstrated positive findings for chromosomal damage.<sup>9</sup>

The present study showed no evidence of excess mortality for major causes of

death. The number of deaths from all forms of cancer was statistically significantly below expectation compared with both general population and occupational controls. There was also a lower than expected death rate from heart disease. Whereas job preplacement screening may have contributed to the low cardiovascular SMR, it would not be expected to substantially affect cancer mortality. In addition, the study did not support the findings of the animal cancer bioassays, which showed an increased prevalence of predominately benign neoplasms of the kidney and liver and of mononuclear cell leukemia. Renal cancer mortality was not statistically significantly different from expectation, and no hepatic cancer or leukemia deaths were observed. Additionally, there were fewer than expected deaths from respiratory cancer, nonmalignant pulmonary diseases, and genitourinary system illness, including nephrotoxicity.

Two cohort men died of kidney cancer. The first worked for TED and affiliated companies for more than 35 years in various jobs, including general laborer, acetic anhydride operator, acetate yarn handler, viscosity analyst, quality control operator, extrusion operator (polyolefins), and plastics analyst. His estimated career HQ exposure of 4.5 mg/m<sup>3</sup>-years was based on less than two years of experience as a "crude process operator" in the early 1950's. Diagnosed with renal cell carcinoma in 1985, he died about two years later at age 62 years. The second employee worked in HQ manufacturing as an oxidation, filtration, and crystallization operator for more than half of his 38-year career, starting in 1933 and ending in 1953 when he was transferred to a non-HQ environment because of progressive visual loss from corneal involvement. His lifetime HQ exposure was estimated to be 86.8 mg/m<sup>3</sup>-years. He retired in 1968 and died 16 years later of a malignant hypernephroma at the age of 78 years.

Both of the employees who died of kidney cancer had a history of long-term tobacco usage (one pack a day) for at least 20 years and 40 years, respectively. There is substantial epidemiologic evidence that smoking is the major known cause of cancer of the kidney. Two early (1966) cohort mortality investigations<sup>28,29</sup> and eight recent

(1963-1982) case-control studies<sup>30-37</sup> have reported statistically significant elevated risks for cigarette smoking as high as 7.6.<sup>32</sup> A 1974-1979 study in the Minneapolis-St. Paul metropolitan area reported that smoking accounted for 30% of the renal cell cancers among males and 24% among females,<sup>34</sup> and an even higher percentage of malignancies of the renal pelvis, 82% and 61% among males and females, respectively.<sup>32</sup> Also, 43% of the male renal cell carcinoma cases in Los Angeles County, 1975-1979, were attributed to cigarette smoking.<sup>31</sup>

Two other personal risk factors which have shown a statistically significant positive association with kidney cancer in more than one case-control study are obesity<sup>31,34,38,39</sup> and chronic use of analgesics containing phenacetin,<sup>34-36,40,41</sup> primarily among women.

There is no consistent evidence linking renal neoplasms with occupational exposures. Although the epidemiologic results have often been contradictory, a statistically significantly increased risk has been reported for truck drivers,<sup>30</sup> newspaper pressmen,<sup>42</sup> and workers in the iron and steel,<sup>43,44</sup> dry cleaning,<sup>44</sup> petroleum refining,<sup>44</sup> asbestos manufacturing<sup>45</sup> and insulation,<sup>46</sup> chemical,<sup>47</sup> and paperboard printing industries.<sup>41</sup> Specific exposures associated with significant excesses are asbestos,<sup>44,49</sup> coal or natural gas,<sup>32,50</sup> petroleum, tar, and pitch products,<sup>34,50</sup> mineral or cutting oils,<sup>32,44</sup> automotive<sup>51</sup> and aviation gasolines,<sup>52</sup> cadmium,<sup>53</sup> and organic solvents.<sup>44</sup>

In interpreting the HQ findings, it is important to consider certain methodologic issues. One of this study's major strengths was the use of both occupational and general population referents. We were limited with respect to the choice of industrial controls, however, since annual death rates at TED, available only since 1972, would be unstable because of the relatively small size ( $n \sim 13,000$ ) of the workforce. The selection of a large imaging and health products company (Eastman Kodak Company, which at the time of the study was TED's parent organization) provided comparability with respect to type of industry, compensation, health insurance coverage, and medical services, and safety practices, including on-site smoking restrictions. In contrast to the

occupational controls, the State of Tennessee comparison group offered the advantage of similar geography and rate stability associated with a large population base.

Cohort definition and case finding are important issues in epidemiologic studies of chronic health effects. In the current investigation, the study population was identified from detailed review of employment files, medical records, personal correspondence, reports prepared from the company's personnel data base, and most importantly lists of employees scheduled for eye examinations. Starting in the 1940's and continuing to the present, all employees (including support personnel) who manufactured and used HQ at TED have received periodic eye examinations, which have also been available to retirees. It is therefore presumed that the study group included essentially all individuals who were exposed to HQ and BQ at TED during the past 50 years.

Although personnel records were available prior to 1942, the year in which the eye examination program was started, the decision was made to begin accumulating person-years only when we were confident that all exposed workers had been identified. The possibility therefore exists that some individuals may have terminated employment for health reasons (e.g., exposure-related symptoms or effects and premature death) before enrollment in the study began. However, selectivity bias was minimized since (1) a large proportion of early HQ personnel was included, and (2) employment stability at TED and the lack of job opportunities during the 1930's presumably reduced turnover rates. In fact, exclusion of pre-1942 person-years represents a small bias in favor of positive findings.

Extensive efforts were undertaken to obtain the vital status of the terminated employees and to retrieve their death certificates. According to Social Security Administration (SSA) records, there were six deaths among the terminees. Although some of the remaining individuals may have died (estimates of mortality ascertainment by the SSA range between 84% and 93%<sup>54,55</sup>), it is unlikely that the study results were affected by the small number of young, short-tenured terminees who were assumed to be alive.

Although the study provided sufficient TFFE for the development of carcinogenic effects (e.g., more than 20% of the subjects were followed for at least 40 years and the median TFFE was greater than 25 years), none were observed. Furthermore, employees with the longest follow-up experienced the highest mean cumulative HQ exposure:  $\geq 35$  years TFFE, 20.0 mg/m<sup>3</sup>-years, compared with 20-34 years TFFE, 4.1 mg/m<sup>3</sup>-years and  $< 20$  years TFFE, 2.3 mg/m<sup>3</sup>-years.

There are at least four factors which must be considered in interpreting the air monitoring data. First, until recent years, the findings were based on short-term sampling, often of 15 minutes or less duration, and therefore may not be representative of an eight-hour TWA exposure rate. Second, both personal and area sampling results were combined. Third, more data may have been collected from those locations (e.g., oxidizers and filter presses) with a potential for high exposure, thus providing overestimates of exposures generally. Finally, the sampling efforts were increased during periods when there was a need to evaluate control measures such as filter press ventilation changes. For these reasons, it should be emphasized that the estimates reported here represent approximations, rather than actual historical eight-hour TWA concentrations, of exposure levels likely to be encountered during HQ production.

The lifetime HQ exposure data were based on employment records and time- and job-specific air sampling measurements. Complete job histories were available for virtually all of the subjects and substantial historical exposure data were collected and analyzed by industrial hygienists with long-term experience with HQ production operations. Although the HQ levels prior to the mid-1980's may have been overstated because of methodologic limitations (e.g., duration and selectivity of sampling), it is believed that the estimated cumulative exposure accurately reflects relative HQ levels by time period and occupational category.

An unfortunate strength of this study is that there can be no doubt that early exposures to HQ and BQ were excessive and significantly greater than current workplace standards. As a consequence, employees in the HQ production area had

clinically detectable biomarkers of exposure and effect as demonstrated by the presence of ocular pigmentation and corneal damage leading in some cases to deficits in visual acuity. As reported in 1958 during the second period of peak exposure to HQ and BQ, 105 employees displayed at least one biomarker of exposure when examined by slit lamp and 38 showed some evidence of an effect, ranging from moderate involvement of the cornea to extreme loss of visual acuity.<sup>2</sup>

While the results of this epidemiology study do not support the concerns arising from the cancer bioassays of HQ or BQ and some of the genotoxicity results, they nevertheless are consistent with the findings of other toxicologic investigations. For example, when HQ was given chronically to Sprague-Dawley rats, no evidence of tumorigenicity or nephrotoxicity was observed.<sup>56</sup> Likewise, subacute or subchronic exposure of humans, dogs, or Carworth rats did not provide evidence of the nephrotoxicity which has been reported in F344 rats.<sup>56,57</sup> Additionally, in a number of cancer model systems, HQ has shown either negative results or slight, beneficial responses. For example, HQ was inactive in studies designed to investigate its ability to cause proliferative lesions in the stomachs of rats,<sup>58</sup> and Syrian Golden hamsters.<sup>59</sup> HQ did not promote gastric neoplasms induced by N-methyl-N'-nitro-N-nitrosoguanidine<sup>60</sup> or tongue and nasal cavity neoplasms and pulmonary alveolar cell hyperplasia induced by methyl-N-aminonitrosamine.<sup>24</sup> Also, in a short-term model for liver carcinogenicity, HQ had an inhibitory effect on the production of glutathione S-transferase-positive foci.<sup>61</sup>

Pancreatic cancer induced in Syrian Golden hamsters by N-nitrosobis (2-oxopropyl)amine was significantly inhibited by a diet containing 1.5% HQ.<sup>62</sup> Chavin *et al.*<sup>63</sup> reported that HQ treatment prolonged the lives of mice injected with melanoma tumor cells. Also, in a dermal cancer bioassay, HQ was not carcinogenic, and exposure to HQ dermally was associated with a slight reduction in the incidence of benzo[a]pyrene-induced skin tumors.<sup>64</sup> Finally, HQ did not initiate carcinogenesis with croton oil<sup>65</sup> or act as a promotor of DMBA-initiated skin tumors.<sup>66</sup>

Additionally, HQ (0.8% diet) did not promote hepatocarcinogenesis induced by N-ethyl-N-hydroxyethylnitrosamine (EHEN) in Wistar rats.<sup>67</sup> The incidence of hepatocellular carcinomas in rats and the number of carcinomas per rat were about half of the control level and not statistically significant. HQ given at a dose level which has been reported to be nephrotoxic in male F344 rats (0.8% diet) did not significantly increase the incidences of preneoplastic and neoplastic lesions in the kidneys of male Wistar rats administered both EHEN and HQ. However, the numbers of microadenomas and renal cell tumors were significantly increased. More importantly, there was no reported indication that HQ promoted the induction of renal cell carcinomas following EHEN pre-treatment.

Similarly, the genotoxicity data for HQ have shown mixed results, some of which have added to the concern about HQ exposure and others of which have tended to reduce the level of concern. It should be noted, for example, that HQ has generally been negative in standard Ames/Salmonella assays.<sup>68-73</sup> The only positive results in bacterial mutagenicity assays have occurred using a nonstandard assay<sup>74</sup> or the fluctuation assay.<sup>75</sup>

In contrast to studies in which HQ has produced significant effects when given by parenteral routes, HQ administered orally has produced weakly positive results for red blood cell micronuclei.<sup>76,77</sup> Orally-dosed HQ is not associated with DNA adducts in the bone marrow, Zymbal gland, liver, or spleen of female Sprague-Dawley rats<sup>78</sup> or the kidneys of F344 rats.<sup>79</sup> Finally, HQ when administered alone did not result in oxidative DNA damage in the bone marrow of mice.<sup>80</sup>

Thus, the human epidemiologic findings presented here are consistent with much of the animal experimental data available for HQ.

## CONCLUSIONS

This study, which examined mortality among persons employed principally in the manufacture of HQ at a large chemical plant during the past 50 years, demonstrated (1) statistically significantly lower than expected death rates for all causes and for cancer

and (2) no evidence of a dose-response relationship with respect to lifetime exposure or latency. None of the observed-expected differences for any of the cause of death categories, including cancer, was significantly increased. Furthermore, the epidemiologic findings do not support a causal relationship between HQ or BQ exposure and renal and hepatic carcinoma and leukemia or nephrotoxicity in humans, as suggested by animal studies. Both of the employees who died of kidney cancer were long-term cigarette smokers; one worked in a HQ environment for less than two years. No deaths were observed for the other hypothesized cancers.

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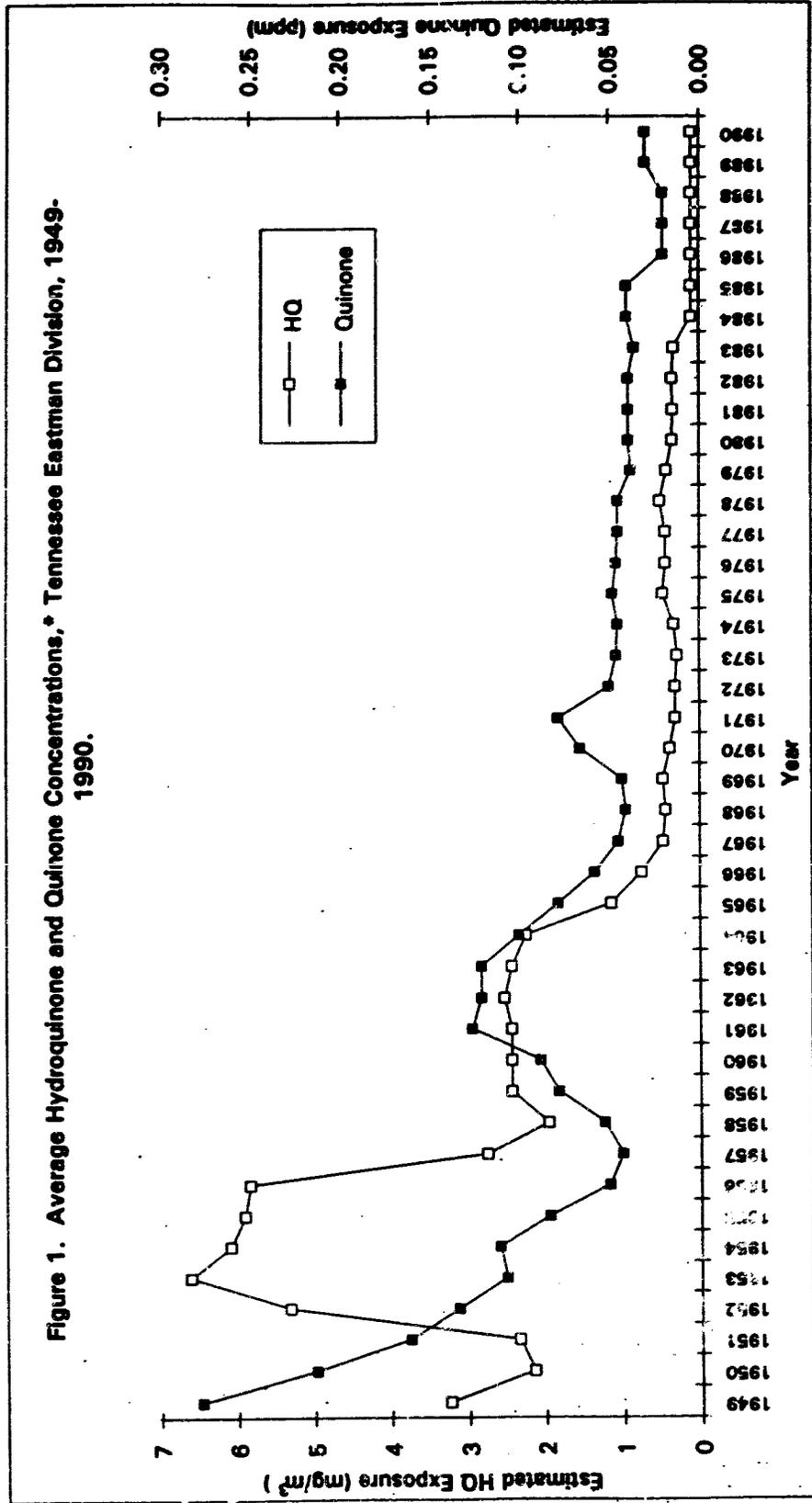
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Figure 1. Average Hydroquinone and Quinone Concentrations,\* Tennessee Eastman Division, 1949-1990.



\* Prior to 1985, short-term studies were conducted. Since the mid-1980s, full-shift sampling representative of eight-hour time weighted averages (TWAs) has been performed.

**Table 1. Description of Hydroquinone Manufacturing and Related Operations, 1930-1990.**

<u>Operation</u>	<u>Approximate Years</u>	<u>Estimated Number of Employees</u>	<u>Employee Job Assignments</u>	<u>Estimated Annual HQ Exposure (mg/m<sup>3</sup>)</u>	<u>Comments</u>
HQ/Quinone Production	1930-1985	508	Collect samples, monitor gauges, and maintain production logs. Operate oxidizers, filter presses, crystallizers, centrifuges, dryers, and packaging equipment.	Mean: 1.4 Median: 0.4 Range: <0.1-6.0	Aniline oxidation method.
HQ/Quinone Production	1986-1991	102	Same as above, except for oxidizer and filter press jobs, which were eliminated.	Mean: 0.4 Median: 0.4 Range: <0.1-0.4	DIPB process, which is essentially a closed system.
TENAMENE Production	1936-1960	40	Produce various gasoline inhibitors from <i>p</i> -nitroaniline in batch chemical operation.	Mean: 0.3 Median: 0.2 Range: 0.1-5.0	Only one product used HQ as a raw material. Exposures limited because of local exhaust ventilation.
Manganese-Ammonium Sulfate Production	1936-1987	217	Operate filtration equipment, dryers, and packaging machines.	Mean: 0.1 Median: <0.1 Range: <0.1-3.5	By-product used as a fertilizer and animal-feed additive.
HQ Material Handling	1944-1961	194	Perform a number of jobs, including operating centrifuges, dryers, and packaging equipment; loading pallets of drummed product; and cleaning.	Mean: 2.2 Median: 1.5 Range: 0.1-6.0	Wide range of HQ exposures, from low (shipping) to high (equipment operation).

Table 1. Description of Hydroquinone Manufacturing and Related Operations, 1930-1990 (Continued).

<u>Operation</u>	<u>Approximate Years</u>	<u>Estimated Number of Employees*</u>	<u>Employee Job Assignments</u>	<u>Estimated Annual HQ Exposure (mg/m<sup>3</sup>)</u>	<u>Comments</u>
Ore Grinding	1936-1980	58	Operate rotary dryers and ball mills used to process manganese dioxide ore for aniline oxidation process.	Mean: 0.5 Median: 0.2 Range: < 0.1-5.9	
HQ Maintenance	1944-1959	54	Maintain and repair equipment.	Mean: 0.2 Median: 0.2 Range: 0.1-0.3	
Quality Control	1947-1991	73	Perform laboratory analyses of production samples.	Mean: 0.1 Median: 0.1 Range: < 0.1-0.3	
Special Chemicals	1945-1991	283	Operate reactors, filters, dryers, and packaging equipment for color developers and food-grade antioxidants.	Mean: 0.4 Median: < 0.1 Range: < 0.1-6.0	HQ used as a raw material for some special chemicals. Limited exposure during drum loading operations.

\*. Employee may have worked in more than one operation.

\*\* Statistics calculated from distributions of estimated average annual HQ exposures for individuals during jobs specific to each operation.

**Table 2. Number of Observed and Expected Deaths, and Standardized Mortality Ratios (SMRs) and 95% Confidence Intervals<sup>a</sup> by Underlying Cause, 1942-1990 Tennessee Eastman Division (TED) Hydroquinone Cohort (n=879), Followed Through 1991.**

ICD-9	Cause of Death Category	State of Tennessee				Kodak Rochester		
		No. of Observed Deaths	No. of Expected Deaths <sup>b</sup>	SMR <sup>c</sup>	95% CI <sup>c</sup>	No. of Expected Deaths <sup>d</sup>	SMR <sup>c</sup>	95% CI <sup>c</sup>
001-139	Infectious and Parasitic Diseases	0	3.4			2.2		
140-208	Malignant Neoplasms	33	57.9↓	57	39-80	53.5↓	62	42-87
140-149	Lip, Oral Cavity, and Pharynx	0	1.4			0.7		
150-159	Digestive System	7	12.5	56	23-116	15.4↓	46	18-94
150	Esophagus	1	1.1			1.6		
151	Stomach	0	1.7			2.5		
153	Colon	5	4.3	115	37-269	5.3	95	31-222
154	Rectum	0	0.9			1.4		
155	Liver and Intrahepatic Bile Ducts	0	1.3	0	0-292	0.8	0	0-434
157	Pancreas	0	2.8			3.5		
152,156, 158,159	Other Digestive Organs	1	0.4			0.3		
160-165	Respiratory System	14	24.5↓	57	31-96	16.8	83	45-140
162	Trachea, Bronchus, and Lung	14	22.3	63	34-105	16.3	86	7-144
170-175	Bone, Connective Tissue, Skin, and Breast	1	1.8			2.4		
172	Malignant Melanoma	0	0.8			1.1		
174,175	Breast	0	0.1			0.2		
170,171	Other Skin	1	0.9			1.1		
179-189	Genitourinary Organs	5	6.8	73	24-171	6.9	73	23-169
185	Prostate	3	3.9	77	16-225	3.7	80	16-234
188	Bladder	0	1.3			1.6		
189	Kidney and Other Urinary Organs	2	1.3	150	17-541	1.3	159	18-574
179-184, 186,187	Other Genitourinary Organs	0	0.3			0.3		
190-199	Other and Unspecified Sites	5	5.4	93	30-216	5.3	95	31-221
191-192	Brain and Other CNS	1	2.0			1.6		
200-203	Lymphatic and Histiocytic Tissue	1	3.2			3.3		
200,202	Non-Hodgkin's Lymphoma	0	1.9			1.9		
201	Hodgkin's Disease	0	0.4			0.7		
203	Multiple Myeloma	1	0.9			0.7		
204-208	Leukemia	0	2.3	0	0-159	2.7	0	0-134
210-239	Benign and Unspecified Neoplasms	0	0.6			0.6		
240-279	Endocrine, Nutritional, and Metabolic Diseases	1	3.9			3.4		
280-289	Diseases of Blood and Blood Forming Organs	0	0.6			0.4		

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**Table 2. Number of Observed and Expected Deaths, and Standardized Mortality Ratios (SMRs) and 95% Confidence Intervals<sup>a</sup> by Underlying Cause, 1942-1990 Tennessee Eastman Division (TED) Hydroquinone Cohort (n=872), Followed Through 1991 (Continued).**

ICD-9	Cause of Death Category	No. of Observed Deaths	State of Tennessee			Kodak Rochester		
			No. of Expected Deaths <sup>b</sup>	SMR <sup>c</sup>	95% CI <sup>c</sup>	No. of Expected Deaths <sup>d</sup>	SMR <sup>c</sup>	95% CI <sup>c</sup>
290-319	Mental Disorders	1	2.2			1.4		
320-389	Diseases of Nervous System and Sense Organs	1	2.5			3.2		
390-459	Diseases of Circulatory System	92	118.3↓	78	64-95	99.6	92	74-113
410-414	Ischemic Heart Disease	62	79.5	78	60-100	70.2	88	68-113
430-438	Cerebrovascular Disease	15	15.8	95	53-156	10.5	142	80-235
480-519	Diseases of Respiratory System	11	19.0	58	29-104	12.2	90	45-162
520-579	Diseases of Digestive System	3	9.1↓	33	7-97	6.6	45	9-133
580-629	Diseases of Genitourinary System	1	3.2			2.5		
680-709	Diseases of Skin and Subcutaneous Tissue	0	0.2			0.3		
710-739	Diseases of Musculoskeletal System	1	0.7			0.2		
740-759	Congenital Anomalies	0	0.4			0.4		
780-799	Symptoms and Ill-defined Conditions	3	5.6	54	11-157	1.3	235	47-688
800-999	Injury and Poisoning	18	29.1↓	62	37-98	16.5	109	65-173
	Unknown Cause of Death	3						
001-999	All Causes of Death	168	256.7↓	65	56-76	204.3↓	82	70-96

<sup>a</sup> For causes with more than one observed death.

<sup>b</sup> Expected numbers based on Tennessee white death rates, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, and 1990.

<sup>c</sup> Calculated for causes with more than one observed death, except for the hypothesized causes of liver cancer and leukemia.

<sup>d</sup> Expected numbers based on Kodak Rochester hourly death rates, 1964-1967, 1968-1972, 1973-1977, 1978-1982, 1983-1987, and 1988-1992.

↓ Statistically significant decrease ( $p < 0.05$ , two-tailed test).

Table 3. Number of Observed and Expected Deaths by Underlying Cause and Career Hydroquinone Exposure ( $\text{mg}/\text{m}^3$  - years), 1942-1988 Tennessee Eastman Division (TED) Hydroquinone Cohort (n=879), Followed Through 1991.

Cause of Death Category	< 3 $\text{mg}/\text{m}^3$ - years				3 to < 16 $\text{mg}/\text{m}^3$ - years				$\geq 16 \text{ mg}/\text{m}^3$ - years			
	No. of Observed Deaths		No. of Expected Deaths		No. of Observed Deaths		No. of Expected Deaths		No. of Observed Deaths		No. of Expected Deaths	
	Tennessee <sup>a</sup>	Kodak Rochester <sup>b</sup>	State of Tennessee	Kodak Rochester	State of Tennessee	Kodak Rochester	State of Tennessee	Kodak Rochester	State of Tennessee	Kodak Rochester	State of Tennessee	Kodak Rochester
Infectious and Parasitic Diseases	0	0.8	1.4	18.7↓	0	0.7	1.1	0.7	0	0.8	1.0	0.8
Malignant Neoplasms	7	20.2↓	20.2↓	18.7↓	15	18.0	19.4	18.0	11	18.3	18.3	16.8
Digestive System	1	5.2	4.2	5.2	3	5.3	4.3	5.3	3	4.0	4.0	4.9
Colon-Rectum	0	2.0	1.8	2.0	3	2.4	1.8	2.4	2	1.7	1.7	2.3
Liver	0	0.1	0.1	0.1	0	0.1	0.1	0.1	0	0.1	0.1	0.1
Trachea, Bronchus, and Lung	1	5.6↓	8.0↓	5.6↓	10	5.5	7.4	5.5	3	7.0	7.0	5.2
Genitourinary Organs	3	2.0	2.0	2.0	1	2.5	2.5	2.5	1	2.3	2.3	2.3
Prostate	3	0.9	1.0	0.9	0	1.4	1.5	1.4	0	1.4	1.4	1.4
Kidney	0	0.4	0.5	0.4	1	0.4	0.4	0.4	1	0.4	0.4	0.4
Other and Unspecified Sites	2	2.0	2.0	2.0	1	1.7	1.7	1.7	2	1.8	1.8	1.8
Lymphatic and Histocytic Tissue	0	1.3	1.2	1.3	0	1.0	1.0	1.0	1	1.0	1.0	0.9
Leukemia	0	1.0	0.9	1.0	0	0.9	0.7	0.9	0	0.7	0.7	0.8
Other Malignant Neoplasms	0	1.6	2.8	1.6	0	1.1	2.5	1.1	1	2.4	2.4	1.1
Endocrine, Nutritional, and Metabolic Diseases	0	1.2	1.5	1.2	1	1.1	1.3	1.1	0	1.2	1.2	1.0
Mental Disorders	0	0.8	0.9	0.8	1	0.4	0.7	0.4	0	0.6	0.6	0.4
Diseases of Nervous System	0	1.1	0.9	1.1	1	1.1	0.8	1.1	0	0.8	0.8	1.0
Diseases of Circulatory System	28	30.9	36.7	30.9	38	35.4	42.3	35.4	28	39.3	39.3	33.3
Ischemic Heart Disease	17	21.8	25.0	21.8	23	24.9	28.2	24.9	22	26.3	26.3	23.5
Cerebrovascular Disease	7	2.9	4.3	2.9	5	4.0	6.1	4.0	3	5.4	5.4	3.8
Diseases of Respiratory System	1	3.1	5.6	3.1	3	4.7	6.9	4.7	7	6.6	6.6	4.4
Diseases of Digestive System	0	2.2	3.5	2.2	1	2.3	2.9	2.3	2	2.7	2.7	2.1
Diseases of Genitourinary System	0	0.7	1.0	0.7	0	1.0	1.2	1.0	1	1.1	1.1	0.8
Diseases of Musculoskeletal System	0	0.1	0.3	0.1	0	0.1	0.2	0.1	1	0.2	0.2	0.1
Symptoms and ill-defined Conditions	2	0.4	1.9	0.4	1	0.5	1.9	0.5	0	1.8	1.8	0.4
Injury and Poisoning	10	9.1	16.0	9.1	6	4.0	7.1	4.0	2	5.9	5.9	3.4
Other Causes of Death	0	0.7	0.7	0.7	0	0.5	0.6	0.5	0	0.5	0.5	0.5
Unknown Cause of Death	2		0.7		0		0.6		1			
All Causes of Death	50	69.6↓	90.5↓	69.6↓	65	69.8	86.3↓	69.8	63	79.9↓	79.9↓	64.9
Standardized Mortality Ratio (SMR)		72↓	55↓	72↓		93	75↓	93		66↓	66↓	82

<sup>a</sup> Expected numbers based on Tennessee white death rates, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, and 1990.

<sup>b</sup> Expected numbers based on Kodak Rochester hourly death rates, 1964-1967, 1968-1972, 1973-1977, 1978-1982, 1983-1987, and 1988-1992.

Table 4. Number of Observed and Expected Deaths by Underlying Cause and Time-From-First Exposure, 1942-1990 Tennessee Eastman Division (TED) Hydroquinone Cohort (n=879), Followed Through 1991.

Cause of Death Category	< 20 years			20 - 34 years			≥ 35 Years		
	No. of Observed Deaths	No. of Expected Deaths		No. of Observed Deaths	No. of Expected Deaths		No. of Observed Deaths	No. of Expected Deaths	
		Tennessee <sup>a</sup>	Kodak Rochester <sup>b</sup>		Tennessee	Kodak Rochester		Tennessee	Kodak Rochester
Infectious and Parasitic Diseases	0	1.6	0.4	0	0.9	0.8	0	0.9	1.2
Malignant Neoplasms	6	11.3	11.9	7	20.7↓	18.5↓	20	25.9	23.1
Digestive System	0	2.5	3.6	3	4.4	5.7	4	5.6	6.1
Colon-Rectum	0	1.0	1.3	2	1.6	2.4	3	2.5	3.0
Liver	0	0.1	0.1	0	0.1	0.1	0	0.2	0.1
Trachea, Bronchus, and Lung	3	3.1	2.7	2	8.7↓	6.1	9	10.6	7.6
Genitourinary Organs	0	0.9	0.9	2	2.0	2.0	3	4.0	4.0
Prostate	0	0.2	0.2	2	1.0	0.9	1	2.7	2.6
Kidney	0	0.3	0.4	0	0.5	0.4	2	0.6	0.5
Other and Unspecified Sites	1	1.4	1.3	0	2.0	1.8	4	2.0	2.2
Lymphatic and Histocytic Tissue	1	0.8	1.0	0	1.0	1.0	0	1.3	1.2
Leukemia	0	0.7	0.9	0	0.7	1.0	0	0.9	0.9
Other malignant neoplasms	1	2.6	1.5	0	2.7	0.9	0	2.4	1.1
Endocrine, Nutritional, and Metabolic Diseases	0	1.0	0.8	0	1.3	1.0	1	1.6	1.6
Mental Disorders	1	0.8	0.3	0	0.6	0.4	0	0.8	0.7
Diseases of Nervous System	0	0.6	0.7	1	0.6	0.9	0	1.2	1.6
Diseases of Circulatory System	16	23.2	20.0	38	42.0	34.0	38	53.1↓	45.6
Ischemic Heart Disease	10	16.1	15.2	28	30.4	25.2	24	33.0	29.6
Cerebrovascular Disease	5	2.7	1.6↑	2	5.0	3.3	8	5.1	5.7
Diseases of Respiratory System	1	2.6	1.3	3	5.5	3.1	7	10.9	7.6
Diseases of Digestive system	0	2.8	1.4	1	3.3	2.2	2	2.9	3.1
Diseases of Genitourinary System	0	0.9	0.2	0	0.8	0.6	1	1.5	1.7
Diseases of Musculoskeletal System	0	0.2	0.1	1	0.2	<0.1	0	0.3	0.1
Symptoms and Ill-defined Conditions	2	1.7	0.2↑	0	1.8	0.4	1	2.1	0.6
Injury and Poisoning	14	18.0	8.5	2	7.4↓	3.8	2	3.6	3.2
Other Causes of Death	0	0.6	0.4	0	0.6	0.5	0	0.7	0.7
Unknown Cause of Death	1			0			2		
All Causes of Death	41	65.2↓	47.2	53	85.8↓	66.1	74	105.7↓	91.0
Standardized Mortality Ratio (SMR)		63↓	87		62↓	80		70↓	81

<sup>a</sup> Expected numbers based on Tennessee white death rates, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, and 1990.

<sup>b</sup> Expected numbers based on Kodak Rochester hourly death rates, 1964-1967, 1968-1972, 1973-1977, 1979-1982, 1983-1987, and 1988-1992.

↓ Statistically significant decrease (p < 0.05, two-tailed test).

**Table 5. Observed/Expected Ratios and Number of Observed Deaths for Hypothesized Causes and Selected Other Causes by Career Hydroquinone Exposure (mg/m<sup>3</sup>-years) and Time From First Exposure (Years), 1942-1990 Tennessee Eastman Division (TED) Hydroquinone Cohort (n=879), Followed Through 1991.**

Cause of Death Category	Career Exposure (mg/m <sup>3</sup> -years)			Time-From-First Exposure (Years)			p value			
	≤3	3 to <15	≥15	Trend <sup>a</sup>	Delta <sup>b</sup>	≤20	20-34	≥35	Trend	Delta
<b>Hypothesized Causes of Death<sup>c</sup></b>										
<b>Kidney Cancer</b>										
TN <sup>d</sup>	0.0	2.25	2.41			0.0	0.0	3.42		
KR <sup>e</sup>	0.0	2.40	2.52			0.0	0.0	4.34		
Within Cohort <sup>f</sup>	0.0	1.45	1.73	0.30	0.58	0.0	0.0	1.33	0.43	0.72
No. of Observed Deaths	0	1	1			0	0	2		
<b>Other Causes of Death</b>										
<b>Total Cancer</b>										
TN	0.35	0.77	0.60			0.53	0.34	0.77		
KR	0.37	0.83	0.68			0.51	0.38	0.88		
Within Cohort	0.65	1.35	0.99	0.41	0.25	1.29	0.57	1.24	0.39	0.17
No. of Observed Deaths	7	15	11			6	7	20		
<b>Trachea, Bronchus and Lung Cancer</b>										
TN	0.13	1.36	0.43			0.96	0.23	0.85		
KR	0.18	1.82	0.58			1.12	0.33	1.18		
Within Cohort	0.21	2.16	0.65	0.48	0.007	1.34	0.40	1.34	0.42	0.24
No. of Observed Deaths	1	10	3			3	2	9		
<b>Digestive Cancer</b>										
TN	0.24	0.70	0.74			0.0	0.68	0.72		
KR	0.19	0.57	0.61			0.0	0.53	0.65		
Within Cohort	0.39	1.28	1.46	0.19	0.45	0.0	0.98	1.33	0.18	0.53
No. of Observed Deaths	1	3	3			0	3	4		
<b>Circulatory Diseases</b>										
TN	0.76	0.85	0.71			0.69	0.91	0.72		
KR	0.91	1.02	0.84			0.80	1.12	0.83		
Within Cohort	1.12	1.06	0.85	0.27	0.54	1.09	1.17	0.65	0.08	0.34
No. of Observed Deaths	28	36	28			16	38	38		
<b>Nonmalignant Respiratory Diseases</b>										
TN	0.18	0.44	1.07			0.39	0.54	0.65		
KR	0.33	0.64	1.57			0.78	0.98	0.89		
Within Cohort	0.40	0.74	1.59	0.11	0.26	1.92	1.51	0.82	0.17	0.54
No. of Observed Deaths	1	3	7			1	3	7		
<b>Total Deaths</b>										
TN	0.55	0.75	0.66			0.63	0.62	0.70		
KR	0.72	0.93	0.82			0.87	0.80	0.81		
Within Cohort	0.94	1.12	0.94	0.99	0.53	1.16	0.96	0.96	0.14	0.55
No. of Observed Deaths	50	65	53			41	53	74		

<sup>a</sup>  $\chi^2$  test for linear trend.

<sup>b</sup> Test for difference among observed/expected ratios.

<sup>c</sup> There were no liver or leukemia deaths.

<sup>d</sup> Expected numbers based on comparison with Tennessee white death rates, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, and 1990.

<sup>e</sup> Expected numbers based on comparison with Kodak Rochester hourly death rates, 1964-1967, 1968-1972, 1973-1977, 1978-1982, 1983-1987, and 1988-1992.

<sup>f</sup> Expected numbers based on the within cohort person-years distribution by age, sex, and calendar-year strata.

**CERTIFICATE OF AUTHENTICITY**

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