

ORIGINAL

**TSCA NON-CONFIDENTIAL BUSINESS INFORMATION**

DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ-10-18050	88100000375	8/2/10

COMMENTS:

**DOES NOT CONTAIN CBI**

Exhibit 98

MR# ~~328869~~  
328869

**Contains No CBI**

8EHQ-0810-18050A



# Collaborative Cohort Mortality Study of Four Chromate Production Facilities, 1958 - 1998

## FINAL REPORT

Prepared for:

Industrial Health Foundation, Inc.  
34 Penn Circle West  
Pittsburgh, PA 15206-3612

September 27, 2002

10 AUG -2 11:10:01  
RECEIVED  
EPA/DOH

DCN:8810000375



**APPLIED  
EPIDEMIOLOGY  
INC.**



IHF29008

**Collaborative Cohort Mortality Study of Four  
Chromate Production Facilities, 1958 - 1998**

**FINAL REPORT**

Prepared for:

Industrial Health Foundation, Inc.  
34 Penn Circle West  
Pittsburgh, PA 15206-3612

Prepared by:

Applied Epidemiology, Inc.  
P.O. Box 2424  
Amherst, Massachusetts 01004

September 27, 2002

---

Copyright © 2002 by Applied Epidemiology, Inc.

IHF29009

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

**AUTHORS**

The design, conduct, and reporting of this epidemiological study were the product of the collective effort by the staff of Applied Epidemiology, Inc. and several associates.

*Epidemiologists:* Kenneth A. Mundt, Ph.D.

Linda D. Dell, M.S.

Robert P. Austin, M.P.H.

Rose S. Luippold, M.S.

*Data managers:* Ann Skillings, M.S.

Rachel Gross, M.S.,

Thomas Birk, Dipl. rer. soc

*Biostatistician:* Carol Bigelow, Ph.D.

*Information systems:* Rainer Noess

*Industrial Hygienist:* James Stewart, Ph.D.

*Physician/Toxicologist:* Dr. med. Leopold Miksche

**PROJECT FUNDING**

Funding for this research project was provided by the Chromium Chemicals Health and Environmental Committee, Industrial Health Foundation, Inc. (IHF) of Pittsburgh, Pennsylvania. Support for identifying, extracting and preparing data for this study was provided by each of the participating companies, including Occidental Chemical Corporation (US), Elementis Chromium (US) and Bayer AG (Germany).

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

**Members of the IHF Chromium Chemicals Health and Environmental Committee**

Dr. William Rinehart, Industrial Health Foundation

Ms. Marianne Kaschak, Industrial Health Foundation

Dr. Joel Barnhart, Elementis Chromium (US)

Ms. Robbin Jackson, Elementis Chromium (US)

Dr. Grant Darrie, Elementis Chromium (UK)

Dr. Tar Ching Aw, Elementis Chromium (UK)

Ms. Mary Manion, Occidental Chemical Corporation

Mr. Gene Renzaglia, Occidental Chemical Corporation

Mr. Russ Morgan, Occidental Chemical Corporation

Dr. Andreas Ossko, Bayer AG

Dr. Ulrich Sewekow, Bayer AG

Dr. med. Leopold Miksche, Bayer AG

**SCIENTIFIC REVIEW AND ADVISORY COMMITTEE**

Dr. Harvey Checkoway, University of Washington

Dr. Edwin van Wijngaarden, University of North Carolina (now with Applied  
Epidemiology, Inc.)

Dr. James Stewart, Harvard University

**INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL**

The study protocol was reviewed by the IRB of the University of Birmingham and the IRB of Applied Epidemiology, Inc. (United States Department of Health and Human Services, Office for Human Research Protections, Federal-wide Assurances approval number FWA00002652).

**DISCLAIMER**

All conclusions, interpretations and opinions presented in this report are those of the investigators and do not necessarily reflect the views of IHF or its member companies.

**ACKNOWLEDGMENTS**

The generous assistance of numerous individuals, identified below, made this complex study possible. We are grateful for valuable help with identification and acquisition of data, and especially with assistance understanding the data obtained from each participating facility. We thank those who assisted with determining vital status of study cohort members, and obtaining cause of death information on decedents. We also appreciate the ideas and insights provided for utilizing various exposure related data.

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

Finally, we thank Drs. Margaret McDonald and Joseph Tritschler, formerly of Applied Epidemiology, Inc., for their early efforts on this study.

**Data acquisition from Bayer, AG, Leverkusen and Uerdingen**

Dr. med Wolfgang Steinmann-Steiner Haldenstedt

Dr. med Leopold Miksche

Dipl. rer. soc. Thomas Birk

**Data acquisition from Elementis, Corpus Christi, Texas**

Dr. Joel Barnhart

Ms. Robbin Jackson

Ms. Flora Landes

Ms. Melanie Fox

**Data acquisition from Occidental Chemical, Castle Hayne, North Carolina**

Mr. Gene Renzaglia

Mr. Thomas Moore

Mr. Tom Meinert

Mr. Richard Lowrey

Ms. Sandra DesChamps

Ms. Linda Riggins

---

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

**Vital status and cause of death information in the United States**

**Mr. Robert Bilgrad, National Death Index**

**Staff of State Vital Statistics Offices, especially North Carolina, Texas, Colorado, and  
New Jersey**

**TABLE OF CONTENTS**

EXECUTIVE SUMMARY ..... 1

INTRODUCTION ..... 6

    2.1 Literature Review..... 6

        2.1.1 Exposure and Health Effects ..... 7

            2.1.1a Trivalent Chromium..... 7

            2.1.1b Hexavalent Chromium ..... 8

            2.1.1c Solubility and Carcinogenicity..... 8

        2.1.2 Toxicology and Kinetics ..... 9

        2.1.3 Biomarkers ..... 10

        2.1.4 Industrial Process for Chromium Chemicals..... 11

        2.1.5 Epidemiological Studies of Chromate Production Facilities ..... 13

            2.1.5a Pre-change Studies ..... 13

            2.1.5b Post-change Studies..... 15

            2.1.5c Smoking..... 17

            2.1.5d Research Needs ..... 18

    2.2 Previous Studies of the Cohorts Participating in this Investigation..... 18

        2.2.1 Plant Histories and Data Sources ..... 18

        2.2.2 Leverkusen Cohort, Bayer, AG..... 19

        2.2.3 Uerdingen Cohort, Bayer, AG..... 21

        2.2.4 Corpus Christi Cohort, Elementis, USA (formerly American Chrome). 23

        2.2.5 Castle Hayne Cohort, Occidental Chemical Corporation ..... 24

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

**2.3 Rationale for a Study Combining these Cohorts..... 26**

**METHODS ..... 29**

**3.1 Cohort Enumeration..... 29**

**3.2 Work History ..... 30**

**3.2.1 German Plants ..... 30**

**3.2.2 U.S. Plants ..... 32**

**3.3 Exposure Data..... 33**

**3.3.1 Personal Air Monitoring Data ..... 33**

**3.3.2 Area Air Monitoring Data ..... 34**

**3.3.3 Biomonitoring Data..... 36**

**3.4 Smoking Habits..... 37**

**3.5 Data Acquisition and Database Construction ..... 38**

**3.6 Exposure Assessment Overview..... 39**

**3.6.1 Identification of Homogenous Exposure Groups..... 40**

**3.6.2 Verification and Standardization of Air Monitoring Data ..... 41**

**3.6.3 Verification and Standardization of Urinary Chromium Data ..... 42**

**3.6.3a Creatinine-Adjusted versus Specific Gravity ..... 43**

**3.6.3b Repeated Measurements of Urinary Data ..... 44**

**3.6.4 Construction of Job Exposure Matrices (JEMs)..... 45**

**3.6.4a Remove Outliers..... 46**

**3.6.4b Rank Exposure Areas Overall ..... 47**

**3.6.4c Collapse Exposure Areas..... 47**

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

3.6.4d Stabilize Sparse Cells and Fill Empty Cells for Average Concentration JEM.....	48
3.6.4e Stabilize Sparse Cells and Fill Empty Cells for Peak Levels JEM	50
3.6.5 Commensuration of Urinary and Air Data.....	51
3.6.6 Estimation of Level of Exposure.....	52
3.7 Vital Status and Cause of Death Ascertainment.....	53
3.7.1 German Plants .....	53
3.7.2 U.S. Plants .....	54
3.8 Statistical Analysis.....	55
3.8.1 Standardized Mortality Ratio (SMR) Analyses.....	55
3.8.1a Reference Rates .....	56
3.8.2 Multivariable Analyses.....	58
RESULTS .....	60
4.1 Description of Cohort .....	60
4.2 Exposure Assessment.....	61
4.3 Mortality Analysis .....	63
4.5 Logistic Regression Analysis.....	67
DISCUSSION.....	72
5.1 Exposure Assessment.....	74
5.2 Lung Cancer Mortality.....	75
5.3 Strengths of this Study.....	81
5.4 Limitations of this Study.....	82
5.5 Future Research Direction .....	83

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

**5.6 Conclusions** ..... 84

**REFERENCES** ..... 86

**APPENDIX** ..... 135

**LIST OF TABLES AND FIGURES**

Table 1: Previously studied cohorts included in the combined analysis ..... 91

Table 2: Types of industrial hygiene data, number of samples, and years for which data are available by plant ..... 92

Table 3: Homogenous exposure groups identified for each plant ..... 93

Table 4: Assignment of peak exposure ranks ..... 94

Table 5: Arithmetic means, variances and the ratio of the means for German plants for years where personal air monitoring samples and urine samples were available..... 95

Table 6: Relationship between CrO<sub>3</sub> concentrations in workplace air and excretion of Cr in urine and conversion factor based on ratio of urine to air ..... 96

Table 7: Exclusions from the database by plant ..... 97

Table 8: Descriptive statistics for the cohort ..... 98

Table 9: Duration of exposure and time since first exposure by plant ..... 99

Table 10: Vital status for study subjects as of December 31, 1998 ..... 100

Table 11: Observed and expected deaths, SMRs and 95% confidence intervals using state rates (US plants) and German national rates (German plants) as referent population (24,590 person-years) ..... 101

Table 12: Observed and expected deaths, SMRs and 95% confidence intervals using state rates (US plants) and Nordrhein Westfalen rates (German plants) as referent population ..... 102

Table 13: Observed and expected lung cancers, SMRs and 95% CI's stratified by duration of exposure and time since first exposure ..... 103

Table 14: Observed and expected deaths, SMR's and 95% confidence intervals for lung cancer stratified..... 104

Table 15: Lagged analysis of cumulative exposure and peak exposure score..... 105

Table 16: Distribution of study subjects and lung cancer deaths according to peak exposure indicator score and cumulative exposure ..... 106

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 17: Study subjects, lung cancer deaths, odds ratios (OR) and 95% confidence intervals (CI) according to cumulative exposure* and cumulative exposure truncated 10 years earlier than end of follow-up** four plants.....	107
Table 18: Summary exposure and cumulative exposure, truncated 10 years before the end of follow-up, odds ratios (OR) and 95% confidence intervals (CI) for lung cancer deaths at four plants: crude and adjusted for age at first exposure, ever smoked and both age at first exposure and history of smoking.....	108
Table 19: Hierarchical exposure models of cumulative high exposure and addition of ever peak exposure: crude and adjusted odds ratios and 95% confidence intervals for lung cancer deaths: German subcohorts (684 with complete data, 18 lung cancer deaths).....	109
Figure 1: Geometric mean over time for Uerdingen plant.....	110
Figure 2: Geometric mean over time for Leverkusen plant.....	111
Figure 3: Geometric mean over time for Corpus Christi plant.....	112
Figure 4: Geometric mean over time for Castle Hayne plant.....	113
Figure 5: Plantwide geometric means (raw data) from personal air sampling.....	114
Figure 6: Saturation - Uerdingen.....	115
Figure 7: ADC/KDC production - Uerdingen.....	116
Figure 8: Shipping - Uerdingen.....	117
Figure 9: Electricians - Uerdingen.....	118
Figure 10: Kiln 1 - Leverkusen.....	119
Figure 11: Maintenance Workers & Foremen - Leverkusen.....	120
Figure 12: Sulfate Separation & Drying - Leverkusen.....	121
Figure 13: Lab Technicians - Leverkusen.....	122
Figure 14: Shipping - Corpus Christi.....	123
Figure 15: DCS Kiln - Corpus Christi.....	124
Figure 16: DCS Hearth - Corpus Christi.....	125
Figure 17: Combined low exposure areas (GM < 1 µg/m <sup>3</sup> over all years) - Corpus Christi.....	126

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Figure 18: Crystal Packing – Castle Hayne .....	127
Figure 19: C.A. Packing – Castle Hayne .....	128
Figure 20: Chromic Acid – Castle Hayne.....	129
Figure 21: Combined low exposure areas – Castle Hayne .....	130
Figure 22: Scatterplot of peak versus cumulative exposure, cohort (n=1472) .....	131
Figure 23: Box and whisker plot of distribution of cumulative exposure by plant .....	132
Figure 24: Year of hire, separation and death for 25 lung cancer cases .....	133

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

EXECUTIVE SUMMARY

Reliable quantitative risk estimates of the well recognized association between occupational exposure to hexavalent chromium compounds and lung cancer have been unavailable until very recently, precluding the establishment of scientifically based workplace and the environmental exposure limits. Further, the risks of lung cancer among employees of more modern production using low-lime or no-lime processing methods, combined with more stringent industrial hygiene controls, have not previously been evaluated in an adequately large study population, largely because studies have focused on the employees of single plants.

This report presents the results of an epidemiological mortality study of the combined employees of four modern chromium chemical production facilities, including two plants in Germany and two in the United States. All employees (n = 1518) included in the study worked one year or more in plants using low- or no-lime chromium production processes. Such a selection of the study cohort eliminates employees of high lime production processes, and prior to many industrial hygiene improvements implemented in more recent decades. Each cohort member was followed for vital status as of December 31, 1998, the end of the study follow-up period. A total of 157 deaths (10.3% of the total study group) were identified, and for 33 (2.2%) vital status could not be ascertained. For all decedents, cause of death information was sought from several sources, mainly death certificates.

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Individual exposure estimates were derived using a job exposure matrix, or JEM, in which all personal industrial hygiene data are pooled by job category and calendar year for each individual working in the same job categories. Because urinalysis data were the best available exposure indicators for a majority of the study cohort, air monitoring data for the remaining employees (i.e., two U.S. plants) were converted to urine equivalents for the exposure analyses. A total of nearly 20,000 exposure measures were available and incorporated into the exposure assessment. Estimates of peak exposure values were also derived for each cohort member to determine whether peak exposure might predict lung cancer risk better than simple cumulative exposure. For both cumulative and peak exposure indicators, analyses were conducted accounting for various lengths of possible disease latency.

Standardized mortality ratios (SMR) and 95% confidence intervals (CI) were calculated for specific causes of death and for all causes combined. Overall mortality experience for the cohort was somewhat lower than expected (SMR = 0.94; 95% CI: 0.80–1.10) based on appropriate United States and German reference rates. Note, however, that for 14 decedents we were unable to determine specific cause of death. Mortality due to ischemic heart disease was considerably decreased in this cohort (SMR = 0.63; 95%CI: 0.40–0.95), based on 23 observed and 36 expected deaths, using national reference rates. For no specific category of cause of death was the SMR meaningfully increased except for cancers of the respiratory system (SMR = 1.59; 95%CI: 1.04–2.33), and more specifically for cancers of the lung (SMR = 1.66; 95%CI: 1.08–2.46), based on 25 observed and 15 expected cases using national reference rates.

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Using state mortality rates (North Carolina and Texas for the United States facilities, respectively, and North Rhine-Westphalia for both German facilities), the all-causes of death SMR fell to 0.88 (95% CI: 0.75–1.03), and the lung cancer SMR fell to 1.35 (95% CI: 0.87–1.99). This decrease reflects the fact that for the states in which plants were located, mortality rates for all causes and for lung cancers were generally higher than national rates, resulting in smaller SMR values.

Stratifying lung cancer deaths by various indicators of exposure (cumulative and peak) generated relatively consistent results: SMRs for the highest exposure category were generally elevated, suggesting roughly a doubling of risk (and 95% CIs approximately 1.0 to 3.0), based on state reference rates. With stratification, though, numbers of observed deaths in each category diminished, and the resulting SMR estimates became less precise (reflected in the wider confidence intervals). Analyses lagging both cumulative and peak exposure indicators generated similar SMRs – with highest values associated with the highest exposure categories – but again with less statistical precision.

We evaluated relationships among cumulative exposure, peak exposure, age, and smoking status using logistic regression modeling. Generally, we found increased odds of lung cancer death for the higher exposure groups, relative to the low exposure group. This pattern persisted in models adjusted for age and smoking status, suggesting an independent role of higher versus lower chromium exposure on lung cancer death.

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Consistent with other recent studies attempting to quantitatively assess occupational chromium exposure and lung cancer, this study demonstrates a modest overall increase in risk among exposed cohort members, largely limited to those in the highest exposure categories (i.e.,  $\geq 200$   $\mu\text{g/L}$ -years, or peak score  $\geq 24$ ).

The last several years have witnessed growing interest in the possible health effects of chromium compounds at lower exposure levels. The United States Environmental Protection Agency (EPA) has repeatedly indicated its intentions to issue a new ruling concerning chromium. Current EPA guidelines indicate a unit risk for inhalation of hexavalent chromium of  $1.2 \times 10^1$  per  $\text{mg}/\text{m}^3$ .<sup>1</sup> This estimate was generated from Mancuso's<sup>2</sup> study of a pre-change cohort, that used a single industrial hygiene area survey<sup>3</sup> to estimate exposures. The EPA cites several uncertainties in using the Mancuso data,<sup>1</sup> and others have criticized the study for its methodological limitations and assumptions.<sup>4,5</sup>

This report describes the methods and results of a multi-center, international epidemiological mortality study of chromium chemical production employees of four relatively modern plants. This study adds to a limited but very recent body of scientific studies of occupational exposure to chromium compounds that attempts to quantitatively characterize chromium chemical exposure and subsequently quantify the risks associated with these exposures. As with the other recent studies, this study is intended to help fill the critical gap in the published literature on which a scientifically sound risk assessment for hexavalent chromium may be based. Though all of these recent studies, including the

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

present one, suffer from methodological limitations (especially sample size and data on potentially confounding factors such as smoking), they represent the best available scientific evidence of the relationship between chromium exposure and human lung cancer risk.

## INTRODUCTION

### 2.1 Literature Review

Chromium is a complex metal that has a wide range of applications including the formation of alloys, particularly stainless steel; corrosion-resistant plating on other metals; and the manufacture of a range of chromium chemicals. Chromium and its compounds are used in many ways, such as providing color for paints, preventing decay, resisting soiling, preserving wood, inhibiting corrosion, and tanning leather.<sup>6,7</sup> Chromium is a transition metal that exists principally in the trivalent (+3) and hexavalent (+6) oxidation states. Metallic chromium (valence 0) and compounds of other valence states also found in industry, such as +2, +4, and +5, are of less importance in industrial exposures. Divalent chromium oxidizes to the trivalent state, and most tetravalent and pentavalent states are unstable intermediates of chemical production not associated with any known human health risks.<sup>7</sup> There are few commercially important compounds with these valence states (e.g., chromium dioxide, a tetravalent compound used as a magnetic pigment). Although the metallic and divalent forms can cause dermal sensitization, they are absorbed minimally upon inhalation with no evidence of adverse effects.<sup>8</sup> Only trivalent and hexavalent compounds have been associated with adverse health effects;<sup>7</sup> however, there is growing evidence that only the hexavalent forms of chromium may be carcinogenic.<sup>9</sup>

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

### 2.1.1 EXPOSURE AND HEALTH EFFECTS

Route of exposure and solubility, in addition to valence state, are important factors in determining health risk associated with occupational exposure to chromium and its compounds.<sup>7,8,10,11</sup> Occupational exposures occur through inhalation, ingestion, or dermal contact; however, inhalation of hexavalent chromium compounds is believed to be the exposure of greatest carcinogenic potential.<sup>6</sup>

#### 2.1.1a Trivalent Chromium

Trivalent compounds are absorbed poorly through inhalation or dermal contact, are generally considered insoluble at physiological pH's,<sup>10</sup> and consequently, have a much lower level of toxicity than the hexavalent forms.<sup>7,8,10,11</sup> Also, occupational exposure to the trivalent forms likely found in industry is considered less hazardous because they are inhibited from crossing cell membranes.<sup>7</sup> In 1990, the International Agency for Research on Cancer<sup>6</sup> reported that there was "inadequate evidence" in humans or experimental animals for the carcinogenicity of chromium (III) compounds.<sup>6</sup> Widely cited reports published by Mancuso, first in 1975 and again in 1997, claimed to demonstrate that both hexavalent and trivalent forms of chromium were associated with increased lung cancer risk.<sup>2,12</sup> However, these conclusions have been criticized, as the investigator was unable to differentiate exposures to the different forms of chromium, and exposure to hexavalent and trivalent forms are correlated, making it impossible to separate the effects of each.<sup>4,5,10</sup>

### *2.1.1b Hexavalent Chromium*

Hexavalent compounds are more often associated with adverse health effects, mainly dermatological conditions, nasal septum irritation and occasionally perforation, and respiratory effects including cancers. The highest occupational exposures to Cr(VI) occur commonly through the chromate compounds utilized during chromate production, stainless steel welding, chrome pigment manufacture, chrome plating, and spray painting using paints containing hexavalent chromium compounds.<sup>6,13</sup>

Occupational exposure to hexavalent chromium occurs primarily through dermal contact and inhalation. Ingestion of Cr(VI) compounds is not a major pathway for absorption in typical industrial settings, as these compounds are reduced readily to Cr(III) by gastric secretions, with only 1 to 25% absorption,<sup>7,8</sup> although corrosive injury to gastrointestinal mucosa is possible if large amounts are ingested due to the formation of chromic acid in the stomach.<sup>8</sup> Several forms of Cr(VI) are easily absorbed through the skin; acute effects range from dermatitis, to skin lesions and ulcerations.<sup>7,8</sup> Inhalation of Cr(VI) dusts and mists has been linked with upper airway irritation and pulmonary sensitization, and nasal lesions and ulcerations.<sup>7,8</sup>

### *2.1.1c Solubility and Carcinogenicity*

Though somewhat controversial, hexavalent chromium alone, and not trivalent or metallic chromium, has been linked with cancer,<sup>6-8,10</sup> specifically lung and sinonasal cancer.<sup>6,10,14</sup> All hexavalent compounds may not be equally carcinogenic; evidence suggests that a compound's solubility in tissue fluids may determine its role, if any, in

carcinogenesis.<sup>10</sup> Slightly or moderately soluble compounds such as calcium and zinc chromate may pose the greatest risk for pulmonary cancer<sup>7,8</sup> because they are retained longer in lungs, which increases the risk of a protracted release of Cr(VI) to pulmonary tissue.<sup>7</sup> Highly soluble hexavalent chromium compounds are absorbed quickly and cleared from the body through the bloodstream after undergoing rapid reduction to Cr(III) (which does not cross cell membranes); a process generally believed to limit the carcinogenicity of these compounds, especially at lower concentrations.<sup>7</sup> This view was challenged in a recent review that suggested that soluble compounds, as well as other hexavalent compounds, can induce cancer at various sites including the respiratory tract.<sup>13,15</sup> However, the review and its conclusions have been sharply criticized.<sup>14</sup> Nevertheless, all hexavalent chromium compounds are currently classified as carcinogenic by the IARC.<sup>6</sup>

### 2.1.2 TOXICOLOGY AND KINETICS

The primary target for Cr(VI) carcinogenicity is the respiratory tract.<sup>14</sup> Though hexavalent chromium readily transits cell membranes, several airway defense mechanisms exist, resulting in reduction to Cr(III) and/or elimination of Cr(VI) particles before reaching alveoli.<sup>13,14,16</sup> Macrophage reduction sequesters chromium particles and eventually results in the expectoration or ingestion of Cr-bearing macrophages. Direct reduction to Cr(III) occurs in bronchial epithelial lining fluids, further limiting the amount of Cr(VI) that reaches alveoli.<sup>13,14</sup> Reduction also occurs at the bronchial tree and peripheral lung parenchyma cells.<sup>14</sup> Hexavalent chromium that escapes these defenses is released into the bloodstream, where it readily transits and accumulates in red

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

blood cells as it is reduced to Cr(III).<sup>14</sup> Experiments have indicated that Cr(VI) loses its mutagenicity in this process; evidence cited as explanation for Cr(VI)'s apparent lack of carcinogenicity at sites beyond the respiratory tract.<sup>14</sup> The human body's capacity to reduce and detoxify hexavalent chromium suggests a threshold mechanism; it may be that Cr (VI) is carcinogenic only when the dose overwhelms the body's reduction capacity.<sup>7,14,16</sup>

Hexavalent chromium has been described as a "Trojan horse": gaining entry to target cells as Cr(VI), then quickly reducing to Cr(III) within the cell.<sup>7,14</sup> It is Cr(III), the stable reduced form that cannot readily transit cell membranes itself, and possibly the intermediate forms Cr(IV) and Cr(V), that are likely responsible for the chromosomal damage potentially leading to carcinogenesis.<sup>7,14,16,17</sup> Further, the intracellular site of reduction is another factor in carcinogenic potential; the hazard may be higher if reduction occurs in close proximity to DNA.<sup>7,14</sup>

### 2.1.3 BIOMARKERS

Biologic monitoring of workers exposed to chromium is considered useful, and may involve analysis of urine, blood or blood components.<sup>7,8,18</sup> Because water soluble Cr(VI) is readily reduced extracellularly to Cr(III) then excreted rapidly in the urine, urinalysis comparing beginning and end of shift samples is a useful practical indicator of recent exposure<sup>19</sup> and is one of the BEI (biological exposure index) measures proposed by the American Conference of Governmental Industrial Hygienists.<sup>20</sup> A second BEI for Cr(VI) is based on the urinary chromium level measured at the end of the work week.<sup>20</sup>

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

However, urinary chromium levels actually reflect total chromium exposure, including dietary, environmental, and occupational exposures to Cr(III), and are influenced by other factors such as recent and past exposure to chromium.<sup>19</sup> Also problematic are the difficulties in obtaining accurate and precise laboratory measurements, and specimen collection and storage issues. Sample contamination and/or poor laboratory technique are noted as particular problems with past monitoring, and remain concerns of any monitoring program.<sup>7,8</sup> Therefore, though useful for monitoring employees' occupational exposures, urinalysis cannot differentiate occupational chromium exposure level from other sources, or indicate chromium oxidation state of exposures. It is believed, however, that urinary chromium reasonably reflects substantial occupational exposures.

Erythrocyte analysis has been proposed as an additional biomarker of exposure to Cr(VI).<sup>18</sup> This method is attractive because erythrocyte chromium levels reflect Cr(VI) exposure, as Cr(III) cannot transit cell membranes. Some believe that this measure may be a better indicator than urinalysis of the body burden of Cr(VI), because it accounts for the extracellular reduction and detoxification processes.<sup>8,18</sup>

### 2.1.4 INDUSTRIAL PROCESS FOR CHROMIUM CHEMICALS

Since the early production days of the 1800s, chromium manufacturing processes have undergone several important changes. The first step in the production of chromium chemicals is the formation of sodium chromate from chromite ore, which is comprised principally of trivalent chrome oxide. Chromite ore is ground and reacted with an alkaline sodium salt at high temperatures in the presence of oxygen to convert the

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

chromium to the hexavalent form. Subsequently, the chromium is extracted with water to convert it to water soluble hexavalent sodium chromate.<sup>21</sup> The original process included the use of lime, or a similar calcium-containing material, added at high levels to control the reaction and optimize the extraction. In the high-lime kiln processes (greater than 0.5:1 lime to ore), soluble calcium chromate compounds were present in the dusts to which workers were exposed.<sup>21</sup> By the late 1950s and early 1960s, the association of this exposure with human respiratory cancers, and the demonstrated animal carcinogenicity of hexavalent chromium, led the industry to develop methods of reducing the calcium-chromium compounds in dust and residue, principally by eliminating, or dramatically reducing, the lime in the process.<sup>21,22</sup> Recognizing the potential health hazards of hexavalent chromium also led to major improvements in industrial hygiene and exposure control.

In the no-lime process, the ground ore is reacted with an alkali and an internally derived diluent. The flit, or roast, leaving the kilns is quenched in water, producing slurry. Prior to filtration, the resulting slurry is subjected to pH adjustment to separate the aqueous sodium chromate. This solution is usually acidified with sulfuric acid (or electrolytically) producing sodium dichromate and sodium sulfate. Following filtration, a concentrated sodium dichromate solution is made by evaporation and crystallization of the sodium sulfate. The concentrated sodium dichromate solution is the raw material for all hexavalent and trivalent chromium chemicals.<sup>21</sup>

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

### 2.1.5 EPIDEMIOLOGICAL STUDIES OF CHROMATE PRODUCTION FACILITIES

Numerous case reports and epidemiological studies have examined the effects of chromate production exposures on workers' health; however, reports quantitatively estimating individual hexavalent exposure levels, at least until very recently, have been scarce.<sup>23,24</sup> Case reports as far back as 1890 and 1911 have linked cancer with chromate production.<sup>6,10</sup> Though lung cancer was reported most often, cases of nasal and gastrointestinal cancer were also cited.<sup>6,10,25,26</sup>

#### *2.1.5a Pre-change Studies*

The first epidemiological study of exposed workers from seven U.S. chromate plants was published in 1948 suggesting that chromium chemical workers were twenty times more likely than unexposed individuals to contract lung cancer.<sup>27</sup> This initial report was followed by a succession of investigations that clearly linked chromate exposure to lung cancer.<sup>2,12,21,22,28-37</sup> Several reviews have been published, including one by IARC<sup>6</sup> that concluded that Cr(VI) was carcinogenic to humans.<sup>6</sup>

Markedly elevated relative risks (calculated for the IARC report) of respiratory system cancer were reported for early cohorts of workers employed in the 1930s to the 1950s, when the high-lime process was the only method employed, and during which period exposure was not well controlled. For example, several studies of slightly overlapping cohorts from U.S. plants showed consistently elevated relative risks:<sup>6</sup> 20.7 for respiratory system cancer based on 42 cases,<sup>27</sup> 14.3 and 80.0 for respiratory system cancer (excluding larynx) in white and non-white populations based on 10 and 16 cases,

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

respectively,<sup>28,29</sup> and 9.4 for respiratory cancer, including maxillary sinus based on 69 cases.<sup>30,31</sup>

Elevated risks for cancer at other sites were also reported, though less often. An excess risk of cancer of the digestive system was reported for two studies:<sup>6</sup> 2.0 based on 13 cases<sup>27</sup> and 1.5 based on 16 cases.<sup>30,31</sup> A five-fold excess of cancer of the oral region was found for the Machle and Gregorius<sup>27</sup> cohort, based on only three cases. Though not without limitations, these studies of early, highly exposed workers provided unequivocal evidence of a major health risk to chromium workers.

Later studies of production industry cohorts that span time periods corresponding to process changes and industrial hygiene improvements also reported consistently elevated risks.<sup>33,35-38</sup> Overall, relative risk estimates for these mixed cohorts reflect a substantial reduction of risk of lung cancer:<sup>6,10</sup> 2.0 based on 59 cases employed 1945-1974;<sup>33</sup> 2.4 based on 116 cases employed 1948-77;<sup>35</sup> 2.1 based on 51 cases employed 1934-79;<sup>38</sup> and 2.2 based on 14 cases employed 1948-85.<sup>37</sup> However, a study of a Japanese cohort<sup>36</sup> reported a higher risk estimate of 9.2 for respiratory cancer (lung and sinonasal cancer) based on 31 cases employed 1918-78. Digestive system or stomach cancer risks were not elevated in the three studies that assessed these outcomes.<sup>6,33,36,38</sup> However, nasal/sinus cancer risk was elevated in two studies: estimated relative risks 7.1 based on 2 cases<sup>35</sup> and 4.2 based on 6 cases.<sup>36</sup>

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

### *2.1.5b Post-change Studies*

Several later studies attempted to assess the effect of plant improvements and process changes on lung cancer risk by identifying pre- and post-change sub-cohorts.<sup>21,22,33,35,38</sup>

While the results were encouraging and suggested a reduction of lung cancer risk in post-change cohorts, they were not conclusive because none fully allowed for the typical latency period of 20-25 years. These studies were limited further by relatively small cohorts, the absence of quantitative exposure data, and the absence of data on confounding factors such as smoking (see 2.1.5c for a discussion on this potential confounder).

Investigation of a U.S. chromate plant built in the early 1970s with the low-lime process design provided further preliminary evidence of a reduction in lung cancer risk due to industrial hygiene improvements and process changes.<sup>39</sup> No increased risk of lung cancer mortality was reported and, though this study benefited from a quantitative exposure assessment and evaluation of potential confounders such as smoking, it too suffered from an inadequate follow-up period.

A recent update of the Baltimore, MD cohort initially studied by Hayes et al<sup>33</sup> also provided the methodological improvements of an extensive exposure assessment and use of smoking data in multivariate analysis.<sup>23</sup> This update restricted the cohort to those hired after the first of two new facilities opened in 1950, through the company closing in 1985.<sup>23</sup> The new facilities, a mill, roast, and bichromate plant, constructed 1950-51, and a chromic acid and special products plant, opened in 1960, were designed to improve

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

process technique and environmental control of exposure to chromium bearing dusts.<sup>33</sup> The minimum follow-up was 18 years, and three-quarters of the cohort had at least 22 years of follow-up, which ended in 1992. Interestingly, an almost two-fold excess of lung cancer mortality was reported for this post-1950 cohort (SMR 1.80; 95% CI: 1.49-2.14); though further analyses indicated that the excess risk was substantial at the two highest cumulative Cr(VI) exposure levels only ( $\geq 0.009$  mg CrO<sub>3</sub>/m<sup>3</sup>-years). No excess nasal or digestive system cancers were found.

Unfortunately, this recent report did not evaluate separately lung cancer risk for those who worked exclusively in the new facilities, though the second new facility opened in 1960. The number of employees employed exclusively in these new facilities was also not provided; however, the earlier report by Hayes et al<sup>33</sup> indicated 509 employees had initial hire dates between 1960 and 1974. Additionally, the Gibb cohort included many very short-term employees; over half worked less than six months, and 42 % worked less than 90 days.

Most recently, Luippold and colleagues reported on the mortality experience of a newly-defined cohort of 482 chromate chemical production workers from the same plant studied by Mancuso.<sup>2,12,24</sup> In contrast with Mancuso's cohort, which was defined as production workers employed between 1930 and 1937, Luippold's cohort consisted of a non-overlapping group of employees hired on or after 1940 until the plant's closing in 1972, and followed for mortality through 1997. Also, unlike Mancuso's study, Luippold's study drew upon data from 20 separate industrial hygiene surveys identified over several

Luippold  
1972

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

decades of the plant's operation to determine individual exposure estimates. Stratified SMR analyses revealed no clear elevation in risk for the first three of five exposure groups, but substantially elevated risk estimates for the two highest exposure groups (SMR=3.65; 95% CI: 2.08–5.92 for 1.05 to <2.70 mg/m<sup>3</sup>-years and SMR=4.63; 95% CI: 2.83–7.16 for 2.70 to <27.80 mg/m<sup>3</sup>-years). By 1950 a number of production improvements were implemented and by 1960, the Painesville plant had started to reduce the amount of lime added to the roast mix. Additional SMR analyses stratified by year of hire showed that lung cancer risk for the 146 employees hired during or after 1960 was essentially as expected: SMR=0.92 (95% CI: 0.34–2.01). Although representing mostly high-lime chromate production employees, this study provided some indication of a threshold effect based on quantified estimates of hexavalent chromium exposure, although a linear model could not be ruled out.

### 2.1.5c Smoking

The role of smoking has largely been ignored in most studies to date, primarily because smoking data have been unavailable. However, incomplete data indicated that smoking levels were probably quite high for many cohorts. Furthermore, the evidence that is available suggests that the effect of smoking on the Cr(VI) – lung cancer relationship is complex. Urinary chromium levels tend to be higher in smokers than non-smokers.<sup>14,40,41</sup> Explanations range from contaminated cigarettes,<sup>40</sup> increased retention of particulates in the bronchial tree, to stimulation of the Cr(VI) reduction mechanism in smokers.<sup>14</sup> Interestingly, there is also evidence that the reduction and detoxification of Cr(VI) by pulmonary alveolar macrophages may be enhanced in smokers and ex-smokers.<sup>14,42,43</sup> An

interaction between Cr(VI) and smoking is a distinct possibility, and an issue that remains to be unraveled.<sup>14</sup> Some evidence suggests that there may be a less than additive effect between Cr(VI) and cigarette smoke at certain steps in the carcinogenesis process,<sup>14</sup> perhaps related to the enhanced reductive capacity of smokers' airways.

#### ***2.1.5d Research Needs***

It is tempting to attribute the apparent reduction of cancer risks suggested by most of the later epidemiological studies to improved workplace conditions and reduced exposure to Cr(VI) compounds. Despite the improvements cited for the three more recent studies, the effects of methodological limitations remain unclear, particularly the effects of inadequate latency periods for post-change cohorts, and low statistical power (and resulting imprecision of relative risk estimates) due to small cohort sizes. Also, recent toxicokinetic evidence seems to provide provocative clues for exploration of non-linear dose-response effects.

## **2.2 Previous Studies of the Cohorts Participating in this Investigation**

### **2.2.1 PLANT HISTORIES AND DATA SOURCES**

Four chromate production plants participated in the current investigation: two Bayer AG plants in Leverkusen (LEV) and Uerdingen (UER), Germany; an Elementis plant in Corpus Christi (CC), Texas, USA; and an Occidental Chemical Corporation plant in Castle Hayne (CH), North Carolina, USA. A fifth plant in the United Kingdom (Elementis plant at Eaglescliffe) was included in the original study protocol, but was unable to participate. All four participating plants converted to no-lime, or were built to

use low-lime processes. Process changeover to no-lime occurred at the two Bayer plants and the Elementis Corpus Christi site, while Occidental Chemical Corporation built the Castle Hayne plant with a low-lime design. All plants continuously implemented industrial hygiene improvements to limit hexavalent chromium exposure, reflected in the very low exposure levels recorded in all facilities in the most recent production years. The Corpus Christi and Castle Hayne plants are still in operation, the Uerdingen plant closed in 1992, and the Leverkusen plant closed in 1999. All of the plants have been studied previously, but the results of the study of the Corpus Christi facility were not published.

#### 2.2.2 LEVERKUSEN COHORT, BAYER, AG

Originally a high-lime facility, the Leverkusen plant converted to a no-lime process in 1958. The modification completion date officially was set at January 1, 1958, although complete changeover probably occurred sometime after that date. The plant stopped production and closed by early 1999, with remaining employees assigned to other production areas in Leverkusen. Several prior cohort studies have been conducted on one or more German facilities, including the Leverkusen plant.<sup>22,38,44</sup>

From the most recent follow-up of these studies,<sup>22</sup> the study cohort included all 695 male chromate workers (mostly German nationality) active on Jan 1, 1948 or later at the Leverkusen dichromate plant. The cohort also included former chromate workers at the other Bayer plant in Uerdingen who were active on January 1, 1948 or living retirees on January 1, 1948. All Leverkusen cohort members had to be employed for at least one

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

year at the dichromate plant and were followed until December 31, 1988. Separate analyses were conducted for three sub-cohorts, defined by time period of first exposure (two pre-change and one post-change group).

The post-change cohort included all employees first employed after 1957 for at least one year (n=416; 4,908 person-years). Compared to the North Rhine-Westphalia region, the post-1957 cohort had an SMR of 1.01 (95% CI: 0.56—1.67) for all malignant neoplasms (15 deaths) and an SMR of 1.45 (95% CI: 0.62—2.86) for bronchial carcinoma (eight deaths). The SMR for all causes of death combined was not reported for this group alone (49 deaths and 22 with unknown vital status), but an SMR of 0.97 from all causes combined was reported for the entire Leverkusen cohort, including the pre-change groups. These post-change results must be considered preliminary because the majority of the group had not had sufficient follow-up to allow for the latency period typical for lung cancer. Former employees of this facility are under continued voluntary medical surveillance.

The database for this previous cohort study was constructed from the central Medical Department's data bank and personnel data maintained by each plant. These records included time spent in the dichromate production area by maintenance workers, engineers and others assigned to multiple production areas. Several exposure zones were identified within the plant, and air chromium and individual urinary chromium values were recorded from 1977 to 1990. However, these exposure data were not used in the data analysis because workers were rotated through all plant areas, making estimation of

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

individual exposure levels difficult. Vital status was determined from medical or personnel records, or from the local population registries. Best-available cause of death information was obtained from hospital, surgical and general practitioner reports obtained by plant physicians to ascertain the possibility of a work-related illness or cause of death (for workers compensation purposes). In Germany, individual cause of death information is difficult to obtain, as death certificates are not public documents. Though there may be a greater proportion of deaths for the German plants without known cause of death, the information that is obtained from the various sources is likely to be more detailed and possibly more accurate than death from death certificates alone.

Data on smoking habits were available but not used in the previous analyses because of lack of information on smoking habits in earlier years. However, smoking information was reported to be available for 82% (341/416) of post-change workers, and of these, 73% (250) were current smokers at the time of their last medical examination. Of the eight bronchial carcinoma deaths, six were among smokers and the remaining two were of unknown smoking status. Using a survey of the general population in West Germany that showed that 52% of males between 40-64 years of age were smokers, the authors estimated that the cohort would be expected to have an 35% increase in lung cancer risk due to smoking alone, although no increase in lung cancer risk was observed.

#### 2.2.3 UERDINGEN COHORT, BAYER, AG

The Uerdingen facility was converted from a high-lime to a no-lime process during the early 1960s. Though the modification completion date officially was set at January 1,

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

1964, the changeover process is known to have continued past that date. This was the second plant investigated in the previous studies mentioned above.<sup>22,38,44</sup> From the most recent follow-up of these studies,<sup>22</sup> the total Uerdingen cohort included 722 male chromate workers (mostly German nationality) with the same inclusion criteria and follow-up period as the Leverkusen cohort (see above).

The employee database, similar to that of the Leverkusen plant, was constructed from the central Medical Department's data bank and plant personnel data. Exposure data were not used in the analyses for the reasons described above for the Leverkusen cohort. Vital status and cause of death determination also were identical to the procedures described above. Data on smoking habits were not used in the analysis because, though complete for the post-change workers, this information was not available for 31% of the pre-change group. However, similar to the Leverkusen cohort, a high proportion (72%) of the total Uerdingen cohort had a history of smoking. As with the Leverkusen cohort, separate analyses were conducted for three sub-cohorts, defined by time period of first exposure (two pre-change and one post-change group).

The post-change cohort included all employees first employed after 1963 for at least one year and followed through 1988 (n=262; 2,659 person-years). Compared to the North Rhine-Westphalian reference mortality rates, the post-1963 cohort had an SMR of 0.51 (95% CI: 0.07—1.73) for all malignant neoplasms (two observed deaths) and an SMR of 0.69 (95% CI: 0.01—3.62) for bronchial carcinoma (one observed death). The all-cause SMR was not reported for this group alone (eight total deaths and 12 with unknown vital

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

status), but an SMR of 1.05 from all causes combined was reported for the entire Uerdingen cohort. The authors acknowledged that the follow-up period was not sufficiently long for many workers in this group. Most sections of the Uerdingen dichromate plant were closed by the end of 1992, and the remaining sections closed by 1995. Former employees are currently under voluntary medical surveillance.

#### 2.2.4 CORPUS CHRISTI COHORT, ELEMENTIS, USA (FORMERLY AMERICAN CHROME)

The Corpus Christi (TX) plant, formerly a high-lime facility, currently uses a no-lime process. The high-lime process was used from 1962 until 1980, and the conversion to a no-lime process was made shortly after the plant was acquired by American Chrome in 1980. Applied Epidemiology, Inc. conducted an epidemiological mortality study and employee survey of this facility in 1995 (unpublished data). An employee database was designed and structured using ProQuest, a PC-based information management system for epidemiological studies (SoftWhere, Inc, Goshen, MA and Applied Epidemiology, Inc., Amherst, MA). This database included detailed employee information obtained from a questionnaire on medical history, smoking history, caffeine and alcohol use, exercise habits, respiratory protection use, and exposures to other hazards. As of the end of the follow-up period (1994), 202 of the 351 current and former employees (58%) responded to the questionnaire. Demographic, and complete work history data were collected on all employees from personnel records. Death certificates were obtained for 23 of the 27 decedents (including 22 males) identified from company records. No exposure data were collected for this study.

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

An internal report (Applied Epidemiology, Inc., unpublished data, 1995) summarized employee mortality experience from the time American Chrome and Chemicals acquired the facility (October 15, 1979) through November 30, 1994. The cohort included 382 workers (4,293 person-years), and mortality analyses were restricted to 310 (3,549 person-years) males (including white, black and Hispanic males). Compared to the Texas white male population, the SMR was 0.64 (90% CI: 0.44—0.92)<sup>1</sup> for all causes (22 deaths), the SMR was 1.24 (90% CI: 0.70—2.05) for malignant neoplasms (11 deaths), and the SMR was 1.67 (90% CI: 0.72—3.29) for respiratory cancers (six deaths). The analysis included both pre- and post-change workers, and the results must be considered preliminary because approximately half of the cohort did not have sufficient follow-up to allow for a minimal latency period for lung cancer.

#### 2.2.5 CASTLE HAYNE COHORT, OCCIDENTAL CHEMICAL CORPORATION

The Castle Hayne (NC) plant was built with the low-lime process design and opened in 1971. The plant produces dichromate solution, sodium dichromate crystal and chromium trioxide flake. The plant was engineered to minimize chromium exposure, and to replace two former high-lime process facilities in Painesville, OH and Kearny, NJ, USA.

Pastides et al<sup>39,45</sup> conducted a retrospective cohort study of the plant as the first step of an ongoing surveillance program. The cohort was comprised of all employees (n=398) working at least one year between the plant opening on September 4, 1971 and December

---

<sup>1</sup> Note that 90% confidence intervals were reported, which are typically used for exploratory analyses.

These will have narrower ranges compared with 95% confidence intervals.

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

31, 1989, and included 45 workers (722 person-years) who had transferred from one of the older facilities (Painesville or Kearny plants). A detailed employee database was designed and structured using an early version of ProQuest. This database included detailed employee questionnaire information on medical history, smoking history, plant work history, previous work history, and exposure to other hazards. Of the 381 living cohort members, 289 completed either the questionnaire or telephone interview. For deceased employees (n=17) and non-respondents (n=92), job histories were reconstructed from plant personnel files. Information on smoking habits was obtained from other employees for deceased employees. Most deaths were identified through company records. Additional searches were conducted using the National Death Index (NDI) of the U.S. National Center for Health Statistics (NCHS), North Carolina death certificate searches, and the Death Master File (DMF) of the Social Security Administration (SSA). Analyses were limited to white male employees (n=311).

Compared to local North Carolina counties, SMRs were 0.72 (90% CI: 0.45—1.10)<sup>2</sup> for all causes (16 observed deaths), 1.25 (90% CI: 0.54—2.46) for all malignant neoplasms (six deaths), and 0.97 (90% CI: 0.17—3.06) for respiratory cancers (two deaths). The reported SMRs combined the employees previously employed at one of the older high-lime facilities with those employed only at the Castle Hayne plant. However, further analysis indicated that the sub-cohort of employees who had transferred from previous chromate producing plants had an elevated respiratory cancer risk (based on two cases,

---

<sup>2</sup> Note again that 90% confidence intervals were reported, which will have narrower ranges compared with 95% confidence intervals.

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

one of which had 31 years employment at the older plant). Both respiratory cancers occurred among smokers. The relatively short follow-up for many in the cohort and the small study sample size limit the interpretation of the results.

This study benefited from an extensive exposure assessment. More than 5,000 industrial hygiene personal air monitoring results were obtained for the period February 1974 to April 1989. In addition, more than 1,500 area air samples were available from 1971 through 1979. Using work history records, about 100 job titles were identified and grouped into 22 discrete exposure areas. Industrial hygiene data were then sorted into the cells of a matrix defined by these 22 work areas over each calendar year. Measures within cells were summarized using geometric means. Individual work histories were used to link individuals to exposure scores, and subsequently to classify individuals as having high, medium or low cumulative exposure estimates. Because of the small number of lung cancer deaths observed, no dose-response analyses were possible. However, a logistic regression model showed that risk of malignant neoplasm (all sites, not limited to respiratory cancers) increased with exposure prior to Castle Hayne (odds ratio=1.22; 90% CI: 1.03—1.45), older age (OR=1.77; 90% CI: 1.06—2.95), and ever smoked (OR=1.78; 90% CI: 0.45—7.01), but not with a cumulative exposure indicator (further reduced to high/low), with OR=0.5 (90% CI: 0.13—2.02).

### 2.3 Rationale for a Study Combining these Cohorts

Although the published literature demonstrates a consistent association between hexavalent chromate exposure and respiratory cancer, the change to no-lime or low-lime

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

processes in the chromium chemicals industry combined with improved production methods and industrial hygiene practices renders this extensive literature unrepresentative of current exposure conditions. Studying the modern chromium chemical industry offers opportunities for filling this gap in the scientific literature, but most facilities have been inadequate for stand-alone analyses of lung cancer risk associated with chromium exposure, primarily due to relatively small exposed employee populations. Further, prior to this point in time, inadequate time has passed since conversion to (or construction of) low-lime or no-lime processes to be able to detect any remaining lung cancer risk associated with lower exposure. For these substantial reasons, a combined study of employees from several similar production facilities was undertaken, with better statistical power than any study of a single plant might provide. Though still modest in size, the combined cohort of employees of four facilities enhanced the ability to derive meaningful and useful results.

The primary goal of this study was to evaluate the possible cancer mortality risks associated with hexavalent chromium exposure in the post-change environment, increasing statistical power for the study by combining employees from four separate but similar facilities. Specific objectives included the following:

- To construct job exposure matrices (JEMs) for each plant using standardized methodology and terminology across plants; to compare and evaluate differences between plants; to validate JEMs using other data sources including expert evaluation;

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

- To calculate individual exposure estimates by linking individual work histories to the appropriate JEMs;
- To conduct standardized mortality ratio (SMR) analyses and calculate all cause and cause-specific SMRs for all plants combined, using appropriate national and regional reference rates;
- To conduct multivariable analyses of lung cancers to evaluate risk, accounting for exposure to hexavalent chromium, smoking status, and age.

## METHODS

### 3.1 Cohort Enumeration

Employees of each of the four participating chromium chemical production plants have been included in previous epidemiological studies. From these cohorts, the post-change employees were extracted to form the core of a combined cohort for this study (Table 1). This multi-plant cohort was expanded further to include all employees hired since the previous studies, as well as any employees who had been excluded from previous studies because they had not completed one year of employment prior to the end of the previous studies. Excluded from this study were all employees who worked at any time in the older, chromium production facilities as well as employees with less than one year total employment in the modern plants. Very short-term employees are more difficult to trace, often have different baseline disease risks from long-term employees, and are less likely to have had occupational exposures that meaningfully influence their ultimate cause of death. Therefore their exclusion enhances the focus of the study on the most relevant employees and long-term exposures.

The enumeration of the German sub-cohorts was based on the databases generated for the previous study (through December 31, 1988). Existing medical databases, mainly for purposes of medical surveillance of chromate-exposed employees, and an employee database for the Uerdingen plant, constructed for other purposes than medical surveillance, were used to identify persons hired after the end of follow-up for the last study. Employees with a history of pre-change exposure or with less than one year of

employment in the plant were excluded. Completeness of the cohort was verified by comparing the cohort listing with shift-books of the plant (Leverkusen) or existing yearly summaries of medical examinations of the plant employees (Uerdingen). During the process of cohort enumeration, all demographic information was verified. In both plants, only male employees who worked in the chromate facilities were included. Nearly all were German nationals, although a few were from other European countries.

For each of the U.S. plants, existing study databases also served as the primary sources of data. Plant personnel records at each of the plants were used to identify all employees who were hired since 1989 and 1994 at the Castle Hayne and Corpus Christi plants, respectively, and to verify the completeness of the existing study databases. Both of the U.S. plants included female employees in the cohort. Approximately one-third of the Corpus Christi employees were Hispanic and nearly 20% of the Castle Hayne employees were black.

## **3.2 Work History**

### **3.2.1 GERMAN PLANTS -**

Using various data sources including the medical records of each employee, we reconstructed detailed employment histories for each cohort member of the German plants. Between 1985 and 1986, the Industrial Hygiene (IH) Department at Bayer conducted a workplace survey and determined exposure areas and exposure levels. This survey identified 15 and 24 work area/job function groupings at Uerdingen and Leverkusen, respectively. These categories were used to reconstruct the individual work

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

histories and to link each employee to the proper work area over the entire period of employment in the plant. Although this approach will assign the same exposure values to employees with the same work histories, their actual individual exposures are likely to differ due to differences in individual work practices, proximity to process emissions, and individual characteristics.

Employees in the production areas at the Uerdingen plant worked in rotational shifts, making it impossible to assign individuals to a single work area at any point in time. Production employees changed specific work areas and tasks weekly; these employees, however, could be clearly assigned to larger work areas or task groups defined by the IH department to reflect the flow of work. Within these broader categories, total working time was apportioned (according to number of areas involved in the rotations) across the related specific areas. This categorization then allowed assignment of "composite" exposure estimates to rotation workers. Non-production employees (e.g., employees working in the fill stations, dispatch or plant workshops) usually worked a day shift, and changes in work areas or tasks for these employees were rare.

Employees at the Leverkusen plant were not assigned to specific work areas or tasks but were allocated to jobs depending on actual need. Most employees, however, remained in one of the buildings that comprised the chromate plant. During routine semi-annual medical examinations, the primary jobs and task of the employee were recorded. We used this information to determine where each employee worked over the period of time since the previous examination. Changes in work areas recorded in the medical records

were verified against information recorded in shift books, including approximate date of job changes.

For the Leverkusen plant information collected during the medical examination included the proportion of time spent by maintenance workers, engineers and others in the dichromate plant (if they were assigned to areas other than the dichromate plant). This information was less complete at Uerdingen, and was reported only occasionally for maintenance workers, engineers and others assigned part-time to the dichromate plant.

### 3.2.2 U.S. PLANTS

For the U.S. plants, job tasks and work area assignments were determined using plant personnel records. For Castle Hayne employees, a survey, conducted in person and via telephone for the previous cohort study, served as the primary source for work history data for those who worked before 1990. The primary source for all employees hired since 1990, and a secondary source for the older employees was a printout of an earlier computerized database of plant personnel. Information from this database was incomplete for the earliest years of the plant. When job assignments and tasks conflicted from the two sources, data from the personal interview were used. For some employees data gaps existed, and it is possible that errors resulted from the process used to adjudicate conflicts in the plant data; however, plant personnel assisted with the decision-making process in order to derive the best possible resolution.

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

### 3.3 Exposure Data

#### 3.3.1 PERSONAL AIR MONITORING DATA

Personal air monitoring samples were collected at all plants, although relatively few samples were available for the German plants (less than 300 samples each), and only for the most recent years (Table 2). Personal air measurements were conducted for the first time by the Industrial Hygiene Departments at Uerdingen and Leverkusen during 1985 and 1986, as mandated by new legal regulations. The sampling strategy was dictated by these legal regulations that specified that an initial work place analysis include the determination of exposure areas and exposure concentrations, and when personal protective equipment was worn, sampling pumps were to be turned off. Presumably this was done to better simulate actual exposure rather than what is normally measured -- potential exposure. Control measurements were taken, usually once per year. For Leverkusen, the sampling results were provided directly by the Industrial Hygiene Department while the data for Uerdingen were extracted and derived from the original sampling protocols and analytical result reports.

Personal air sampling was conducted at Corpus Christi and Castle Hayne over most years of the study; however, there were several years when no personal air sampling was conducted at Corpus Christi (1982, 1985-1987, 1989) or at Castle Hayne (1971-1973, 1993-1994, very few samples during 1997-1998). Otherwise, more than 5,200 industrial hygiene personal air-monitoring results were obtained for the period February 1974 to April 1989 (Table 2) at the Castle Hayne plant, while approximately 230 samples were obtained for the later years.

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

From approximately 1981 to 1985, personal air sampling was conducted twice yearly for each job title at the Corpus Christi plant. Both total chromium and hexavalent chromium were sampled. During the early 1990's, the sampling strategy changed so that every person with potential chromium exposure was sampled once per year and every job was sampled once per quarter year. In January 1995, the Corpus Christi plant initiated a strategy of random sampling of personnel. Each job title was assigned seven random dates and each job was sampled seven times over 17 months. All personnel who were assigned to administration, laboratory or technical jobs, and/or were engineers, production supervisors or maintenance supervisors were excluded from personal air sampling. Overall, over 1200 personal air monitoring results were available.

The personal air sampling strategy at Castle Hayne for the years 1974 to 1978 was to collect a sample from each employee every eight to ten weeks, though records indicate that sampling did not occur that frequently for most employees. After 1978, sampling was based on the NIOSH recommended exposure limit (REL) and the plant action level, which determined the amount and type of follow-up sampling. Generally, each employee was sampled at least once per year, or more often if there were engineering problems or unusually high chromium levels in a particular area of the plant.<sup>45</sup>

### 3.3.2 AREA AIR MONITORING DATA

In contrast to the few personal air monitoring measurements available for Leverkusen and Uerdingen, stationary area air measurements were available over a longer time and were

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

more abundant. Though area air measurements had been conducted in the German plants since the early years, results were only available since 1973 at Leverkusen and 1978 at Uerdingen (Table 2). For the Leverkusen plant, more than 3,400 area measurements were taken by the Industrial Hygiene Department and analyzed in the inorganic analytic laboratory of the company. The samples were usually taken monthly and mostly at 18 distinct locations, and the reported results, available in paper form as typed lists, were adjusted for volume, air pressure and temperature. For the Uerdingen plant, about 1,160 area measurements were available from hand-written lists. There were two different measurement series. The first series included measurements for eight to 12 locations in the plant for the years 1978 to 1988. The second series included measurements for 25 locations for the years 1985 to 1990. All measurements were conducted by plant personal and analyzed in the plant laboratory. No information about the measurement strategy or details of the measurements was available. The Industrial Hygiene Department of Uerdingen expressed concern about the quality of the measurements and the validity of the results because personnel conducting the sampling were not adequately qualified and the measurement process was not standardized.

Over 1500 area air samples were available for the period 1971 to 1979 at the Castle Hayne plant. Most were short-term ceiling samples, and no data were found for 1973. Results of area sampling conducted 1979-1989 were not available because those data, existing in paper format only, were not abstracted for the first study, as the amount of personal air samples available for that time period was considered sufficient. These area data obtained from 1979-1989, as well as some additional area sampling data from 1990

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

and 1991, were not used for the current study because of the greater amount of personal air monitoring data available.

During the 1980's, area air monitoring for hexavalent chromium was conducted quarterly for 23 locations at the Corpus Christi plant. The sample runs lasted 300 minutes. During the 1990's, plant personnel scheduled 18 monitoring stations to be sampled once every quarter, while the remaining five areas, with very low expected exposures, were sampled once every 17 months.

### 3.3.3 BIOMONITORING DATA

Urinary, whole blood and serum analysis data were available for both Leverkusen and Uerdingen (Table 2). These data were collected during the routine medical examinations of the employees. More than 5,400 urinalysis results for Uerdingen employees and almost 7,000 for Leverkusen employees were available over the follow-up. Fewer blood samples were available than urinary samples, and in more recent years only: from 1969 to 1971 and since 1983 at the Leverkusen plant and since 1972 at the Uerdingen plant. Serum analyses were first conducted during the mid-1980's in both plants.

All biomonitoring data for the Uerdingen plant were extracted from the employees' medical records. Biomonitoring data for Leverkusen cohort members were provided from the Institute for Biomonitoring of the Bayer Leverkusen AG for the years since the late 1970's. The data for the earlier years were extracted from the employees' medical records. Usually no biomonitoring data were available for maintenance workers who

were assigned part-time to the dichromate plant and part-time to other plants at Leverkusen. At Uerdingen, biomonitoring data were available for all cohort members.

No biomonitoring data were available at the U.S. plants.

### 3.4 Smoking Habits

Data on smoking habits were not used in the previous analyses of the two German plants because of lack of information on smoking habits in earlier years. During the most recent decades, however, information on smoking habits was collected during routine medical examination. Smoking status information was available for approximately 90% of employees hired after 1957 at Leverkusen and nearly all employees hired after 1963 at Uerdingen. Although the data were not complete for all employees, information collected included smoking status, age began smoking, number of cigarettes or cigars smoked per day, grams of pipe tobacco smoked per week and the year the employee quit smoking. Some of this information was obtained from the database of the earlier study. Each study subject's medical record was checked to verify this information as well as obtain smoking information for study subjects who were hired since the end of the previous study.

For the Corpus Christi plant, data on smoking habits were obtained from a questionnaire sent in 1993 to current and former employees, of whom 202 (of 351 total) responded, including a large proportion of retirees. Additional smoking information was provided from plant personnel who conducted pulmonary function and audiometry screenings. In

the latter case, smoking information was generally available only as ever smoked or never smoked.

For the Castle Hayne plant, data on smoking habits were obtained in 1989 for the first study from a self-administered questionnaire for active and most former employees, or a telephone interview for former employees who did not respond to the initial request. Of 381 total cohort members, 289 responded. For the current study, company medical records provided smoking information for employees hired since conclusion of the first study. For deceased employees, information on smoking habits was obtained from other employees at the plant who were likely to know their colleagues' smoking habits.

### **3.5 Data Acquisition and Database Construction**

A database of study cohort members was constructed using the ProQuest modular database system (SoftWhere, Inc., Goshen, Massachusetts, USA, and Applied Epidemiology, Inc., Amherst, MA, USA). Several modules were constructed and designed to contain distinct types of data, such as smoking data, mortality data, exposure data, and job history data. Each record in a module was linked to a demographics module record for that study subject. For the German plants, medical department staff or other authorized persons linked all study data for each employee and removed all personal identifiers before sending the data to AEI for inclusion in the database. The anonymization of the data assures confidentiality; only the plants hold the key to employee identities. Personal identifiers for the U.S. plants were included in the study

database, as these were needed to conduct vital status searches and to obtain mortality information.

### 3.6 Exposure Assessment Overview

The goal of the exposure assessment was to derive one or more estimates of each employee's exposure to hexavalent chromium. Estimates were based necessarily on data compiled from various sources, as no single source or type of exposure data was available at all four plants, or for the entire study period. Further, estimates were based on the compiled exposure data relevant to groups of individuals, as no source of data -- single or combined -- could provide adequate estimates of exposure for each individual in the study. The general approach selected was to construct job exposure matrices (JEMs) using existing industrial hygiene data. JEMs are simply matrices whose axes are typically exposure areas and calendar periods. In this case, the exposure areas were based on homogenous exposure groups (HEGs), work areas having exposure potential discrete from others and within which all employees would be expected to have similar exposure, and the calendar period represents one year. Industrial hygiene measures obtained for each HEG and time period in the JEM (i.e., JEM cells) were summarized to obtain an average exposure level for that specific time period and location. Because exposure data are usually not normally distributed, but strongly skewed, exposure measures within cells of the JEM were summarized by calculating geometric means. Each employee's exposure to hexavalent chromium was then estimated by linking individual employee work histories (i.e., the amount of time each employee spent in each of the HEGs) to these summary measures in the JEMs.

Exposure assessment was conducted to characterize exposure over time using two measures: cumulative exposure and peak exposure indicator score. Cumulative exposure was measured as the sum of the geometric mean exposure over the years in chromium-exposed work areas. Peak exposure was measured by the sum of peak exposure ranks in chromium-exposed work areas. These measures are described in greater detail below.

### 3.6.1 IDENTIFICATION OF HOMOGENOUS EXPOSURE GROUPS

Where possible, homogeneous exposure groups were identified using existing exposure groups defined in earlier studies. This grouping was supplemented with information obtained from industrial hygienists and other knowledgeable personnel at each plant to derive a manageable number of exposure areas with discrete job tasks and therefore potentially discrete exposure levels. Operational areas of each plant often formed the basis for identifying these exposure areas where jobs and tasks had similar exposure levels and similar opportunities for exposure within an area, but had exposures different from any other area. These homogenous exposure areas are summarized in Table 3. All job titles and tasks from the work histories were identified and linked to the corresponding exposure area.

The surveys conducted in 1985 and 1986 by the Industrial Hygiene Departments at Leverkusen and Uerdingen identified 24 and 15 homogenous exposure groups, respectively, that existed during some period of plant operation within the study period. All job titles were mapped to these exposure areas, based on extensive consultations with

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

medical personnel at each plant. Using work history records at Castle Hayne, about 100 job titles were identified and similarly mapped to 22 discrete exposure areas. The Corpus Christi plant had hundreds of job titles, but most of these reflected administrative changes in title without change in work tasks. As with the other plants, these all were mapped to one of 17 discrete exposure areas.

### 3.6.2 VERIFICATION AND STANDARDIZATION OF AIR MONITORING DATA

At Corpus Christi chromium measurements were reported as chromic acid ( $\text{CrO}_3$ ) in earlier years and as hexavalent chromium in later years. The Castle Hayne plant alternated between the two reporting conventions ( $\text{CrO}_3$  and  $\text{Cr(VI)}$ ) during the early years, and, similar to Corpus Christi, reported results as hexavalent chromium in later years. Data from all locations were standardized to hexavalent chromium in  $\mu\text{g}/\text{m}^3$  unit values. Because personal air monitoring samples should be collected over full-shift durations, or at least close to full-shift durations to be representative of daily exposure, we excluded from the exposure assessment all samples of less than four hours duration. All personal air monitoring samples at the Corpus Christi plant were full-shift samples; however, 69 out of about 5500 personal air samples at Castle Hayne were less than four hours (i.e., less than 50% of an eight-hour shift) and therefore excluded from the analysis. For both of these plants, data below the level of detection (LOD) were substituted by the midpoint between the LOD and zero (i.e.,  $\text{LOD}/2$ ).

Although personal air samples were available at all plants, the German plants provided very few, and only for years beginning with 1986. Instead of personal air sampling, the

German plants relied primarily on biomonitoring data, especially chromium in urine and blood, for individual exposure surveillance. In contrast, the two U.S. plants relied on relatively extensive air monitoring data, and had no biomonitoring data.

### 3.6.3 VERIFICATION AND STANDARDIZATION OF URINARY CHROMIUM DATA

The urinary data posed two challenges. First, urinary measurements for some years were reported as creatinine-adjusted values while urinary measurements for other years either were corrected for specific gravity or were not corrected for hydration. Correction for hydration is important because urinary concentration is influenced by the amount of fluids an employee consumes, and various techniques have been used historically. Creatinine adjustment became popular under the belief that humans excrete a relatively constant quantity of creatinine in their urine despite urinary volume (which is partly a function of hydration). However, more recently, it has been demonstrated that despite fairly constant excretion rates within individuals, there is substantial variability between individuals in the amount of creatinine excreted, and exposure may be systematically under or over estimated for some. For this reason creatinine adjustment has grown out of favor. Nevertheless, hydration remains an important issue in the interpretation of urinalysis results.

Second, many employees had multiple measurements of urinary data over very short periods of time. These possibly reflect the medical monitoring of employees following known or suspected overexposure, possibly related to spills or other upset conditions. If so, these measurements would not constitute routine, independent exposure estimates.

On the other hand, they do describe real exposure opportunity, and should be incorporated in some way in the exposure assessment.

### *3.6.3a Creatinine-Adjusted versus Specific Gravity*

For Leverkusen, measurements of chromium concentrations in urine were available from 1958 to 1979 expressed as  $\mu\text{g/L}$ . From 1980 to 1992, urinary chromium concentrations were available expressed as  $\mu\text{g/g}$  creatinine only. From 1992 to 1998, chromium concentrations appear to have been analyzed and reported as both  $\mu\text{g/L}$  and  $\mu\text{g/g}$  creatinine. We performed a simple analysis of the 1,341 paired sample data (1992-1998) to consider whether an appropriate conversion factor could be derived. Although a proportional relationship was observed, no consistent conversion factor could be imputed. The ratio of creatinine to urine ranged from 0.25 to 1.68. As a result, we elected to use the data in the units reported, rather than transform creatinine-adjusted values to urine measurements or urine values to creatinine-adjusted measurements. Bayer Medical personnel reported that the two measurements were considered interchangeable for their purposes, which was to monitor relative changes over time in individual employee urinary chromium concentrations. We subsequently used measurements expressed as  $\mu\text{g/L}$  until 1979 (although it is not known if these were adjusted for specific gravity) and as creatinine-adjusted values from 1980 to 1998.

Urine measurements reported in  $\mu\text{g/L}$  and adjusted for specific gravity were available for Uerdingen from 1964 to 1995. Creatinine adjustments apparently were not performed on

samples analyzed at the Uerdingen plant (Dr. med Steinmann-Steiner Haldenstedt, personal communication, October 15, 2001).

### *3.6.3b Repeated Measurements of Urinary Data*

Bayer medical department personnel routinely collected urine samples from each employee at the two plants during semi-annual medical examinations. After accidents, spills or other upset conditions, medical protocol specified that additional urine samples were to be collected. As a result, multiple repeated measurements existed for many employees, but these samples were not necessarily identified as samples collected following upset conditions. To avoid using multiple measures representing upset conditions, thereby giving inappropriate weight to these measures, we applied a simple criterion to identify which urine samples constituted a series of repeated measurements. We assumed that multiple urine samples collected during any 30-day period indicated that an accident, spill or upset condition had occurred. To identify all possible measures associated with such a situation, we identified the earliest measurement in the series and evaluated each subsequent measurement until a 30-day period passed without a urine sample for the individual. For Leverkusen, we identified 622 series of two to five measurements. These occurred among a total of 120 individuals, and generated a total of 1309 samples. For Uerdingen, we identified 64 series of two to ten measures among 52 individuals, representing a total of 174 samples. The initial urine sample after the exposure event could not be identified in many instances because only month and-year of sample were reported, and therefore several results would be associated with the same reporting date. For each of the series of measures associated with apparent upset

conditions, we chose only the single highest urinary chromium value to represent the event in the calculation of a mean exposure value, and discarded the remaining values.

#### 3.6.4 CONSTRUCTION OF JOB EXPOSURE MATRICES (JEMS)

A job exposure matrix (JEM) was developed for each plant, as each facility had a different array of homogeneous exposure groups (Table 3). Each cell represented one calendar year and one exposure area at the respective plant. Because of the different types of personal exposure data available from the German and U.S. plants (urine and air samples, respectively), the JEMs for the German plants were based on urinalysis results while those for the U.S. plants were based on air monitoring results. This difference required commensuration of the measures (described below) so that exposure estimates would be reasonably comparable regardless of source of exposure data.

Two types of JEMs were constructed for each plant: average exposure concentration and peak exposure index. The two types of matrices differed according to the method used to summarize the monitoring results data in each cell. While average concentration is the most frequently used summary measure, it can mask true differences between exposure areas by ignoring the variability of exposure data obtained within areas. For example, two areas with identical average exposure concentrations may differ drastically with respect to the range of exposure values recorded in each: one area may have consistently moderate levels, whereas the other may have generally low levels with occasional high-level periods (or peaks). To determine whether this occurs, and if so whether it is associated with risk, both measures can be applied and results compared. For the average

exposure concentration, the geometric mean of all values in a given cell was calculated. For the peak exposure index, the values in each cell were evaluated for the presence of measurements (air or urine) exceeding a specified (arbitrarily chosen) value, and a peak index score was generated that accounts for the relative frequency and magnitude of peak measurements. In either type of JEM, exposure values for individual cohort members were derived by summing the exposure values (concentrations or peak scores) associated with each work area/year cell, weighted by the amount of time worked in that area.

The construction of both types of job exposure matrices involved several steps: evaluating and removing, if necessary, data outliers; ranking exposure areas to determine the areas of greatest interest (e.g., areas more intensively monitored, areas with highest exposures); collapsing exposure areas that were not substantially different with respect to average exposures, due to very low exposure concentrations; and stabilizing sparse cells and filling empty cells.

#### *3.6.4a Remove Outliers*

Exposure values that were so high that they were deemed implausible in the opinion of an industrial hygiene expert or plant personnel were removed from the database. Outliers may be obtained if the sample collection medium is contaminated with chromium, or as a result of a calculation error.<sup>3</sup> Next, we examined the distribution of exposure values for

---

<sup>3</sup> There were five such values: an area air measurement of 33,250.6  $\mu\text{g}/\text{m}^3$  at Corpus Christi, area air measurements of 1915  $\mu\text{g}/\text{m}^3$  and 0.0  $\mu\text{g}/\text{m}^3$  at Leverkusen, and an area air measurement of 1024.92  $\mu\text{g}/\text{m}^3$  and a urine value of 1660  $\mu\text{g}/\text{L}$  at Uerdingen.

each exposure area by year. Several "distributional" outliers, or outliers that were considerably higher than the next highest value, were observed. These distributional outliers, however, were considered plausible exposures and therefore were included in the calculation of summary exposure estimates.

#### ***3.6.4b Rank Exposure Areas Overall***

For each homogenous exposure group identified at each plant, we calculated an arithmetic mean and a geometric mean based on all years to identify the areas over time that experienced the highest exposures on average. We then used the geometric and arithmetic mean values, separately, to rank the areas from highest to lowest average exposure. These rankings, whether based on the geometric mean values or arithmetic mean values, were similar for nearly all of the exposure areas. We further used these averages over all years to determine what differences in average exposure, if any, could be discerned between exposure areas.

Because our primary goal in the cumulative exposure assessment was to communicate "typical" values in distributions that were skewed, we chose the geometric mean as a summary measure.

#### ***3.6.4c Collapse Exposure Areas***

Exposure data in each cell (representing calendar year and exposure area) were summarized using the geometric mean of the samples. For the U.S. plants, there were a number of HEGs identified with minimal exposures. When the geometric mean over all

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

years was  $1 \mu\text{g}/\text{m}^3$  or lower, indicating consistently minimal exposure, homogenous exposure groups were collapsed into a single exposure area, designated as "low." Collapsing reduced the number of small or empty cells. Eleven of 17 homogenous exposure groups met this criterion and were collapsed into a single low exposure area at Corpus Christi. At the Castle Hayne plant, 17 homogenous exposure groups were collapsed into a single low exposure area. For each U.S. plant, a total of six exposure areas remained.

Because the geometric mean for all exposure areas at the German plants was greater than one  $\mu\text{g}/\text{L}$ , an arbitrarily selected cut point for collapsing data, no exposure areas at the German plants were combined into a single low exposure area.

#### *3.6.4d Stabilize Sparse Cells and Fill Empty Cells for Average Concentration JEM*

Even after collapsing exposure areas, sparse cells, containing only one or two samples, and empty cells, remained. We evaluated several methods to fill empty cells and stabilize sparse cells. These included pooling cells across time periods and exposure groups; interpolating from adjacent cells with larger numbers of observations; estimating exposure for unknown jobs or areas based on the ratio of exposures in similar jobs or exposure areas in another plant; weighting short-term personal monitoring samples, if available, by time to produce a full shift TWA; and using professional judgment to estimate exposure. Based on several factors, but mainly the availability of reasonable numbers of exposure measurements across most exposure areas and calendar periods, we

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

chose to fill gaps and stabilize exposure estimates by generating a running average algorithm.

A geometric mean for each cell in the matrix was calculated as follows. For the first year of each work area in the JEM, data were added to the data for the following year, and a geometric mean was computed based on the two years of data. For the second year and all subsequent years, data for each exposure area/year cell were added to the previous year and the successive year, and a geometric mean was computed based on three years of data, provided that the previous year and successive year contained a minimum of three exposure values. For exposure area /year cells with fewer than three exposure values, the algorithm found the nearest cell with at least three measurements and summed all data from these "anchor" cells (i.e., cells with at least three measurements) and all cells between to calculate a geometric mean for that exposure area/year. The rationale for calculating the three year moving average for each cell, and not, for example, cells with fewer than three values only, was based on the small sample size overall. That is, even cells with greater than three observations still had relatively few samples. This approach to imputation filled sparse or vacant cells, based on the nearest years' information, and effectively reduced the variability over time, as well as filled gaps and reduced the reliance upon small numbers of observations occurring in any exposure area/year cell. The proportion of imputed values ranged from fewer than 30% (one area in Leverkusen required no imputation) to about 45%, and tended to be greater for earlier years (except for the Castle Hayne plant, where no industrial hygiene measurements were recorded in 1993 and 1994) and for areas with lower average exposures.

*3.6.4e Stabilize Sparse Cells and Fill Empty Cells for Peak Levels JEM*

The peak levels JEM was used to calculate a peak exposure indicator score. We identified all samples that were greater than or equal to 40 µg/L chromium in urine (German samples) or greater than or equal to 50 µg/m<sup>3</sup> hexavalent chromium in air (U.S. plants). We considered these samples to be representative of peak exposures. These exposures equal, or exceed, the threshold limit value of 0.05 mg/m<sup>3</sup> for hexavalent chromium<sup>20</sup> and/or are roughly equivalent to a biological exposure index of 30 µg/g creatinine for urinary chromium. We summed all "peak" measurements that occurred within each cell (exposure area and year) and assigned a rank score based on the sum of peak measurements for any cell with three or more samples (Table 4). We assigned rank scores (2,3,4) based on cut-points that approximated the less than 50<sup>th</sup>, 50<sup>th</sup> to 90<sup>th</sup>, and greater than 90<sup>th</sup> percentiles of the distribution for the sum of peak values. Zeroes were assigned to all years where exposure was measured but no peak measurements were observed. Because we did not want to assume that peak exposures did not occur in years when exposure was not measured (or in work areas with no measures), we filled empty cells by calculating an average peak level based on the peak level assigned to the anchor cells (i.e., cells with three or more samples) and inclusive of peak levels for cells with one or two samples. Consequently, some peak level scores were represented by fractional numbers.

### 3.6.5 COMMENSURATION OF URINARY AND AIR DATA

Personal air data were very sparse for the German plants and urine samples were never taken at the U.S. plants. Because urine data were available over all years of the study for the Germans and personal air monitoring data were available only for more recent years, we elected to summarize the average air concentrations in U.S. plants in terms of urine concentration equivalents for use in the JEMs. We chose to convert air data to urine data because urine data were abundant relative to personal air data, and because urine data are presumably a better measure of dose. Dose represents the actual amount of toxin entering the body and reaching the target organ (lungs), whereas exposure reflects the amount of toxin present in the environment. This makes the urinary data appropriate for epidemiological assessment of the relationship between an indicator of dose and the occurrence of lung cancer.

After reviewing the published medical literature on urinalysis and air monitoring data, including alternatives for standardizing urinalyses using specific gravity or creatinine adjustments, we conducted extensive statistical analyses on the data available from the two Bayer facilities for the years where both air and urine samples were collected. The statistical analyses included crude comparisons of all urine samples and all air samples for years in which both existed (Table 5). In addition, ratios of urine measurements to personal air measurements were calculated by exposure area and year, but these ratios proved unstable due to very small numbers of personal air samples. Additional analyses compared air and urine samples for study subjects matching on same month and year

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

(n=25 for Leverkusen and n=0 for Uerdingen). A consistent relationship between air and urine did not emerge from these analyses.

Our search for an alternative to an empirically derived conversion factor resulted in an exposure equivalent for carcinogenic substances (EKA) published by the Deutsche Forschungsgemeinschaft.<sup>46</sup> This factor was used to convert air data for the U.S. plants to urinary equivalents (Table 6). Although the EKA is based on data from at least one of the German plants in the current study, we considered this conversion factor a reasonable alternative because it is the only one available in the literature that pertains to chronic exposure scenarios. This conversion factor (0.77) was slightly smaller than the overall ratio of urine data to air data that we calculated for each plant (0.92 for Uerdingen and 0.85 for Leverkusen). Ultimately we chose to use this published value rather than our own derived value(s) mainly because the agreement, or correlation between the air and urinary values in our data was very poor, and the estimates we derived were not very different from this published value. Clearly, much more work is needed to clarify the relationship between air and urinary measures of chromium. This relationship is, and will remain, an important issue, as the American Conference of Governmental Industrial Hygienists (ACGIH) in the United States recently published its intention to establish a biological exposure index (BEI) for urinary chromium.

### 3.6.6 ESTIMATION OF LEVEL OF EXPOSURE

Exposure estimates for each employee were calculated by linking individual job history information to the exposure summary measurement in the job exposure matrices. The

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

use of JEMs assumes that each employee working in a specific exposure area (based on HEGs) at any time during a given year was similarly exposed at the level estimated in the respective cell in the JEM. Due to limitations in the available exposure data, however, individual variability cannot validly be documented. Therefore, employees with the same employment history will by definition have the same estimated exposure, although it is likely that their actual exposure differed due to individual work practices, proximity to process emissions, and differences in uptake and metabolism. On the other hand, use of the JEM allows the estimation of individual exposure estimates based on the averages contained in the JEM, and provides a reasonable quantitative basis for contrasting risk across different employment histories. Quantitative exposure estimates were derived using cumulative concentration as well as cumulative peak exposure scores.

### 3.7 Vital Status and Cause of Death Ascertainment

#### 3.7.1 GERMAN PLANTS

Vital status was determined from medical and/or personnel records, or from the local population registry. In the United States, cause of death information, although confidential, is relatively easy to obtain for bona fide research purposes. In contrast, cause of death information is very difficult to obtain in Germany, and therefore available data from several sources must be pieced together. Data sources for determining cause of death among the German subcohort included death certificates provided to plants to determine whether cause of death was work-related; letters from community health departments to plant physicians indicating causes of death as listed on the death certificate; clinical reports from treating physicians and hospitals where the death

occurred; autopsy reports; clinical reports and letters from the treating physician, that included diagnosis and medical history and that were dated earlier than the date of death; and medical certificates, sometimes including histology and pathology results. Because of the difficulties in obtaining cause of death information in Germany, a specific cause of death could not be determined for 14 of the decedents.<sup>4</sup>

Cause of death information was obtained from death certificates when possible, or best available information when a death certificate was not available. Professional nosologists coded cause of death, regardless of the source or year of death, according to the ninth revision of the International Classification of Diseases (ICD-9).

### 3.7.2 U.S. PLANTS

Data sources from each company were used initially to determine vital status for as many cohort members as possible. These sources included lists of individuals known to have died since the previous studies, as well as rosters of cohort members (active or retired) known to be alive.

For the U.S. plants subcohort, searches of the National Death Index (NDI) and the Social Security Administration's (SSA) Vital Status Service database were also conducted to identify decedents. The latter search also provided the unique feature of identifying cohort members believed to be living, based on several SSA data sources. We obtained

---

<sup>4</sup> The investigators received additional cause of death data more than one year after the request to the German officials was filed, but after the study database was closed for statistical analysis.

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

cause of death information from the NDI-Plus for deaths that occurred between the establishment of the National Death Index in the United States in 1979 and the most recent year for which death data were available, 1998. We identified deaths prior to 1979 from plant records and from the Social Security database search, and obtained death certificates for these deaths directly from the state offices of vital statistics where the deaths occurred. Cause of death was coded according to the 9<sup>th</sup> revision of the International Classification of Diseases.

### 3.8 Statistical Analysis

#### 3.8.1 STANDARDIZED MORTALITY RATIO (SMR) ANALYSES

Person-years at risk began accruing one year after the date of first exposure to chromium. The earliest date for person-years to begin accruing was one year after the following process changeover dates: January 1, 1958 for Leverkusen; January 1, 1964 for Uerdingen; September 4, 1971 for Castle Hayne; and October 15, 1979 for Corpus Christi. Person-years were accrued for all cohort members until date of death or until the end of the study follow-up period, December 31, 1998. Person-years were censored as of the date last known to be alive for those who were lost to follow-up.

Standardized mortality ratio (SMR) analyses were performed for all categories of death combined and for all specific categories for which at least two deaths were observed or for which at least two deaths were expected. SMRs compare of the number of deaths actually observed in the cohort to the number of deaths expected in the cohort if mortality rates from some general "reference" population were applied. To derive the expected

number of deaths for any age-, sex-, and race-specific group, the appropriate reference rate is multiplied by the number of person-years at risk observed in the corresponding category for the cohort.

More detailed analyses were conducted incorporating a number of occupational variables, such as duration of employment, time since first exposure, cumulative exposure, and peak exposure indicator score. In addition, SMR analyses were conducted in which exposures were lagged in a time-dependent manner by 10 years and 20 years. Lagging of exposure is an analytic technique for which each person-year at risk is evaluated at the exposure level associated with some earlier time period, in this case 10 and 20 years earlier. In effect, this method is a latency analysis that discounts the most recent years of exposure prior to death on the basis that they are not relevant to development of the cancer of interest, which is likely already to have been initiated by the time of these exposures. Because different diseases have different minimum latency periods, this method is disease-specific. For lung cancer, one generally expects that a minimum of 10 or 20 years from initial exposure is necessary for the underlying cancer to manifest, though actual latency may be as long as 30 to 40 years.

### *3.8.1a Reference Rates*

Reference rates by specific cause of death for each country and state were obtained from public sources. We obtained mortality rates for 92 causes of death from the National Institute of Occupational Safety and Health (NIOSH) for the states of North Carolina and Texas. We obtained mortality counts by specific cause of death and population counts

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

for the entire German population and calculated mortality rates for 65 causes of death for all years between 1968 and 1998 inclusive. Though individual cause of death information and death certificates are difficult to obtain in Germany, group-level data such as cause-specific mortality rates are publicly available. We calculated mortality rates in 5-year age (15-19, 20-24, 25-29, etc.) and calendar intervals (1955-1959, 1960-1964, 1965-69, etc) to correspond as closely as possible with NIOSH mortality rates. In addition, we obtained mortality and population counts for lung cancer, all cancers and all causes combined for North Rhine-Westphalia for the years between 1979 and 1998 and calculated mortality rates as described above. Although we obtained other mortality counts for North Rhine-Westphalia, these counts were readily available for broader categories of death than the NIOSH categories and only for the years since 1979. In addition, the counts were available for 10-year age intervals only. For the entire German population, we used mortality rates for the years 1968 and 1969 combined for mortality rates for the earliest calendar intervals (1955-1959, 1960-1964, 1965-1969). For the North Rhine-Westphalia referent population, we used the mortality rates for 1980 to 1984 and applied them to all earlier five-year calendar intervals.

All mortality rates from Germany were based on the three-digit rubric of the international classification of diseases (ICD). Because some categories of death used in NIOSH rates were based on the four-digit rubric of the ICD, we constructed German categories that were as concordant as possible with the NIOSH categories; however, some small differences remain (see Appendix).

All SMR analyses were conducted using ProSMR (SoftWhere, Inc., Goshen, Massachusetts and Applied Epidemiology, Inc., Amherst, Massachusetts). ProSMR incorporates reference rate data from multiple locations simultaneously, weighting each person-year observed with the appropriate reference rate by location, gender, age, race and calendar year. The results obtained with regional reference rates were contrasted with those obtained with national reference rates to determine to what extent the observed results were sensitive to choice of reference rates. Regional rates often provide the best comparison, especially for causes of death with strong geographical variability.

### 3.8.2 MULTIVARIABLE ANALYSES

Multivariable regression analyses represent powerful statistical tools for examining complex relationships. Advantages of multivariable analyses include the possibility of examining the simultaneous contributions of multiple predictor variables to an outcome of interest. Unlike SMR analyses, multivariable analyses draw comparisons among subgroups of the study population, such as groups defined by category of cumulative exposure, without invoking a population-based referent. While these analytical techniques benefit from an efficiency of fitting mathematical models to the data, they are also sensitive to small sample sizes and especially small numbers of outcomes (i.e., lung cancer deaths).

With this analysis in mind, several logistic regression models were developed to evaluate lung cancer risk associated with chromium exposure. Logistic regression was used to derive estimates of relative risk (i.e., odds ratios) of intermediate and high levels of

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

exposure, relative to low exposure, adjusting for the potential effects of age and smoking.

The best available data on smoking for each cohort member were evaluated to determine

whether the cohort member ever smoked or never smoked. Analyses were also

conducted in which the last 10 years of exposure was truncated, as a means of

approximating analyses taking into account a ten-year latency. These analyses were

conducted using Stata.<sup>47</sup>

## RESULTS

### 4.1 Description of Cohort

The total study cohort numbered 1,518 employees, after excluding 173 short-term employees identified as having less than one year employment, and 993 employees identified as having worked previously in plants using high lime processes. An additional 166 were excluded from the Uerdingen subcohort because they had a history of employment in other plants with possible Cr(VI) exposure. Only three potential cohort members were excluded due to missing key data (date of birth or date of hire) (Table 7).

Several differences among the subcohorts were documented, and these differences tended to align according to country: the members of the two German subcohorts were different on several indicators from those of the two U.S. subcohorts. For example, although the overall cohort was predominantly male (94%), all German cohort members were men, and the percentage of female employees at the U.S. plants was 12% at Castle Hayne and 25% at Corpus Christi (Table 8). The German cohorts almost completely consisted of employees of German nationality; however, we could not completely verify the nationality of all cohort members in the Leverkusen subcohort. In the U.S. subcohorts, approximately 17% of Castle Hayne employees were black and approximately 37% of Corpus Christi workers were Hispanic.

The employees from the German subcohorts also were older than those from the U.S. subcohorts; approximately half of the cohort members of the German plants were born

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

before 1940. For the U.S. plants, 16% of the cohort members were born before 1940 at Castle Hayne and only 2% were born before 1940 at Corpus Christi (Table 8).

Overall, 57% of the cohort reported that they were current or former smokers, but the proportion of ever and never smokers varied by subcohort. Although the proportion of ever smokers was similar for Leverkusen, Uerdingen and Castle Hayne, the two German plants had the highest prevalence. Smoking status was not known for 9% of the cohort. The proportion of employees whose smoking status was unknown was highest at Corpus Christi (19%) (Table 8).

Although the German subcohorts were older on average than the U.S. subcohorts, the average duration of exposure was similar across all plants, ranging from about eight years at the Corpus Christi plant to 12 years at the Castle Hayne plant (Table 9). Average time since first exposure was only 10 years for Corpus Christi, but substantially longer for the other subcohorts: 16 years for Leverkusen, 19 years for Uerdingen, and 20 years for Castle Hayne. Age at first exposure was also greatest for the German plants, roughly 38 years old, versus 29 and 31 years old for the Castle Hayne and Corpus Christi subcohorts, respectively.

#### 4.2 Exposure Assessment

Plant-wide indicators of chromium exposure (indicated by geometric mean urinary values for the German plants and geometric mean air concentrations for the U.S. plants) varied substantially by location and time period. Although aggregate measures of exposure

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

depend on the proportion of samples included from different areas with high or low levels, they do provide a general basis for comparison. In general, exposures appeared to be higher in earlier years of operation, with general reductions over time. Exposures in the German plants were consistently higher than in the U.S. plants, where average exposures were extremely low (Figures 1 - 5).

Mean urinary chromium values decreased over the years of the study for Uerdingen (Figure 1) and Leverkusen (Figure 2). Thus, the urinary chromium values were highest in the earliest years of the study. Leverkusen experienced a spike in average urine values in 1968. Average urine values at the Uerdingen plant peaked in 1966.

Average personal air concentrations of hexavalent chromium remained well below 1.5  $\mu\text{g}/\text{m}^3$  for most years at both Corpus Christi (Figure 3) and Castle Hayne (Figure 4). Due to the introduction of a chromic acid compacting process that was later discontinued at Corpus Christi, average personal air concentrations of hexavalent chromium more than doubled in 1994 and 1995, compared to earlier years at the plant. There were several years during the 1980's when exposure data were not collected at the Corpus Christi plant. The highest personal air concentrations at the Castle Hayne plant were measured in 1990 and 1992. In contrast, average personal air concentrations were higher at Leverkusen and Uerdingen for most years (Figure 5).

At Uerdingen, the three exposure groups with the highest average urine values over all years were Saturation (Figure 6), ADC/KDC production (Figure 7) and Shipping (Figure

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

8). The exposure group with the lowest average urine values over all years was Electricians (Figure 9).

Employees assigned to Kiln I (Figure 10) at Leverkusen produced the highest urine values, followed by Maintenance Workers & Foremen (Figure 11) and Sulfate Separation and Drying (Figure 12). Very high urinalysis results recorded among Kiln 1 employees and Maintenance Workers and Foremen in 1968 probably influenced the spike seen in the plant wide mean value that year. The lowest exposure group was Lab Technicians (Figure 13), although urine samples were not collected during the 1960's and early 1970's and were based on sample sizes of fewer than 3 for 1959-1961 and 1974.

The work areas with the highest average personal air sampling values at Corpus Christi (Figures 14 to 16) and Castle Hayne (Figures 18 to 20) were generally below  $10 \mu\text{g}/\text{m}^3$  for most years. Some areas did report higher air concentrations, most notably Shipping (Figure 14) at Corpus Christi during 1994 and 1995, when exposures were high plant wide. Data for the DCS Kiln work area (Figure 15) at Corpus Christi are available since 1987, when the DCS Kiln was commissioned. The combined low exposure areas were below  $1 \mu\text{g}/\text{m}^3$  over all years at Corpus Christi (Figure 17) and most years at Castle Hayne (Figure 21).

### 4.3 Mortality Analysis

Vital status was successfully determined for 98% of the total cohort (Table 10). Follow-up was most complete for Corpus Christi, Castle Hayne and Uerdingen. Vital status

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

could not be determined for approximately 5% of the Leverkusen subcohort. Through December 31, 1998, the cohort accrued 24,589 person-years, during which a total of 157 deaths (10% of the cohort) were identified. Specific cause of death could not be determined for 14 decedents (9% of all deaths), all German employees. As expected due to the older average age, a higher percentage of employees of the German plants were deceased (12% for Uerdingen and 16% for Leverkusen, respectively) than at the American plants (5% for Castle Hayne and 3% for Corpus Christi).

Mortality from all causes combined was 6% lower than the referent populations (Texas and North Carolina mortality rates for the Corpus Christi and Castle Hayne subcohorts, respectively, and German mortality rates for Uerdingen and Leverkusen) (Table 11). Mortality from all heart disease was 20% lower than the referent population, and ischemic heart disease mortality exhibited a considerable deficit of 37% (SMR=0.63; 95% CI: 0.40-0.95). Mortality from cerebrovascular disease was similar to that experienced by state and German populations.

Mortality from all cancers combined showed a slight excess of 15% (Table 11). However, this increase was mainly due to an excess of mortality from trachea, bronchus and lung cancer (SMR=1.66; 95% CI: 1.08-2.46), based on 25 deaths (15 expected).

SMRs for all causes combined, all cancers, all respiratory cancers as well as trachea, lung and bronchus cancers specifically were also computed using North Rhine-Westphalia mortality rates for the German subcohorts (Table 12). Mortality from all causes

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

combined was 12% lower for the cohort (SMR=0.88). Mortality from all cancers was 5% higher (SMR=1.05) and lung cancer mortality was 37% higher (SMR=1.37). These differences in the SMRs using state rates suggest that mortality rates for lung cancer are higher in North Rhine-Westphalia than in Germany as a whole. Because we were primarily interested in whether cohort members experienced greater risks of lung cancers than in the general population, regardless of regional variability in background risk, we used North Rhine-Westphalia, Texas and North Carolina rates in all subsequent stratified SMR analyses.

As qualitative indicators of exposure, duration of exposure (defined as time employed in a job with potential for exposure), time since first exposure and age at first exposure were evaluated separately as predictors of lung cancer mortality. Although SMRs for lung cancer were lowest among the group with the shortest duration of exposure and highest among the group with longest duration of exposure, there was no consistent trend: the SMRs were 0.77, 1.91, 1.18 and 2.38, respectively (Table 13). Mortality from lung cancer showed no pattern with time since first exposure: the excess was greatest among those with 1 to 9 years since first exposure (SMR=1.72) and those with 20 to 29 years since first exposure (SMR=1.60). Similarly, no clear trend with age at first exposure could be discerned; however, most observed and expected cases occurred in the stratum of those 35 years or older at first exposure, and results were imprecise due to the loss of statistical precision associated with very small numbers in each stratum.

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

The SMR analyses stratified by levels of the quantitative exposure measures generated slightly more precise estimates. A two-fold increase in lung cancer mortality was seen for employees with a cumulative exposure of 200  $\mu\text{g/L}$ -years Cr(VI) or more (SMR=2.09; 95% CI: 1.08-3.65), based on 12 observed and 5.7 expected (Table 14). For exposures less than 200  $\mu\text{g/L}$ -years Cr(VI), however, there was no apparent increase in risk for any specific category or combined categories (total of 13 observed and 12.5 expected).

The analysis of peak exposure score showed an increase in SMRs for the two highest categories of peak exposure score: the SMRs were 1.59 (95% CI: 0.84-2.71) for scores of 5 to 23.9 and SMR =1.97 (95% CI: 0.94-3.62) for scores of 24 or more (Table 14). Only one observed death was included in the two lowest peak exposure categories, when about 3.8 were expected. This suggests that those employed in work areas unlikely to experience peak exposures were not at any increased risk of lung cancer.

A second analysis of peak exposure scores demonstrated an increased risk for the category with the highest score (SMR=1.84; 95% CI: 1.12-2.84) and no increases among categories with lower scores. The two lowest categories again had only one observed lung cancer death with only 2.4 expected under this classification scheme. For the three lowest peak score categories, however, four lung cancer deaths were observed with 6.4 expected.

A lagged analysis of cumulative exposure showed that the lung cancer SMR did not increase when exposure was lagged 10 years, but rose to 2.74 (95% CI: 0.75-7.03) in the highest exposure group when exposure was lagged 20 years (Table 15). On the other hand, with increasing category of latency, the number of observed deaths decreased from 12, with no lagging of exposures, to 8 to 4, respectively. Results were similar across lag intervals, as indicated by point estimates that fell within the 95% confidence intervals. The imprecise estimates for the higher exposure categories, as indicated by wider confidence intervals, demonstrates that very few study subjects had opportunity to accrue exposure for 20 years or more before the end of the study. Other categories of cumulative exposure were similar regardless of lagging period.

The lagged analysis of peak exposure score showed increasing SMRs for lung cancer mortality for those with peak scores of 5 to 23.9, and the greatest excess was seen with the 20-years lag (SMR=2.09; 95% CI: 0.84-4.30) (Table 15). For the highest peak exposure score category, SMRs increased slightly when exposure was lagged by 10 years, but fell off due to a lack of observed and expected deaths (1 and 0.8, respectively) when exposure was lagged by 20 years.

#### 4.5 Logistic Regression Analysis

Because there were no lung cancer deaths among women, we did not include gender in any logistic regression analyses. A preliminary evaluation of the combined relationship of cumulative chromium exposure and peak exposure score was restricted to 1472 cohort members for whom a peak exposure indicator score could be assigned. Among this

of 24 lung cancer deaths occurred. Cumulative exposure and peak exposure indicator score were highly correlated (Table 16 and Figure 22) and low values for both measures predominated. Cumulative exposure and peak exposure showed a similar relation among the lung cancer deaths (Figure 22), although the deaths are not concentrated among the low exposure levels. We combined the two measures into a primary exposure measure as follows: low exposure, if peak exposure indicator score is less than 1 and cumulative exposure less than 40  $\mu\text{g/L-years}$ ; intermediate exposure, if peak exposure indicator score is at least 1 and less than 24 and cumulative exposure is at least 40 and less than 200  $\mu\text{g/L-years}$ ; and high exposure, if peak exposure indicator score is 24 or greater and cumulative exposure is 200  $\mu\text{g/L-years}$  or greater.

In the analysis, the high exposure group experienced increased odds of lung cancer death relative to the low exposure group (OR=42.5; 95% CI: 5.4 - 337.1). The wide confidence interval reflects the imprecision due to the small numbers of events (1, 13, and 10 in the low, intermediate and high exposure groups, respectively). Due to one lung cancer death in the referent group (the lowest summary exposure category), results of the additional analyses are too imprecise and therefore are not presented.

Instead, we conducted logistic regression analyses based on cumulative exposure alone: low exposure, if cumulative exposure less than 40  $\mu\text{g/L-years}$ ; intermediate exposure, if cumulative exposure is at least 40 and less than 200  $\mu\text{g/L-years}$ ; and high exposure, if cumulative exposure is 200  $\mu\text{g/L-years}$  or greater. In the crude analysis, the intermediate and the high exposure group had increased odds of lung cancer death relative to the low exposure

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

group (OR=4.9; 95% CI: 1.5 - 16.0 and OR=20.2; 95% CI: 6.2 - 65.4, respectively) (Table 17). Because there were no deaths among those first exposed before 25 years and only one death among those first exposed between 25 and 34 years, further age-related analysis was possible for only those 35 years or older at the time of first exposure (OR=10.2; 95% CI: 2.7 - 37.7 for high exposure relative to low exposure).

Among smokers, the risk of lung cancer death was elevated among the intermediate and high exposure groups relative to low exposure (OR=5.3; 95% CI: 1.4 - 19.7 and OR=18.7; 95% CI: 5.0 - 70.6). Although odds ratios for the high exposure group were both attenuated among the oldest age group and smokers, they remained substantially greater than one, suggesting a possible independent role of high chromium exposure on lung cancer death.

Because recent chromium exposure may not be biologically relevant to the development of lung cancer, we conducted an analysis that truncated cumulative exposure 10 years prior to the end of follow-up for each cohort member. The crude odds ratios showed increased odds of lung cancer death among the intermediate exposure group (OR=7.0; 95% CI: 2.1 - 22.9) and the high exposure group (OR=16.1; 95% CI: 4.6 - 55.8), relative to the low exposure group (Table 17). Among smokers, intermediate cumulative exposure and high cumulative exposure were each associated with increased risk of lung cancer death (OR=7.0; 95% CI: 1.8 - 26.8 and OR=16.9; 95% CI: 4.3 - 66.9, respectively) relative to the low exposure group. Risk was increased for the oldest category of age at

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

first exposure for the intermediate exposure group (OR=4.1, 95% CI: 1.1 – 15.5) and for the high exposure group (OR=9.5; 95% CI: 2.4 – 37.6).

A logistic regression model was fitted for 1,378 cohort members who had complete data on smoking (Table 18). Controlling for age 35 years or older at first exposure and ever smoker, the odds of lung cancer death were considerably elevated among the high exposure group relative to low exposure group (OR=8.0; 95% CI: 2.4 – 27.1).

A second logistic regression model was fitted for cumulative exposure among 1,273 cohort members who were first exposed at least 10 years before the end of follow-up. Intermediate and high cumulative exposure, adjusted for 35 years or older age at first exposure and smoking, were each associated with an increased risk of lung cancer (OR=3.4; 95% CI: 1.0 – 11.6 and OR=7.7; 95% CI: 2.1 – 27.6, respectively).

We also performed a hierarchical analysis to investigate the possibility of an independent risk associated with a peak exposure. For this analysis, we restricted the cohort to the German population for the following reasons: 1) 22 of the 25 lung cancer deaths occurred among the German population; 2) cumulative exposures were highest at the German plants (Figure 23); and 3) unique to the German population, individual urinary data were available to assess the occurrence of a peak exposure. For this analysis, a chromium-in-urine sample of  $\geq 40$   $\mu\text{g/L}$  (arbitrarily selected) indicated an occurrence of a peak exposure. Peak exposure was then parameterized as a dichotomous variable: ever

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

peak exposure versus never peak exposure, with 264 subjects with at least one urinalysis result suggesting a peak exposure.

In the crude analysis, a model that included occurrence of one or more peak exposures in addition to cumulative exposure did not indicate an additional risk of death beyond the model that fit cumulative exposure alone (OR=7.6; 95% CI: 2.9 – 19.7). Rather, the risk attributed to cumulative exposure was reduced and attributed to the peak exposure term (peak exposure OR=2.2; 95% CI: 0.7 – 7.6, cumulative exposure OR= 4.9; 95% CI: 1.6 – 15.0), suggesting that these measures are highly correlated. In the analysis controlling for smoking history (ever), the result was similar. As stated previously, controlling for age at first exposure was not possible because all lung cancer deaths occurred among those 35 years or older at first exposure. The models presented in Table 19 show that high cumulative exposure is associated with increased risk of lung cancer death among the German subcohorts and the risk is unchanged after controlling for smoking (OR=6.7; 95% CI: 2.5 – 17.9).

## DISCUSSION

Few studies have been conducted on employees who have worked in the manufacture of chromium chemicals using low-lime or no-lime processes and with enhanced industrial hygiene controls. This study updated vital status through December 31, 1998 for 1,518 employees who worked for at least one year at one of four chromium chemical manufacturing facilities located in Germany and the United States. The study cohort is restricted to employees who have no prior experience working in a high lime process; three of the facilities had converted from a high-lime to a no-lime process and one was built to use the low-lime process. This restriction resulted in greatly reduced numbers, increasing the need to aggregate employees from several facilities to achieve adequate statistical power to address the main research questions. All four plants had been studied previously, but each of these studies included employees exposed to high lime processes, and each were limited by an inadequate follow-up period that did not allow for a sufficiently long latency interval for lung cancer. Although the follow-up for the current study is substantially longer and has adequate latency to detect work-related cancers, the risk period may continue beyond the study period. For this study, mean time since first exposure was less than 20 years, and the average latency for lung cancer may be greater than 20 years.<sup>48</sup>

Cause of death was determined for 143 cohort members (91% of the decedents) who died since January 1, 1958 (Leverkusen), January 1, 1964 (Uerdingen), January 1, 1971 (Castle Hayne) or October 1, 1980 (Corpus Christi). In the United States, cause of death

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

information is readily available for legitimate research purposes, and officially coded cause of death information is available electronically from the National Center for Health Statistics, National Death Index (NDI) on all deaths beginning in 1979. Because of the NDI and other national search tools available for tracking study cohort members, vital status of all but one individual was ascertained, and for all identified decedents cause of death could be determined. In contrast, cause of death information is difficult to obtain in Germany due to laws severely restricting access to death certificates, and the routine destruction of official death certificates after 10 years of the death. These restrictions partially explain why we were unable to determine cause for several German deaths. For most of the deaths, reliable alternative sources of cause of death information had to be used, mainly letters provided by employees' primary physicians to occupational physicians at the plants. These letters were generally requested and supplied to document whether or not the causes of death were work-related, and consequently whether or not decedents' families were entitled to compensation. This system of documenting cause of death is remarkably complete, probably because next-of-kin are motivated to release death certificates because of the potential compensation. Relative to usual reporting of cause of death on death certificates, this information is likely to be more detailed and possibly more accurate.

Overall, mortality patterns for chromium chemical workers in Germany and the United States were similar to mortality patterns seen in their respective general populations. Slight deficits in mortality for all causes combined and all heart disease suggest that a healthy worker effect may exist. The healthy worker effect is a type of selection bias

frequently seen in occupational mortality studies when mortality for a healthy working population compares favorably to the general population that includes people who are unable to remain employed due to ill health.

Despite the slightly favorable overall mortality and mortality from heart diseases, mortality from lung cancer was increased. Given this modest excess of lung cancer, the data were explored further to determine whether and to what extent the excess might be related to chromium exposure. The general approach used to assess exposure-relatedness was to estimate SMRs stratified by various exposure indicators, including two quantitative metrics: cumulative urinary concentrations and cumulative peak exposure scores. The quantitative exposure indicators were also assessed further using multivariable analyses that took into account other important risk factors for lung cancer such as smoking and age.

### 5.1 Exposure Assessment

Because exposure to hexavalent chromium is not uniform across time and production areas, a detailed exposure assessment was undertaken. This assessment allowed derivation of individual-specific estimates of exposure that in turn were assessed as correlates or predictors of lung cancer risk.

In general, exposure levels appeared higher at the German plants than the U.S. plants, and tended to decrease over time. These measurements were not comparable directly, however, because exposure levels for the German plants were reported using urinary

chromium levels while exposure levels at the U.S. plants were reported using air concentrations of hexavalent chromium from personal air sampling measurements. Biomonitoring has not been conducted at the U.S. plants. A comparison of personal air monitoring data for the four plants since 1986 (when personal air sampling was first conducted at the German plants) showed higher plant-wide average exposure levels for the German plants (Figure 5), except for the years 1994 and 1995 when exposure levels spiked at the Corpus Christi plants due to a new process for compacting chromic acid. These high exposures proved difficult to control and this process was subsequently discontinued. Exposures received during these more recent years, however, were unlikely to impact mortality results through 1998.

Urinary chromium measurements have some limitations as well. Due to the reduction of Cr(VI) in the blood and other tissues, urinary chromium is detected as Cr(III).<sup>6,49</sup> Therefore, increased urinary levels of chromium may reflect increased exposure to Cr(VI) or to Cr(III). Chromium (III) is an essential nutrient required for metabolism of carbohydrates and lipids. Beer consumption increases urinary chromium levels.<sup>50</sup> In addition, smokers may excrete higher concentrations of urinary chromium,<sup>14,41</sup> due to either enhanced retention of particulates in the lung and bronchus or stimulation of Cr(VI) reduction, leading to a subsequent increase in urinary chromium.<sup>14</sup>

## 5.2 Lung Cancer Mortality

Despite the complexities of estimating individual exposure to hexavalent chromium, we identified an increase in lung cancer mortality among those with the highest cumulative

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

exposure. Figure 24 is a graphical presentation of the 25 lung cancer cases, showing the date of hire (and presumably earliest exposure), date of separation (end of exposure) and date of death for each, according to cumulative exposure level. For 11 of the 12 lung cancer decedents with cumulative exposure of 200  $\mu\text{g/L}$ -years or more, at least 15 years had passed between first exposure and death, and for more than half there was at least 20 years latency. Though no firm conclusion may be drawn from these data, it does suggest that these cases plausibly may be work-related. The SMR was 2.09 (95% CI: 1.08 – 3.65) for cohort members with cumulative urinary chromium concentrations of 200  $\mu\text{g/L}$ -years or more, based on 12 deaths. For cumulative concentrations less than 200  $\mu\text{g/L}$ -years, however, there was no excess mortality from lung cancer. Figure 23 shows for the 13 lung cancer deaths with lower cumulative exposure, seven occurred within 15 years of first exposure, suggesting that the relationship with work exposures is less plausible. Regardless of the method used to characterize hexavalent exposure, similar results were obtained, with slightly stronger and more precise estimates derived when using the quantitative exposure indicators, and when taking some latent period into account.

Because there were 13 lung cancer deaths in the highest cumulative exposure category of  $\geq 200$   $\mu\text{g/L}$ -years, it was possible to further subdivide this category into 200 – 299.9 and  $\geq 300$   $\mu\text{g/L}$ -years, to see whether the excess risk tended to be evenly distributed across exposure estimates or more associated with the highest cumulative exposures (which ranged up to more than 500  $\mu\text{g/L}$ -years). The two resulting SMR estimates were 1.85 (95% CI: 0.68 – 4.04) and 2.39 (95% CI: 0.87 – 5.20), but because of the smaller number of expected deaths in each stratum, the precision of these estimates was poorer.

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

The SMRs were elevated for cohort members who had worked from five to nine, 10 to 19, and 20 years or more, but there was no clear pattern of increasing mortality with increasing duration of employment. Twenty-three of the 25 lung cancer deaths occurred among those who were 35 years or older at hire. This result largely reflects the older age at first exposure (mean approximately 38 years) in the German plants compared to average age at first exposure of 29 years for Corpus Christi and 31 years for Castle Hayne. Very few cohort members were exposed to chromium at ages less than 25 years old as indicated by the very small number of expected deaths (0.13) for this age group. In contrast to the U.S. plants, which produced chromium chemicals only, production at the Leverkusen and Uerdingen plants was not limited to chromium. Many other chemicals were produced at these facilities and employees at the chromium plant often worked elsewhere at the plant first. In fact, policy at the German plants required that, to minimize risks associated to chromium exposures, only men over 35 years could be assigned to the chromium plant. Because the age at first exposure to chromium was higher among the Germans, we examined plant work and medical history records of the lung cancer decedents to determine if prior exposure to other known lung carcinogens, most notably asbestos, was likely among the German employees. We found no evidence of occupational exposure to other agents known to cause lung cancer.

Lung cancer mortality was increased for peak exposure scores of five or higher: the SMR was 1.59 based on 13 deaths for scores of five to 23.9 and the SMR was 1.97 based on 10 deaths for scores equal to or exceeding 24. Among the lung cancer decedents,

however, cumulative exposure and peak exposure indicator score were correlated. Of the 12 lung cancer deaths that occurred among those with cumulative urinary chromium values of  $200 \mu\text{g}/\text{m}^3$  or more, 10 occurred among those with a peak exposure score of 24 or more. Consequently, teasing apart effects due to cumulative exposure versus effects due to peak exposure was difficult. In an attempt to separate these, we generated logistic regression models that incorporated terms for both cumulative and peak exposure. From these results, it was clear that both parameters are likely to contribute to risk. However, due to small total numbers of lung cancer deaths, and the correlation between cumulative and peak exposures, the relative contribution of each to the risk of lung cancer cannot be validly determined. The logistic regression analyses, taking smoking into account, suggested that smoking was not strongly confounding the modeled exposure-lung cancer relationship.

Our SMR results may suggest a threshold effect for chromium (VI)-induced lung carcinogenesis; however, the lack of a clear increased risk at lower exposure categories may be due to lower statistical power in these categories, indicated by the wide confidence intervals. De Flora<sup>14</sup> reported that Cr(VI) is reduced to Cr(III) in the epithelial-lining fluids, pulmonary alveolar macrophages, bronchial tree and peripheral lung parenchyma cells of the respiratory tract. Chromium (VI) exposure levels must be high enough to overwhelm the body's defense mechanisms which may lead to the development of lung cancer. This theory suggests that a necessary threshold level must be reached before the reduction-activation and/or reduction-detoxification mechanisms are overwhelmed. A study of Cr(VI) exposures that occurred at a Painesville, OH

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

chromate production plant that used a high-lime process reported increased mortality among employees exposed to Cr(VI) at levels of approximately  $1 \text{ mg/m}^3$ -years or higher (SMR=3.65, 95% CI: 2.08 - 5.92) for Cr(VI)  $\geq 1.05$  to  $< 2.70 \text{ mg/m}^3$  and (SMR=4.63, 95% CI: 2.83 - 7.16) for Cr(VI)  $\geq 2.70$  to  $< 27.80 \text{ mg/m}^3$ -years.<sup>24</sup> Lung cancer mortality for the three lowest exposure categories (all less than  $1 \text{ mg/m}^3$ -years) showed no meaningful excess.

Our logistic regression results also showed the greatest relative risk for the high exposure category; however, risk among the intermediate exposure group was slightly elevated, when controlling for age and smoking status. When lagging exposure, the intermediate exposure group had a relative risk estimate roughly half that of the high exposure group, indicating a more linear relationship. Unfortunately, the different logistic models are not adequately stable to suggest a dose-response relationship. Furthermore, the exposure categories in the logistic regression are not defined in a time-dependent fashion, as in the SMR results. Although the available number of lung cancer cases may not be adequate to generate stable results, risk associated with time-dependent exposure measures can be evaluated using a Cox proportional hazards analysis. Such results in theory would be directly comparable to the SMR results.

In a recently released study of a high-lime chromate production facility, Gibb et al.<sup>23</sup> reported a two-fold excess of lung cancer mortality (SMR=1.80; 95% CI: 1.49 - 2.14) among employees of two Baltimore, MD facilities. The first plant opened in 1950 and the second in 1960, and both were designed to improve process techniques and

#### MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

environmental control of exposure to chromium bearing dusts. The SMRs were moderately elevated for the two highest exposure levels: SMR=1.57 (95% CI: 1.07 — 2.20) for exposures of 0.009 to 0.0769  $\text{CrO}_3/\text{m}^3\text{-yrs}$ , and SMR=2.24 (95% CI: 1.60 — 3.03) for exposures of 0.077 to 5.25  $\text{CrO}_3/\text{m}^3\text{-yrs}$ . These exposure levels correspond to Cr(VI) levels of approximately 5 to 40  $\mu\text{g}/\text{m}^3$  and 40 to over 2700  $\mu\text{g}/\text{m}^3$ , respectively. The two lower exposure levels showed no important increased risk of lung cancer, again suggesting a possible threshold.

Although our study did not find any excess of lung cancer among those with less than 200  $\mu\text{g}/\text{L}\text{-years}$  —urinary chromium in the SMR analyses, substantial differences in risk by quantitative exposure level can be expected across studies, or within studies under different exposure assessment approaches. Because none of the recent studies presenting risk estimates by quantitative exposure categories had actual individual exposure measures, exposure was estimated based on job exposure matrices (JEMs). In the Luippold study, the JEM assimilated industrial hygiene data from 20 plant wide surveys describing over 800 airborne concentrations of speciated Cr(VI); for most years of the study period no industrial hygiene measurements were available.<sup>24</sup> In the Gibb study, the JEM was based on approximately 70,000 area and personal air samples of hexavalent chromium over the entire study period, however a large proportion of the employees had very short duration of employment.<sup>23</sup> Given the numerous assumptions necessary to construct individual exposure estimates, all of which are ultimately ecological averages (i.e., based on aggregate data from groups of individuals); differences in risk would be

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

expected even if the underlying relationship between exposure and lung cancer risk were identical in each study.

### 5.3 Strengths of this Study

This study benefited from the multi-site design that provided a reasonably large cohort of post-change chromium chemical workers, along with the corresponding increase in statistical power generally lacking in previous studies of post-change cohorts. Another strength was the additional years of follow-up. Over 40% of this post-change cohort was followed for at least 20 years, sufficiently allowing for the typical latency period for lung cancer. Long-term follow-up varied among the individual plants: 60%, 42%, and 38% of Castle Hayne, Uerdingen, and Leverkusen employees, respectively, had 20 or more years of follow-up. Because the changeover did not occur at the Corpus Christi plant until 1980, the maximum follow-up possible for these employees was 18 years. Also, because the average latency for lung cancer may be longer than 20 years, and for some individuals as long as 40 years, the future mortality experience of this cohort could shed additional light on the actual risks associated with post-change chromium exposures.

Although not comprehensive, and certainly not standardized across facilities and over time, substantial industrial hygiene data were available to derive quantitative exposure estimates. Relatively large numbers of samples were taken at each facility in nearly all study years, and for most work areas. At a minimum, these data made possible identification at an individual level for each year of employment, whether an employee was likely to have worked in an area of substantial potential exposure. To a lesser extent,

the data could identify areas in which peak exposures were more likely to occur. Therefore, despite the limitations, the exposure data incorporated into our analysis of lung cancer risk may be among the best available today for risk estimation and risk assessment purposes.

Other strengths of the study include a number of methodological attributes, especially the simultaneous use of multiple referent groups in the SMR analyses, where each person-year observed is weighted by the appropriate age- gender- and geographical location-specific reference rate to obtain the most valid expected numbers. Additionally, the time-dependent evaluation of exposure indicators is important, but rarely used even in recent occupational mortality studies. Finally, we were able to obtain and incorporate basic smoking information as a potential confounding variable, on a large majority of the cohort. Gibb et al <sup>23</sup> also controlled for smoking status in their analysis, and similar to our results, found that smoking was not a strong confounder. Therefore, the absence of smoking history for some workers probably did not affect the results or interpretation of this study.

#### 5.4 Limitations of this Study

Personal air monitoring data were not available for the Castle Hayne plant for the first three years of operation (1971-1973), nor for 1993 and 1994, and were sparse after 1996. Similarly, personal air monitoring data were not available for the Corpus Christi plant for the years 1983 to 1985 and 1989. Nevertheless, anecdotal reports from the first study of the Castle Hayne plant<sup>39</sup> indicated that exposures during those early years might have

## MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

been high relative to later years due to many engineering problems encountered in bringing the plant into operation.

We are reasonably certain that employees at the U.S. plants were not exposed to other known lung carcinogens while working at the plants. In addition to chromium products, however, the German plants produced other chemicals. Because German employees were rotated through various production areas, employees may have sustained exposure to other lung carcinogens. We examined medical and work history records for the lung cancer decedents at the German plants to evaluate whether exposures incurred before or after assignment to the chromium plants included any known lung carcinogens, such as asbestos, cadmium, nickel, and coke oven fumes.<sup>51</sup> There was no apparent evidence of such exposures, although the possibility cannot be completely ruled out.

### 5.5 Future Research Direction

The data obtained to conduct this exposure assessment and mortality analysis represent a valuable resource not easily obtained elsewhere. Once a cohort is defined and all exposure data obtained and structured, updating of cohort mortality becomes straightforward. Beyond continued mortality surveillance, however, this database could provide many more clues regarding the relationships between chromium air concentration and chromium urinary concentration, and between air and blood, and urine and blood concentrations. These issues are becoming increasingly relevant as biological exposure indices have been proposed, and relevant to the interests of proper employee exposure surveillance.

More directly related to the results presented herein, additional analyses of the data may help to elucidate the possibility of a threshold for Cr(VI) induced lung cancer risk. Future data may be especially useful in estimating a threshold as the number of available lung cancer deaths increases over time (inevitable with increasing age of the cohort). However, further work is needed in defining peak exposures and evaluating their contribution to lung cancer risk, either alone or in combination with other exposure indicators. As the toxicology and pathology of chromium-induced cancers is better understood, these epidemiological data may prove helpful in supporting or refuting various hypotheses.

## 5.6 Conclusions

Lung cancer risk among the study population was moderately elevated, mainly due to an elevation among those in the highest categories of cumulative and peak chromium exposure indicators. Based on SMR analyses, no excess of lung cancer deaths is detected among cohort members with less than of 200  $\mu\text{g/L}$ -years cumulative urinary exposure. While logistic regression results also suggested a substantial risk associated with the highest exposure category, controlling for age and smoking status, a modest elevation in risk was seen for the intermediate exposure category. Additional analyses will be needed to clarify whether the difference was related to the non-time dependent exposure assessment used in the logistic regression. The logistic regression analyses additionally demonstrated that smoking was associated with a six-fold risk of lung cancer, but did not materially confound the independent association between chromium exposure and lung

**MULTI-PLANT CHROMATE COHORT MORTALITY STUDY**

cancer. Whether exposure to hexavalent chromium is characterized as cumulative, peak, or some combination of these indicators, risk was substantially elevated in the highest categories. However, due to the strong correlation between cumulative and peak exposure estimates on an individual level, the relative contribution of each cannot be determined.

## REFERENCES

1. U.S. Environmental Protection Agency. Toxicological review of hexavalent chromium. Washington, DC: U.S. Environmental Protection Agency; Integrated Risk Information System (IRIS), 1998;1-70.
2. Mancuso T. Consideration of Chromium as an Industrial Carcinogen. International Conference on Heavy Metals in the Environment. Toronto, Ontario, Canada, 1975;343-356.
3. Bourne HG, Yee HT. Occupational cancer in a chromate plant - an environmental appraisal. *Industrial Medicine and Surgery* 1950;19(12):563-567.
4. Mundt KA, Dell LD. Carcinogenicity of trivalent and hexavalent chromium. *The Occupational and Environmental Medicine Report* 1997;11(11):95-100.
5. Proctor DM, Panko JM, Finley BL, Butler WJ, Barnhart RJ. Need for improved science in standard setting for hexavalent chromium. *Regul Toxicol Pharmacol* 1999;29(2 Pt 1):99-101.
6. International Agency for Research on Cancer (IARC). Chromium, Nickel and Welding. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 49. Lyon, France: IARC, 1990.
7. Sawyer HJ. Chromium and its compounds. In: Zenz C, ed. *Occupational Medicine*. "3rd" ed. St. Louis: Mosby-Year Book, Inc., 1994;487-495.
8. Geller RJ. Chromium. In: Sullivan JB, Krieger GR, eds. *Clinical Environmental Health and Toxic Exposures*. "2nd" ed. Philadelphia: Lippincott Williams & Wilkins, 2001;926-930.
9. Hayes RB. The carcinogenicity of metals in humans. *Cancer Causes Control* 1997;8(3):371-385.
10. Langard S. One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. *Am J Ind Med* 1990;17(2):189-215.
11. Cohen MD, Costa M, eds. Chromium. *Environmental Toxicants: Human Exposures and Their Health Effects*. 2nd ed. New York, NY: John Wiley & Sons, Inc., 2000.
12. Mancuso TF. Chromium as an industrial carcinogen: Part I. *Am J Ind Med* 1997;31(2):129-139.
13. Cohen MD, Costa M. Chromium compounds. In: Rom WN, ed. *Environmental & Occupational Medicine*. "3rd" ed. Philadelphia: Lippincott-Raven, 1998;1045-1055.
14. De Flora S. Threshold mechanisms and site specificity in chromium(VI) carcinogenesis. *Carcinogenesis* 2000;21(4):533-41.
15. Costa M. Toxicity and carcinogenicity of Cr(VI) in animal models and humans. *Crit Rev Toxicol* 1997;27(5):431-442.
16. Jones RE. Hexavalent chrome: threshold concept for carcinogenicity. *Biomed Environ Sci* 1990;3(1):20-34.
17. Wetterhahn KE, Hamilton JW. Molecular basis of hexavalent chromium carcinogenicity: effect on gene expression. *Sci Total Environ* 1989;86(1-2):113-129.

18. Miksche LW, Lewalter J. Biological monitoring of exposure to hexavalent chromium in isolated erythrocytes. In: Mendelsohn ML, Peeters JP, Normandy MJ, eds. *Biomarkers and occupational health: Progress and perspectives*. Washington, D.C.: Joseph Henry Press, 1995:313-323.
19. Lauwerys R, Hoet P. *Chromium. Industrial Chemical Exposure: Guidelines for Biological Monitoring*. "3rd" ed. Boca Raton: Lewis Publishers, 2001:77-87.
20. American Conference of Government Industrial Hygienists (ACGIH). *2002 TLVs and BEIs: Threshold Limit Values for Chemical Substances and Physical Agents*. Cincinnati, OH: ACGIH, 2002.
21. Davies JM, Easton DF, Bidstrup PL. Mortality from respiratory cancer and other causes in United Kingdom chromate production workers. *Br J Ind Med* 1991;48(5):299-313.
22. Korallus U, Ulm K, Steinmann-Steiner-Haldenstaett W. Bronchial carcinoma mortality in the German chromate-producing industry: the effects of process modification. *Int Arch Occup Environ Health* 1993;65(3):171-178.
23. Gibb HJ, Lees PS, Pinsky PF, Rooney BC. Lung cancer among workers in chromium chemical production. *Am J Ind Med* 2000;38(2):115-26.
24. Luippold R, Austin R, Mundt K, Liebig E, Panko J, Crump C, Crump K, Proctor D. *Lung Cancer Mortality Among Chromate Production Workers*. Occupational and Environmental Medicine (in press).
25. Newman D. A case of adeno-carcinoma of the left inferior turbinated body, and perforation of the nasal septum, in the person of a worker in chrome pigments. *Glasgow Med J* 1890;33:469-470.
26. Teleky L. Krebs bei Chromarbeitern. *Dtsch Med Wochenschr* 1936;62:1353.
27. Machle W, Gregorius F. Cancer of the respiratory system in the United States chromate-producing industry. *Public Health Rep* 1948;63:1114-1127.
28. Brinton HP, Frasier ES, Koven AL. Morbidity and mortality experience among chromate workers. *Public Health Rep* 1952;67:835-838.
29. Gafafer W. *Health of Workers in Chromate Producing Industry: A Study*. Washington, DC: U.S. Public Health Service, Division of Occupational Health Publications, 1953.
30. Taylor FH. The relationship of mortality and duration of employment as reflected by a cohort of chromate workers. *Am J Public Health Nations Health* 1966;56(2):218-222.
31. Enterline PE. Respiratory cancer among chromate workers. *J Occup Med* 1974;16(8):523-526.
32. Mancuso TF. Occupational cancer and other health hazards in a chromate plant: a medical appraisal. II. Clinical and toxicologic aspects. *Industrial Medicine and Surgery* 1951;20(9):393-407.
33. Hayes RB, Lilienfeld AM, Snell LM. Mortality in chromium chemical production workers: a prospective study. *Int J Epidemiol* 1979;8(4):365-374.
34. Bidstrup PL, Case RAM. Carcinoma of the lung in workmen in the bichromates-producing industry in Great Britain. *Brit J industr Med* 1956;13:260-264.
35. Alderson MR, Rattan NS, Bidstrup L. Health of workmen in the chromate-producing industry in Britain. *Br J Ind Med* 1981;38(2):117-124.

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

36. Satoh K, Fukuda Y, Torii K, Katsuno N. Epidemiological study of workers engaged in the manufacture of chromium compounds. *J Occup Med* 1981;23:835-838.
37. de Marco R, Bernardinelli L, Mangione MP. [Death risk due to tumors of the respiratory system in workers employed in chromate production]. *Med Lav* 1988;79(5):368-376.
38. Korallus U, Lange H-J, Neiss A, Wuestefeld E, Zwingers T. Zusammenhaenge zwischen Sanierungsmassnahmen und Bronchialkarzinommortalitaet in der chromatherstellenden Industrie. *Arbeitsmed Sozialmed Praeventivmed* 1982;13:159-167.
39. Pastides H, Austin R, Lemeshow S, Klar J, Mundt KA. A retrospective-cohort study of occupational exposure to hexavalent chromium. *Am J Ind Med* 1994;25(5):663-75.
40. World Health Organization. Chromium. Biological Monitoring of Chemical Exposure in the Workplace. Geneva: World Health Organization, 1996;91-111.
41. Kortenkamp A. Problems in the biological monitoring of chromium(VI) exposed individuals. *Biomarkers* 1997;2:73-80.
42. Petrilli FL, Rossi GA, Camoirano A, Romano M, Serra D, Bennicelli C, De Flora A, De Flora S. Metabolic reduction of chromium by alveolar macrophages and its relationships to cigarette smoke. *J Clin Invest* 1986;77(6):1917-24.
43. Kondo K, Hino N, Sasa M, Kamamura Y, Sakiyama S, Tsuyuguchi M, Hashimoto M, Uyama T, Monden Y. Mutations of the p53 gene in human lung cancer from chromate-exposed workers. *Biochem Biophys Res Commun* 1997;239(1):95-100.
44. Korallus U, Ulm K. Life expectancy, mortality and its spectrum of male employees of a chemical plant. *Arbeitsmed Sozialmed Praeventivmed* 1989;Sonderheft 12:3-25.
45. Pastides H, Mundt KA. Occupational Epidemiology. Resource Manual. Washington: Chemical Manufacturers Association, 1991;83.
46. Deutsche Forschungsgemeinschaft. Alkali chromates (Cr(VI)). In: Henschler D, Lehnert G, eds. Biological exposure values for occupational toxicants and carcinogens: critical data evaluation for BAT and EKA values. Weinheim, Germany: VCH Verlagsgesellschaft, 1994;187-203.
47. StataCorp. Stata Statistical Software: Release 7.0. College Station, TX: Stata Corporation, 2001.
48. Blot WJ, Fraumeni JF. Cancers of the Lung and Pleura. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention*. 2nd ed. New York: Oxford University Press, 1996;637-665.
49. Kerger BD, Finley BL, Corbett GE, Dodge DG, Paustenbach DJ. Ingestion of chromium(VI) in drinking water by human volunteers: absorption, distribution, and excretion of single and repeated doses. *J Toxicol Environ Health* 1997;50(1):67-95.
50. Bukowski JA, Goldstein MD, Johnson BB. Biological markers in chromium exposure assessment: confounding variables. *Arch Environ Health* 1991;46(4):230-236.

51. Steenland K, Loomis D, Shy C, Simonson N. Review of occupational lung carcinogens. *Am J Ind Med* 1996;29(5):474-90.

**Tables and Figures**

Table 1: Previously studied cohorts included in the combined analysis

Plant/Company	Location	Study period	Inclusion criterion	Cohort	Person-years	All causes		Respiratory cancer		Reference
						Obs	SMR	Obs	SMR	
Leverkusen, Bayer, AG	North Rhine-Westphalia, GERMANY	Jan. 1, 1958 to Dec. 31, 1988	Worked $\geq 1$ year	416 men	4,908	49	Not reported	8	1.45	Korallus et al., 1993
Uerdingen, Bayer, AG	North Rhine-Westphalia, GERMANY	Jan. 1, 1964 to Dec. 31, 1988	Worked $\geq 1$ year	262 men	2,659	8	Not reported	1	0.69	Korallus et al., 1993
Castle Hayne, Occidental Chemical	North Carolina, USA	Sept. 4, 1971 to Dec. 31, 1989	Worked $\geq 1$ year	398 men and women	4,483	16	0.72	2	0.97	Pastides et al., 1994
Corpus Christi, Elementis, USA	Texas, USA	Oct. 15, 1979 to Nov. 30, 1994	Worked $\geq 1$ day	310 men	3,549	22	0.64	6	1.67	Applied Epidemiology, Inc., 1995

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 2: Types of industrial hygiene data, number of samples, and years for which data are available by plant

IH measure	Leverkusen		Uerdingen		Castle Hayne		Corpus Christi	
	No. samples	Years	No samples	Years	No samples	Years	No. samples	Years
Personal air	252	1985—1998	215	1986—1994	5,461	1974—1992 1995—1998	1,249	1980—1982 1986—1988 1990—1998
Area air	3,422	1973—1998	1,161	1978—1995	1,555	1971—1972 1974—1979 1990—1991	1,656	1980—1998
Urine	6,940	1958—1998	5,402	1964—1995	--	--	--	--
Blood	3,036	1969—1971 1983—1998	4,792	1972—1995	--	--	--	--
Serum	2,782	1984—1998	2,200	1985—1995	--	--	--	--

IHF29113

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 3: Homogenous exposure groups identified for each plant

Plant	Homogenous exposure group
Leverkusen	Ball mills, Material mixing, Control room in building U17, Kiln1, Kilns 2 & 3, Filtration, Residue drying/recycle, Residue reduction, Vanadium separation, Pressure acidify/soda production, Final acid/evap, Sulfate separation & drying, NDC crystallization & drying, Shipping, Foremen & supervisors, Lab technicians, Maintenance workers & foremen, Plant managers/office workers/engineers, Entire building U17
Uerdingen	Kilns, Saturation, ADC/KDC production, KCA production, Shipping, Laboratory, Clothing handout, DCH shop, Electricians, Supervisors/administrators
Castle Hayne	Ore handling, Ball mills, R/M mix, Recycle, Kilns, Quench, Boilers, Neutralization, Acid/Evap, Chromic acid, CA packer, Crystal packing, Warehouse, Storeroom, Tank farm, Waste treatment, Laboratory, Administration/Technical, Maintenance, Utility/plantwide, Production supervisors, Engineers
Corpus Christi	Ball mills/material mixing, DCS hearth, Filtration, DCS kiln, Residue treatment, Acid/evap, Chrome oxide, Chromic acid, Chrome hydrate, Shipping, Administration, Laboratory/technical, Utilities, Engineers, Maintenance, General services, Production supervisors

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 4: Assignment of peak exposure ranks

Peak rank	Sum of peak measurements ( $\mu\text{g/L}$ chromium in urine)	Sum of peak measurements ( $\mu\text{g}/\text{m}^3$ chromium in air)	Percentile of distribution of sum of peak measurements
0	No peak measurements	No peak measurements	Excluded
1	Not used	Not used	Not used
2	40—99	50—124	0—~50 <sup>th</sup>
3	100—199	125—624	~50 <sup>th</sup> —~90 <sup>th</sup>
4	$\geq 200$	$\geq 625$	~90 <sup>th</sup> —100 <sup>th</sup>

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 5: Arithmetic means, variances and the ratio of the means for German plants for years where personal air monitoring samples and urine samples were available.

	Uerdingen	Leverkusen
Urine samples, n	2074	2829
Mean, $\mu\text{g/L Cr}$	8.12	6.80
Variance	376.58	218.23
Air samples, n	215	256
Mean, $\mu\text{g/m}^3 \text{Cr (VI)}$	8.83	8.04
Variance	942.91	270.96
Ratio of means	0.92	0.85

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 6: Relationship between CrO<sub>3</sub> concentrations in workplace air and excretion of Cr in urine and conversion factor based on ratio of urine to air

Air CrO <sub>3</sub> mg/m <sup>3</sup>	Air Cr(VI) µg/m <sup>3</sup> (CrO <sub>3</sub> / 1.92 x 1000)	Cr-urine (µg/L) Sampling: end of exposure	Ratio of urine to air
0.03	15.63	12	0.77
0.05	26.04	20	0.77
0.08	41.67	30	0.72
0.10	52.08	40	0.77

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 7: Exclusions from the database by plant

	Plant			
	Castle Hayne	Corpus Christi	Leverkusen	Uerdingen
Total in database	589	426	875	966
Exclusions:				
Missing date of birth	1	0	0	0
Missing date of hire	2	0	0	0
Began working after study end date	0	1	0	0
Contract worker	1	0	0	0
Unexposed trainee	1	0	0	0
Worked less than 1 year	108	33	4	28
Previous high lime exposure	46	205	278	464
Worked in other plants with possible Cr(VI) exposure	0	0	0	166*
Total in study analysis	430	187	593	308

\*Employed in plants other than the Dichromate plant and included in the database for regular medical examination

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 8: Descriptive statistics for the cohort

Variable	Plant							
	Leverkusen		Uerdingen		Castle Hayne		Corpus Christi	
	n	%	n	%	n	%	n	%
<b>Gender</b>								
Male	593	100.0	308	100.0	379	88.1	140	74.9
Female	0	0.0	0	0.0	51	11.6	47	25.1
<b>Race/Ethnicity</b>								
White/Caucasian	593	100.0	306	99.4	349	81.2	108	57.8
Black	--		--		74	17.2	8	4.3
Hispanic	--		--		4	0.9	70	37.4
Asian	--		--		0	0.0	1	0.5
Native American	--		--		3	0.7	0	
Non-European	0	0.0	2	0.6	--	--	--	--
<b>Year of birth</b>								
1900-1909	8	1.3	0	0.0	1	0.2	0	0.0
1910-1919	41	6.9	2	0.6	4	0.9	0	0.0
1920-1929	132	22.3	55	17.9	13	3.0	0	0.0
1930-1939	147	24.8	92	29.9	49	11.4	3	1.6
1940-1949	83	14.0	90	29.2	145	33.7	34	18.2
1950-1959	76	12.8	47	15.3	166	38.6	75	40.1
1960-1969	50	8.4	21	6.8	50	11.6	63	33.7
1970-1979	56	9.4	1	0.3	2	0.5	12	6.4
<b>Smoking status</b>								
Ever smoked	381	64.2	208	67.5	242	56.3	30	16.0
Never smoked	150	25.3	96	31.2	149	34.7	122	65.2
Unknown status	62	10.5	4	1.3	39	9.1	35	18.7

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 9: Duration of exposure and time since first exposure by plant

	Leverkusen (n=593)	Uerdingen (n=308)	Castle Hayne (n=430)	Corpus Christi (n=187)
<b>Duration of exposure</b>				
Mean	9.2	11.0	12.4	7.8
SD	6.3	6.6	9.5	5.1
Range	1.0-40.7	1.0-29.4	1.0-27.9	1.0-17.9
<b>Time since first exposure</b>				
Mean	16.4	19.1	20.1	10.1
SD	9.9	8.2	7.7	5.0
Range	1.0-40.9	2.0-34.9	1.4-28.8	1.0-17.9
<b>Age at first exposure</b>				
Mean	38.4	37.7	28.9	31.3
SD	10.6	6.2	8.3	7.4
Range	14.6-60.5	19.2-53.1	17.4-62.9	19.9-53.5

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 10: Vital status for study subjects as of December 31, 1993

Vital status	Leverkusen		Uerdingen		Castle Hayne		Corpus Christi		Total Cohort	
	N (%)	P-YRS (%)	N (%)	P-YRS (%)						
Alive	472 (79.6)	7,503.5 (82.4)	267 (86.7)	4,863.6 (87.3)	407 (94.7)	7,869.7 (96.0)	182 (97.3)	1,662.5 (97.3)	1328 (87.5)	21,899.3 (89.1)
Dead	92 (15.5)	1,524.2 (16.7)	38 (12.3)	703.3 (12.6)	22 (5.1)	327.0 (4.0)	5 (2.7)	46.1 (2.7)	157 (10.3)	2,600.6 (10.6)
Unknown	29 (4.9)	82.2 (0.9)	3 (1.0)	6.7 (0.1)	1 (0.2)	0.4 (0.0)	0 (0.0)	0.0 (0.0)	33 (2.2)	89.2 (0.4)
Total	593 (100.0)	9,109.9 (100.0)	308 (100.0)	5,573.7 (100.0)	430 (100.0)	8,197.0 (100.0)	187 (100.0)	1,708.6 (100.0)	1518 (100.0)	24,589.2 (100.0)

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 11: Observed and expected deaths, SMRs and 95% confidence intervals using state rates (US plants) and German national rates (German plants) as referent population (24,590 person-years)

Cause of death	Observed	Expected	SMR	95% CI
All causes	157*	167.27	0.94	0.80—1.10
All cancers	56	48.74	1.15	0.87—1.49
Oral cavity & pharynx	2	2.05	0.98	0.12—3.52
Digestive organs	11	16.21	0.68	0.34—1.21
Stomach	2	4.06	0.49	0.06—1.78
Intestine, except rectum	4	3.76	1.06	0.29—2.72
Rectum	2	1.96	1.02	0.12—3.68
Pancreas	2	2.49	0.80	0.10—2.90
Respiratory system	26	16.36	1.59	1.04—2.33
Trachea, bronchus & lung	25	15.02	1.66	1.08—2.46
Prostate	3	2.98	1.01	0.21—2.95
Kidney, bladder & other urinary organs	4	3.33	1.20	0.33—3.07
Lymphatic & hematopoietic tissue	3	3.32	0.90	0.19—2.64
Unspecified sites	4	2.89	1.38	0.38—3.54
Diabetes mellitus	0	2.62	0	—
Alcoholism	1	2.02	0.49	0.01—2.76
Diseases of the heart	39	49.31	0.79	0.56—1.08
Ischemic heart disease	23	36.34	0.63	0.40—0.95
Other diseases of the circulatory system	16	16.04	1.00	0.57—1.62
Cerebrovascular disease	9	10.79	0.83	0.38—1.58
Diseases of the respiratory system	4	9.26	0.43	0.12—1.11
Diseases of the digestive system	7	11.84	0.59	0.24—1.22
Accidents	5	7.01	0.71	0.23—1.67
Suicide	3	5.24	0.57	0.12—1.67

\*Includes 14 with unknown cause of death

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 12: Observed and expected deaths, SMRs and 95% confidence intervals using state rates (US plants) and North Rhine-Westphalia rates (German plants) as referent population

Cause of death	Observed	Expected	SMR	95% CI
All causes	157*	178.83	0.88	0.75—1.03
All cancers	56	53.28	1.05	0.79—1.37
Respiratory cancer	26	19.90	1.31	0.85—1.91
Trachea, bronchus & lung cancer	25	18.22	1.37	0.89—2.03

\*Includes 14 with unknown cause of death

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 13: Observed and expected lung cancers, SMRs and 95% CI's stratified by duration of exposure and time since first exposure

Variable	Obs	Exp	SMR	95% CI
<b>Duration of exposure</b>				
1-4 years	3	3.89	0.77	0.16-2.25
5-9 years	8	4.19	1.91	0.82-3.77
10-19 years	10	8.46	1.18	0.57-2.17
20 years or more	4	1.68	2.38	0.65-6.10
<b>Time since first exposure</b>				
1-9 years	6	3.48	1.72	0.63-3.75
10-19 years	8	7.51	1.06	0.46-2.10
20-29 years	9	5.63	1.60	0.73-3.04
30 years or more	2	1.60	1.25	0.15-4.52
<b>Age at first exposure</b>				
<25 years	0	0.13	--	--
25-34 years	2	1.18	1.69	0.20-6.11
35 years or older	23	16.91	1.36	0.86-2.04

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 14: Observed and expected deaths, SMR's and 95% confidence intervals for lung cancer stratified

Exposure	Obs	Exp	SMR	95% CI
<b>Cr in urine (<math>\mu\text{g/L}</math>)</b>				
0 - 39.9	4	2.97	1.35	0.37-3.46
40 - 99.9	4	4.20	0.95	0.26-2.44
100 - 199.9	5	5.30	0.94	0.31-2.20
$\geq 200$	12	5.72	2.09	1.08-3.65
<b>Peak exposure score (3 levels)</b>				
0 - 0.9	1	1.12	0.89	0.02-4.96
1 - 4.9	0	2.72	0	-
5 - 23.9	13	8.19	1.59	0.84-2.71
$\geq 24$	10	5.08	1.97	0.94-3.62
<b>Peak exposure score (2 levels)</b>				
0 - 0.9	1	1.06	0.94	0.02-5.26
1 - 4.9	0	1.33	0	-
5 - 23.9	3	3.84	0.78	0.16-2.28
$\geq 24$	20	10.88	1.84	1.12-2.84

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 15: Lagged analysis of cumulative exposure and peak exposure score

	No lag			10-year lag			20-year lag		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
<b>Cr in urine (<math>\mu\text{g/L}</math>-years)</b>									
0-39.9	4	1.35	0.37-3.46	9	1.34	0.62-2.56	17	1.31	0.76-2.10
40-99.9	4	0.95	0.26-2.44	3	0.78	0.16-2.28	2	1.01	0.12-3.65
100-199.9	5	0.94	0.31-2.20	5	1.31	0.43-3.07	2	1.10	0.13-3.96
$\geq 200$	12	2.09	1.08-3.65	8	2.05	0.88-4.04	4	2.74	0.75-7.03
<b>Peak exposure score</b>									
0-0.9	1	0.89	0.02-4.96	6	1.30	0.48-2.84	15	1.32	0.74-2.18
1-4.9	0	0	-	0	0	-	1	0.60	0.02-3.36
5-23.9	13	1.59	0.84-2.71	11	1.61	0.80-2.88	7	2.09	0.84-4.30
$\geq 24$	10	1.97	0.94-3.62	7	2.21	0.89-4.55	1	1.31	0.03-7.28

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 16: Distribution of study subjects and lung cancer deaths according to peak exposure indicator score and cumulative exposure

Cumulative exposure	Peak exposure score								TOTAL	
	0-0.9		1-4.9		5-23.9		24+		Study subject	LC death
	Study subjects	LC death	Study subjects	LC death	Study subjects	LC death	Study subjects	LC death	Study subjects	LC death
0-39.9	337	1	230	0	371	3	5	0	943	4
40-99.9	33	0	61	0	157	4	0	0	251	4
100-199.9	0	0	11	0	111	4	39	0	161	4
200+	1	0	1	0	21	2	94	10	117	12
<b>TOTAL</b>	<b>371</b>	<b>1</b>	<b>303</b>	<b>0</b>	<b>660</b>	<b>13</b>	<b>138</b>	<b>10</b>	<b>1472</b>	<b>24</b>

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 17: Study subjects, lung cancer deaths, odds ratios (OR) and 95% confidence intervals (CI) according to cumulative exposure\* and cumulative exposure truncated 10 years earlier than end of follow-up\*\* four plants

Exposure, by age or smoking status	Cumulative exposure*				Cumulative exposure truncated 10 years earlier than end of follow-up**			
	Study subjects	LC deaths	OR	95% CI	Study Subjects	LC deaths	OR	95% CI
Overall								
Low	855	4	Ref	—	890	4	Ref	—
Intermediate	394	9	4.9	1.5–16.0	286	9	7.0	2.1–22.9
High	106	10	20.2	6.2–65.4	97	7	16.1	4.6–55.8
35 years or older at first exposure								
Low exposure	268	3	Ref	—	326	3	Ref	—
Intermediate	309	9	2.6	0.7–9.7	236	9	4.1	1.1–15.5
High exposure	88	10	10.2	2.7–37.7	80	7	9.5	2.4–37.6
Never smoked								
Low exposure	369	1	Ref	—	368	1	Ref	—
Intermediate	118	0	Undef		88	1	4.2	0.3–67.5
High exposure	28	1	13.2	0.8–216.4	25	0	Undef	
Ever smoked								
Low exposure	486	3	Ref	—	522	3	Ref	—
Intermediate	276	9	5.3	1.4–19.7	198	8	7.0	1.8–26.8
High exposure	78	9	18.7	5.0–70.6	72	7	16.9	4.3–66.9

Ref = referent

Undef = undefined

\*n=1378, 23 lung cancer deaths

\*\*n=1293, 20 lung cancer deaths

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 18: Summary exposure and cumulative exposure, truncated 10 years before the end of follow-up, odds ratios (OR) and 95% confidence intervals (CI) for lung cancer deaths at four plants: crude and adjusted for age at first exposure, ever smoked and both age at first exposure and history of smoking

Variable	Crude		Age at first exposure $\geq$ 35 years		Adjusted for: Ever smoked		Age at first exposure $\geq$ 35 and ever smoked	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
<b>Cumulative*</b>								
Low	Ref	—	Ref	—	Ref	—	Ref	—
Intermediate	4.9	1.5–16.0	2.3	0.7–7.6	4.2	1.3–13.8	2.0	0.6–6.9
High	20.2	6.2–65.4	8.8	2.6–29.9	16.8	5.2–55.0	8.0	2.4–27.1
Age at first exposure $\geq$ 35 years	22.8	3.0–169.8	11.8	1.5–94.2	—	—	11.4	1.4–90.1
Ever smoked	6.4	1.5–27.6	—	—	4.8	1.1–20.6	4.7	1.1–20.3
<b>Truncated exposure**</b>								
Low	Ref	—	Ref	—	Ref	—	Ref	—
Intermediate	7.0	2.1–22.9	3.6	1.1–12.2	6.3	1.9–20.6	3.4	1.0–11.6
High	16.1	4.6–55.8	8.3	2.3–29.8	13.6	3.9–47.7	7.7	2.1–27.6
Age at first exposure $\geq$ 35 years	18.7	2.5–139.9	9.1	1.1–73.2	—	—	8.6	1.1–68.5
Ever smoked	5.5	1.3–23.7	—	—	4.1	0.9–18.0	3.9	0.9–17.2

Ref=referent

\*Cumulative exposure, smoking, age (N=1378, 23 lung cancer deaths)

\*\*Cumulative exposure truncated 10 years before end of follow-up (N=1273, 20 lung cancer deaths)

Low exposure = cumulative exposure  $<$  40  $\mu\text{g}/\text{m}^3$

Intermediate exposure = cumulative exposure 40 –  $<$  200  $\mu\text{g}/\text{m}^3$

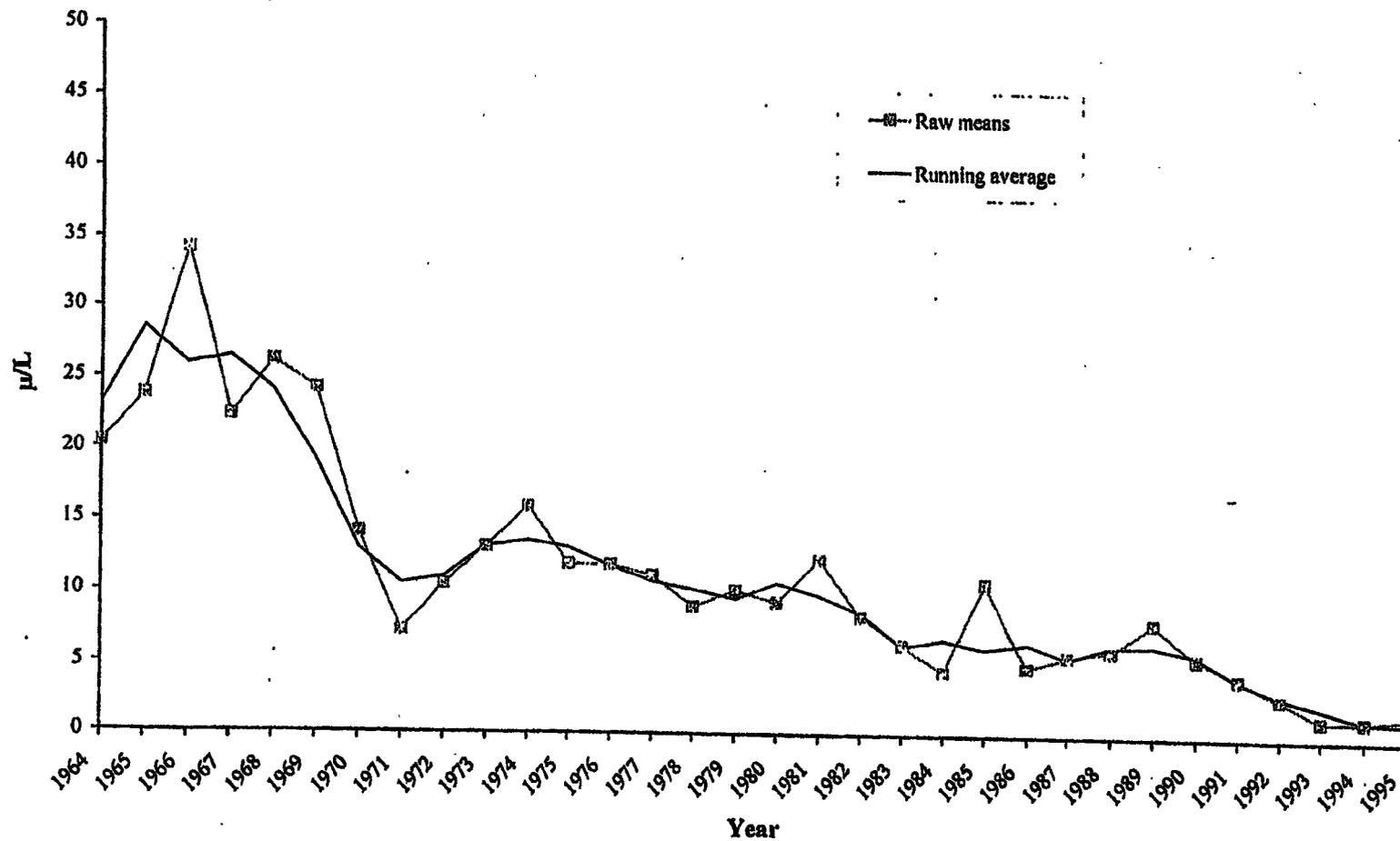
High exposure = cumulative exposure  $\geq$  200  $\mu\text{g}/\text{m}^3$

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Table 19: Hierarchical exposure models of cumulative high exposure and addition of ever peak exposure: crude and adjusted odds ratios and 95% confidence intervals for lung cancer deaths; German subcohorts (684 with complete data, 18 lung cancer deaths)

Variable	1 predictor Cum or Smoke		2 predictors Cum + Peak		2 predictors Cum + Smoke		3 predictors Cum+Peak+Smoke	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
High exposure	6.9	2.6 - 18.2	3.7	1.2 - 11.2	6.7	2.5 - 17.9	3.8	1.2 - 11.5
+ Ever peak			3.6	0.9 - 12.1			3.1	0.9 - 11.3
Smoking	6.9	0.9 - 52.4			6.6	0.9 - 50.7	6.2	0.8 - 47.7

Figure 1: Geometric mean over time for Uerdingen plant



IHF29131

Figure 2: Geometric mean over time for Leverlusen plant

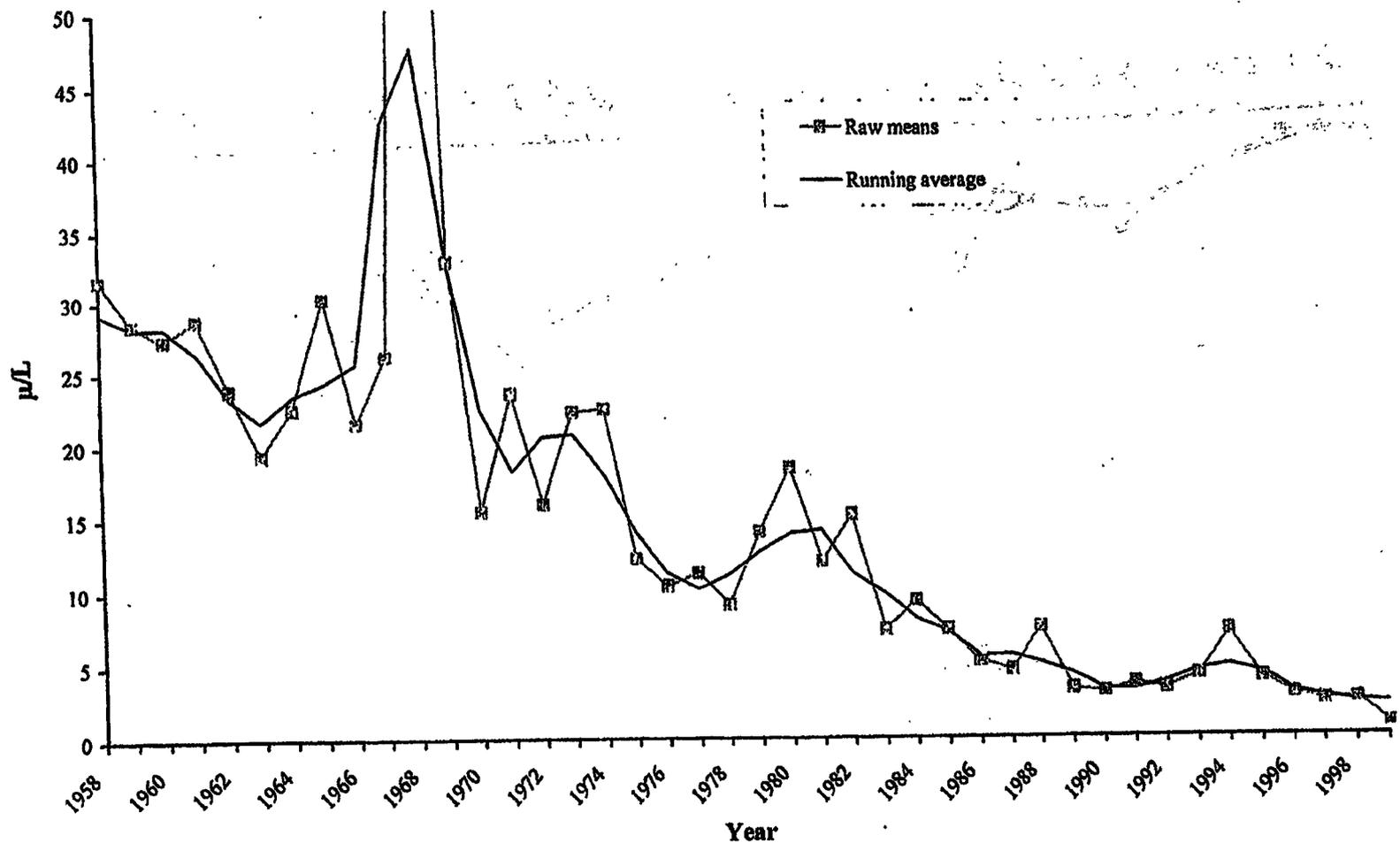
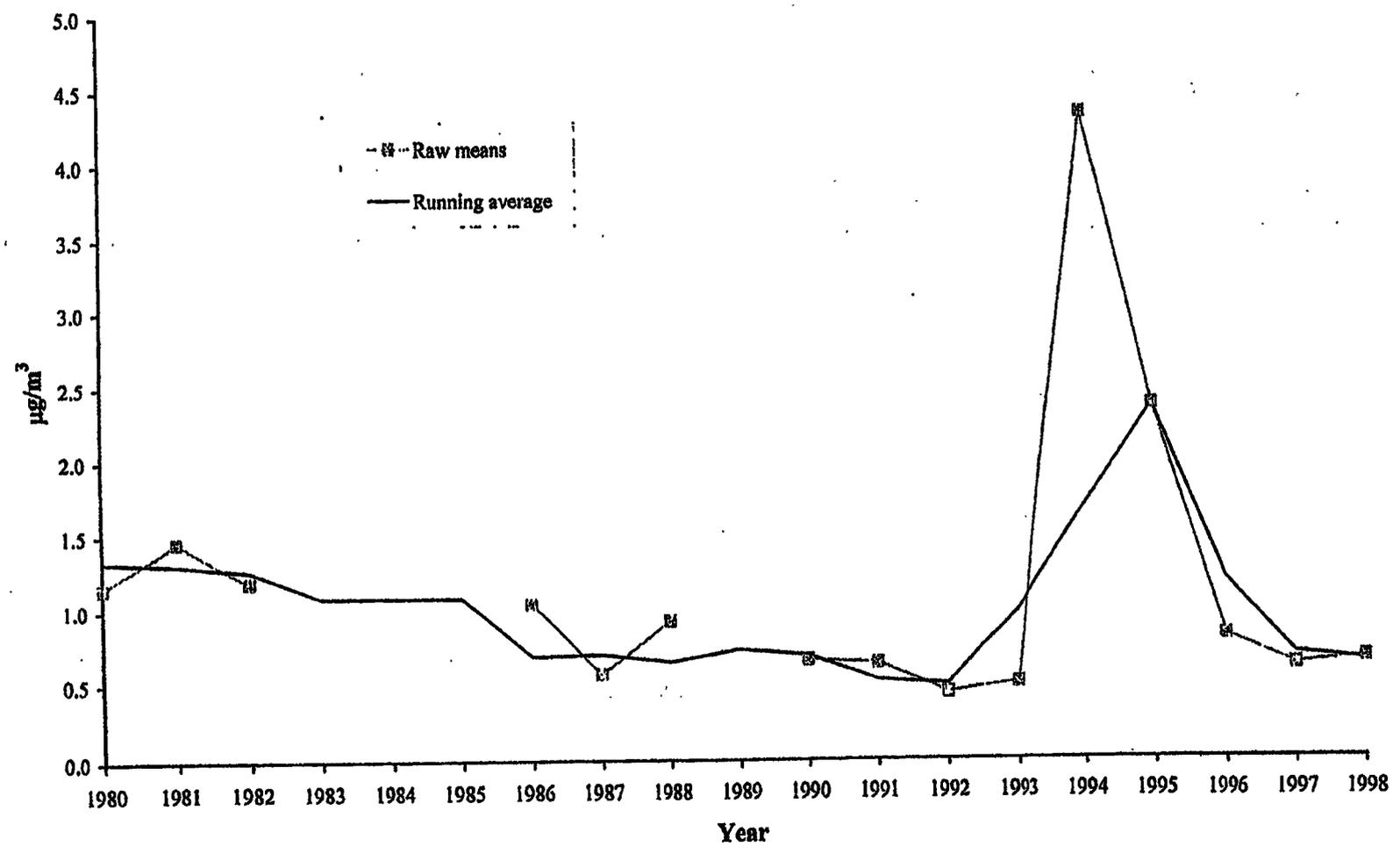


Figure 3: Geometric mean over time for Corpus Christi plant



IHF29133

Figure 4: Geometric mean over time for Castle Hayne plant

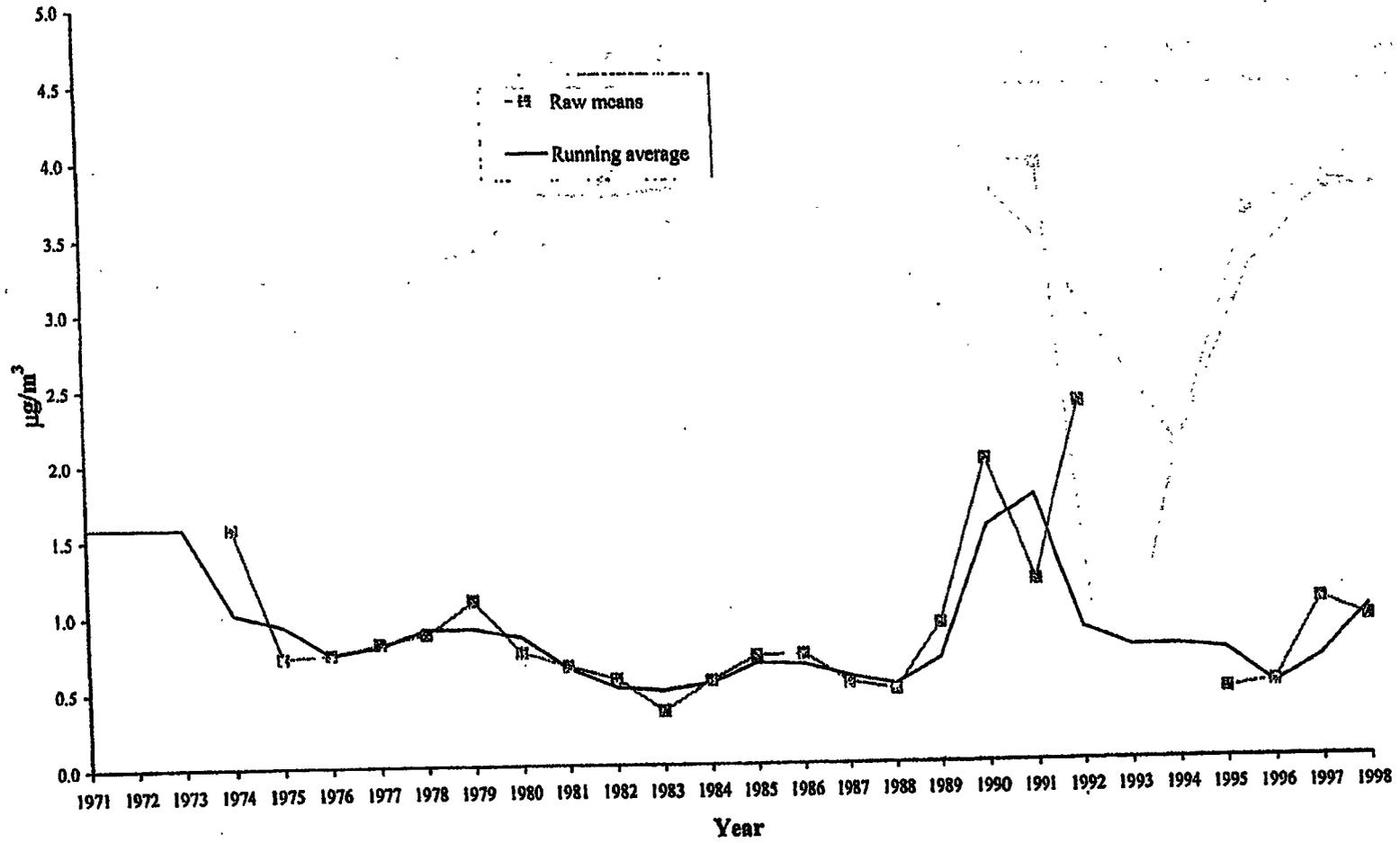


Figure 5: Plantwide geometric means (raw data) from personal air sampling

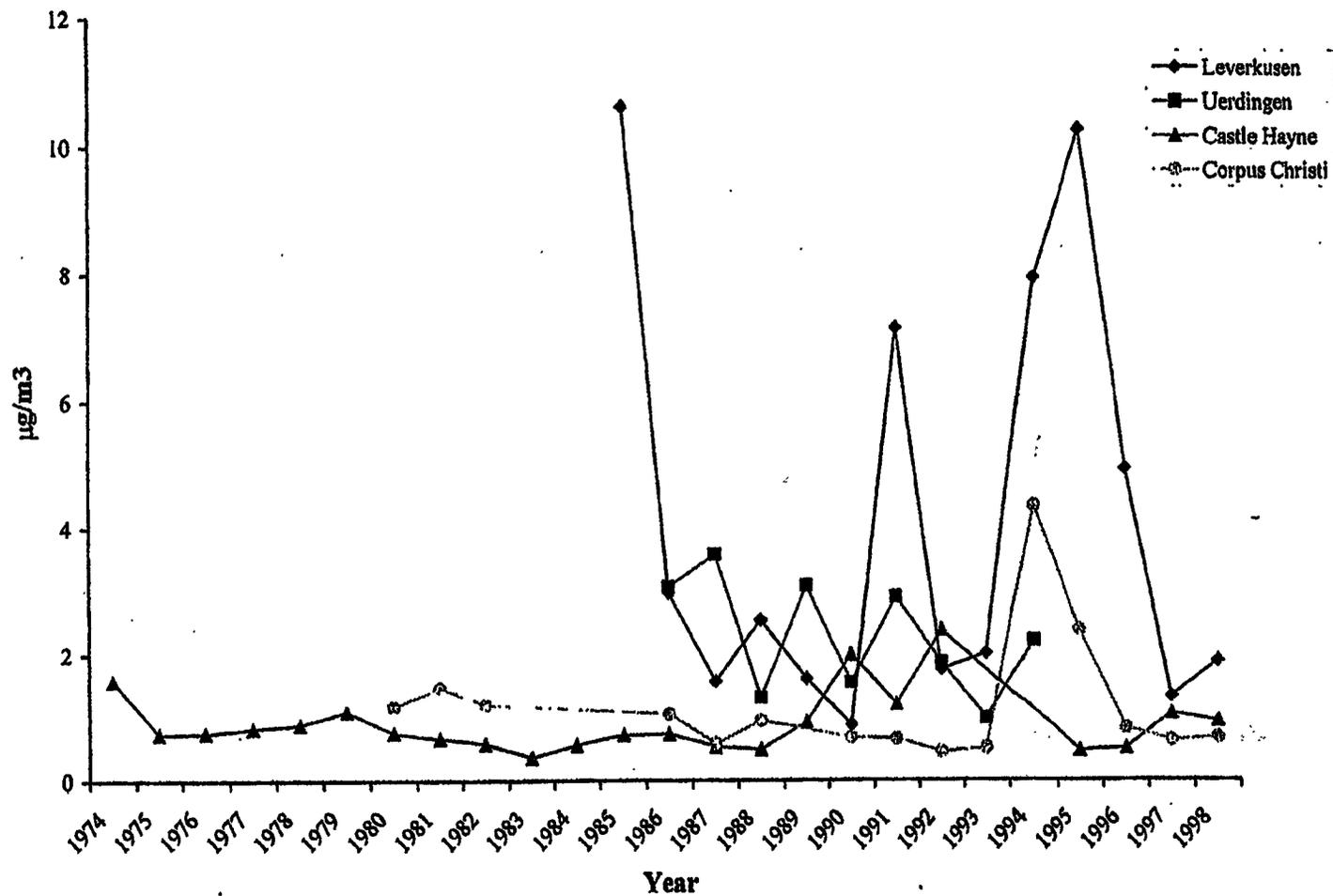


Figure 7: ADC/KDC production - Uerdingen

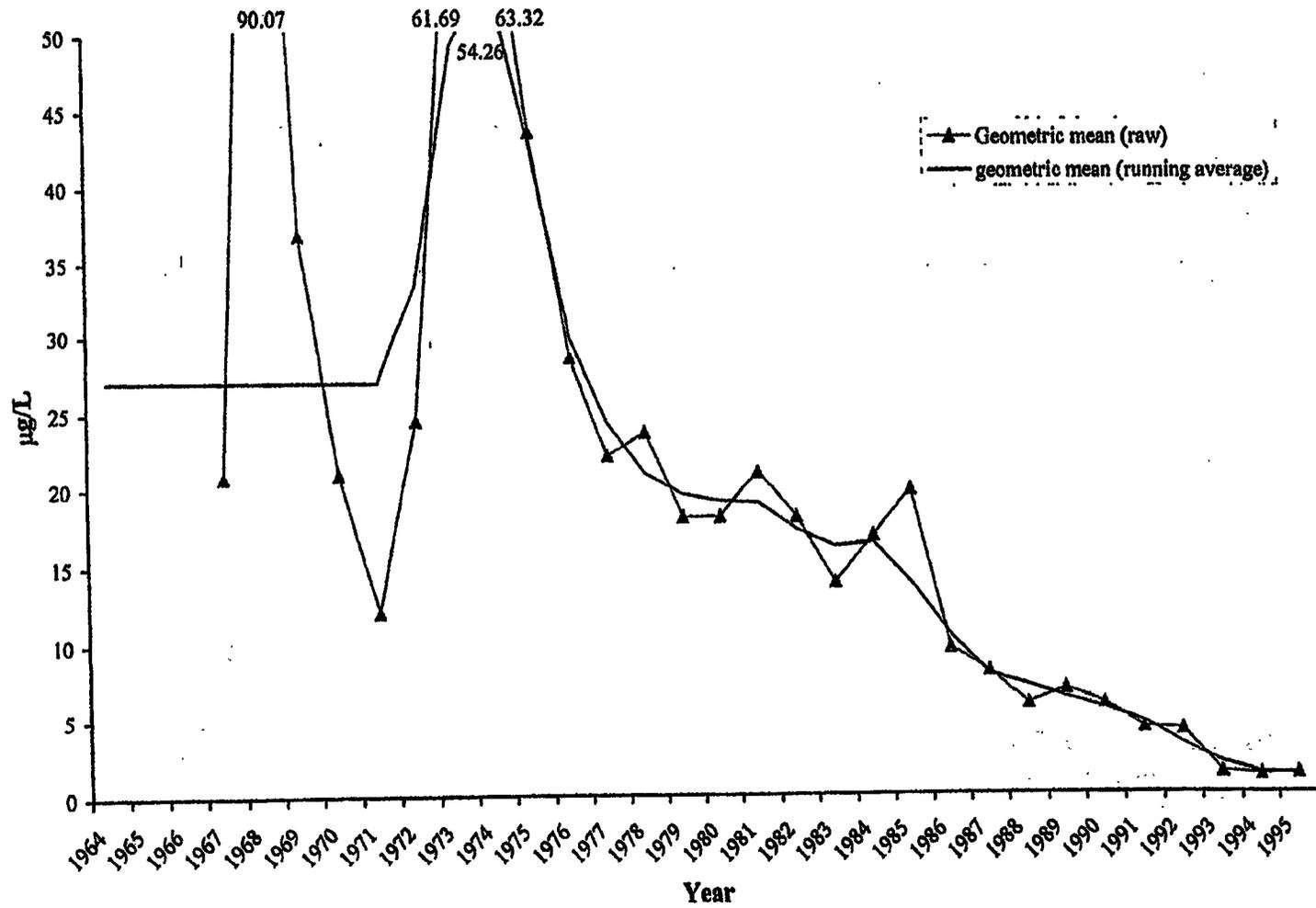


Figure 6: Saturation - Uerdingen

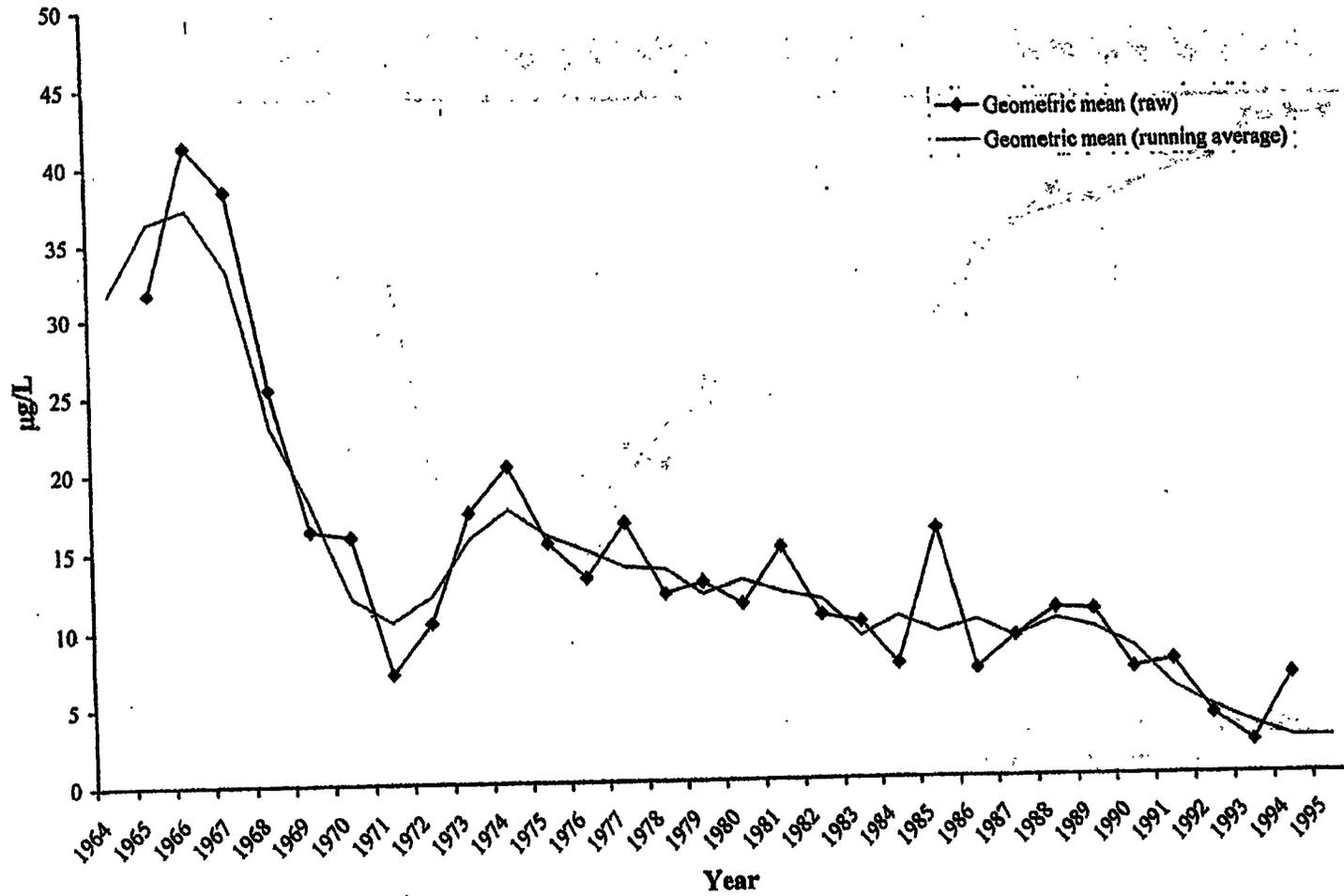
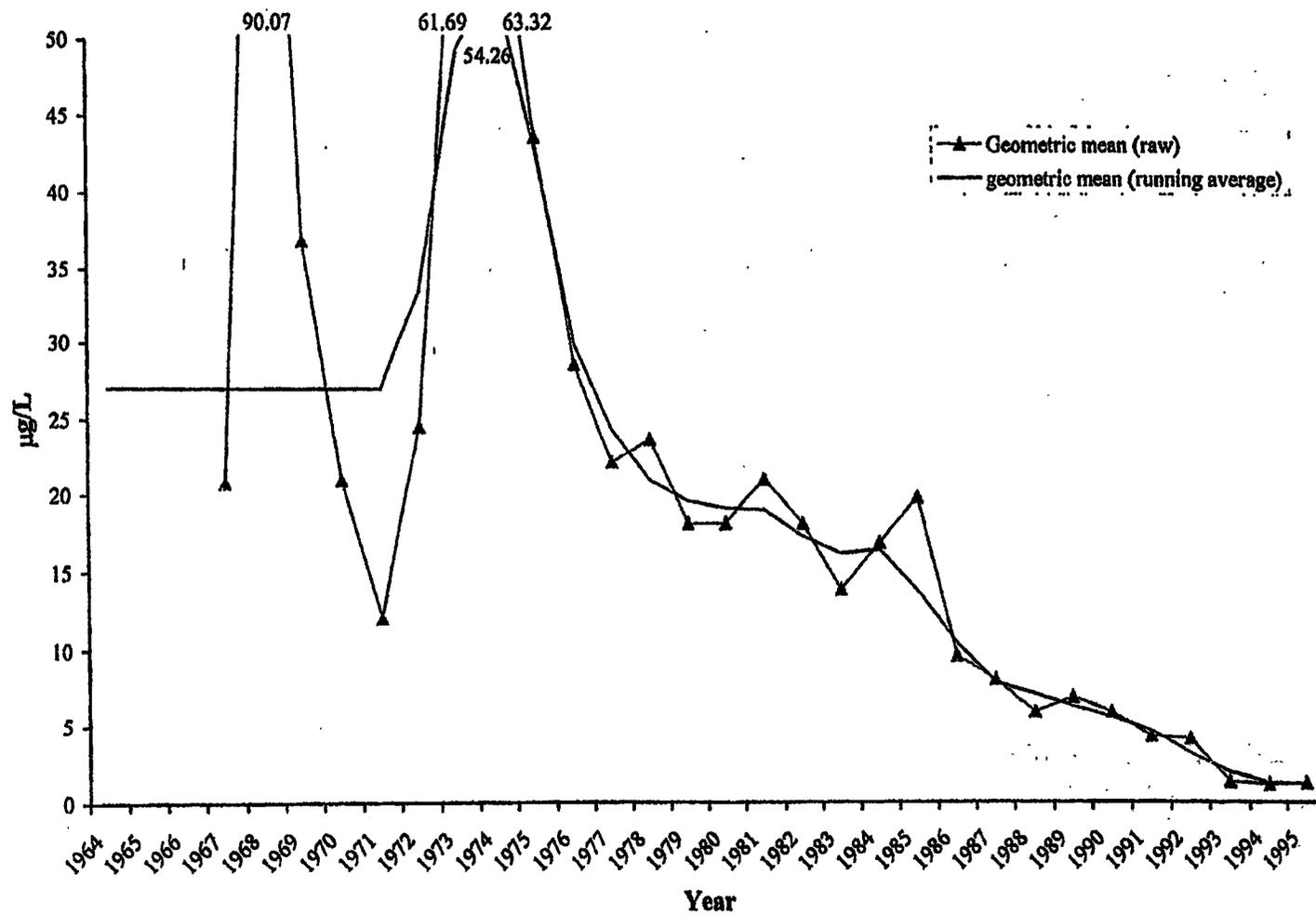


Figure 7: ADC/KDC production - Uerdingen



IHF29137

Figure 8: Shipping – Uerdingen

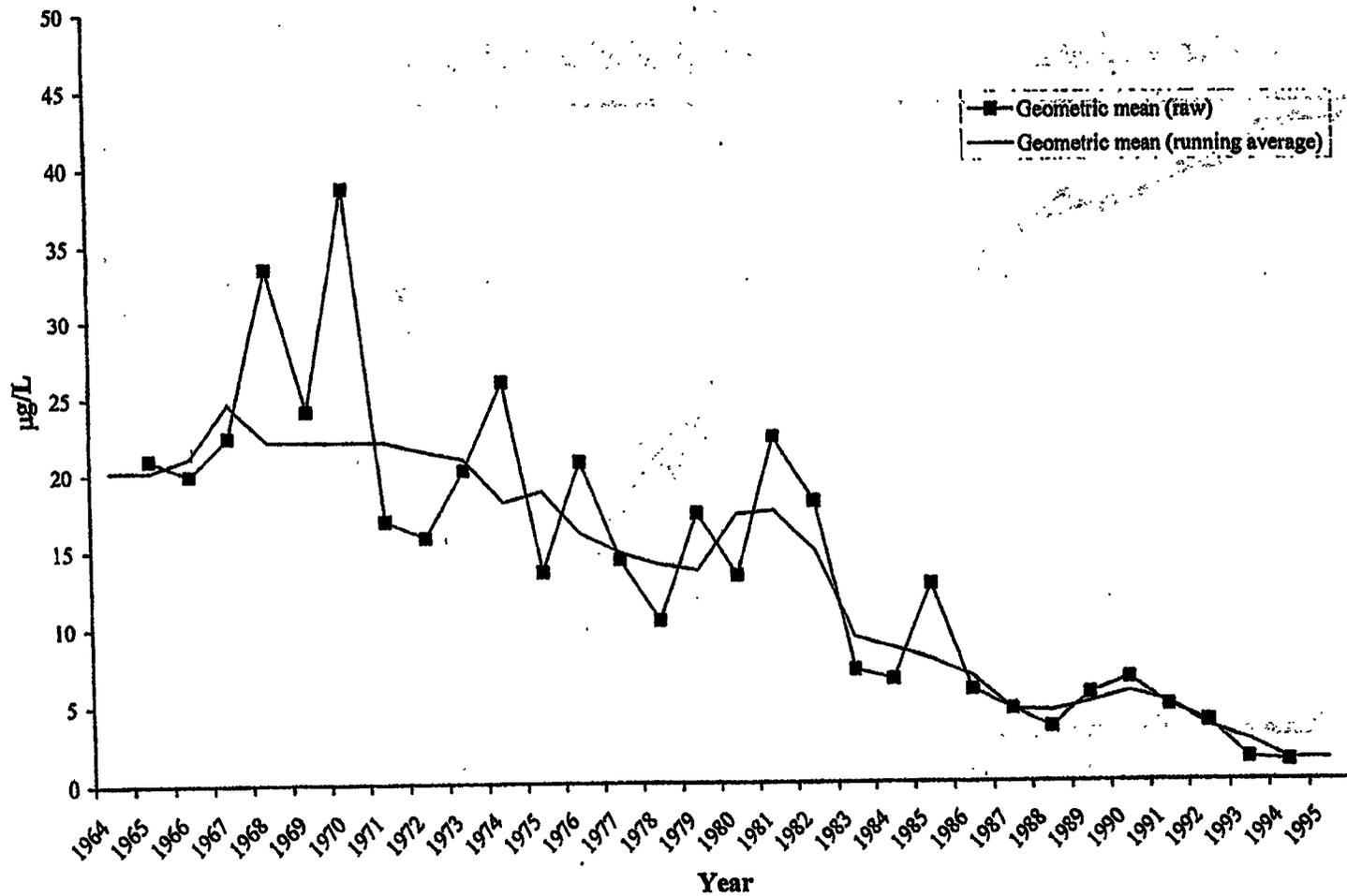


Figure 9: Electricians - Uerdingen

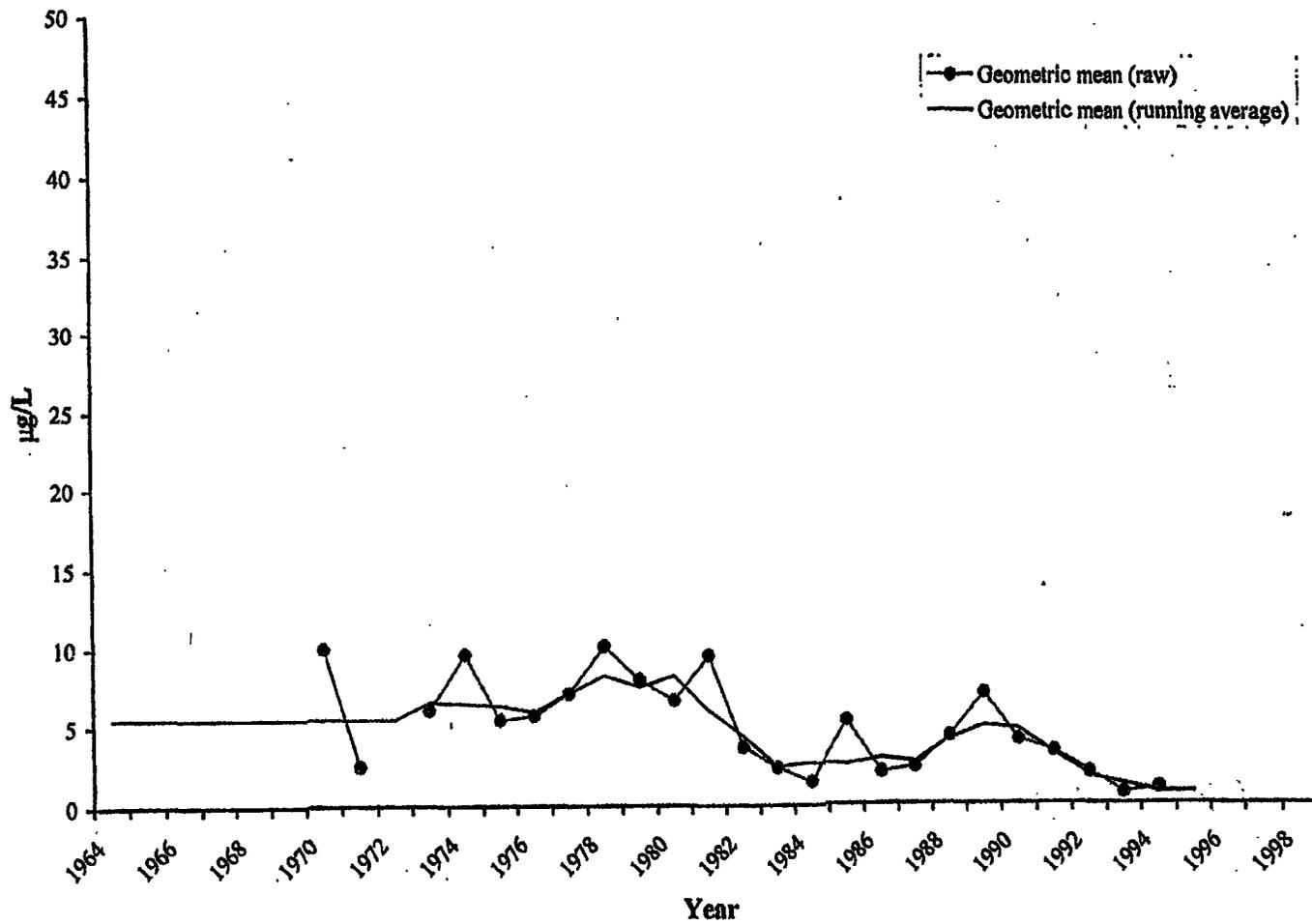


Figure 10: Kiln 1 - Leverkusen

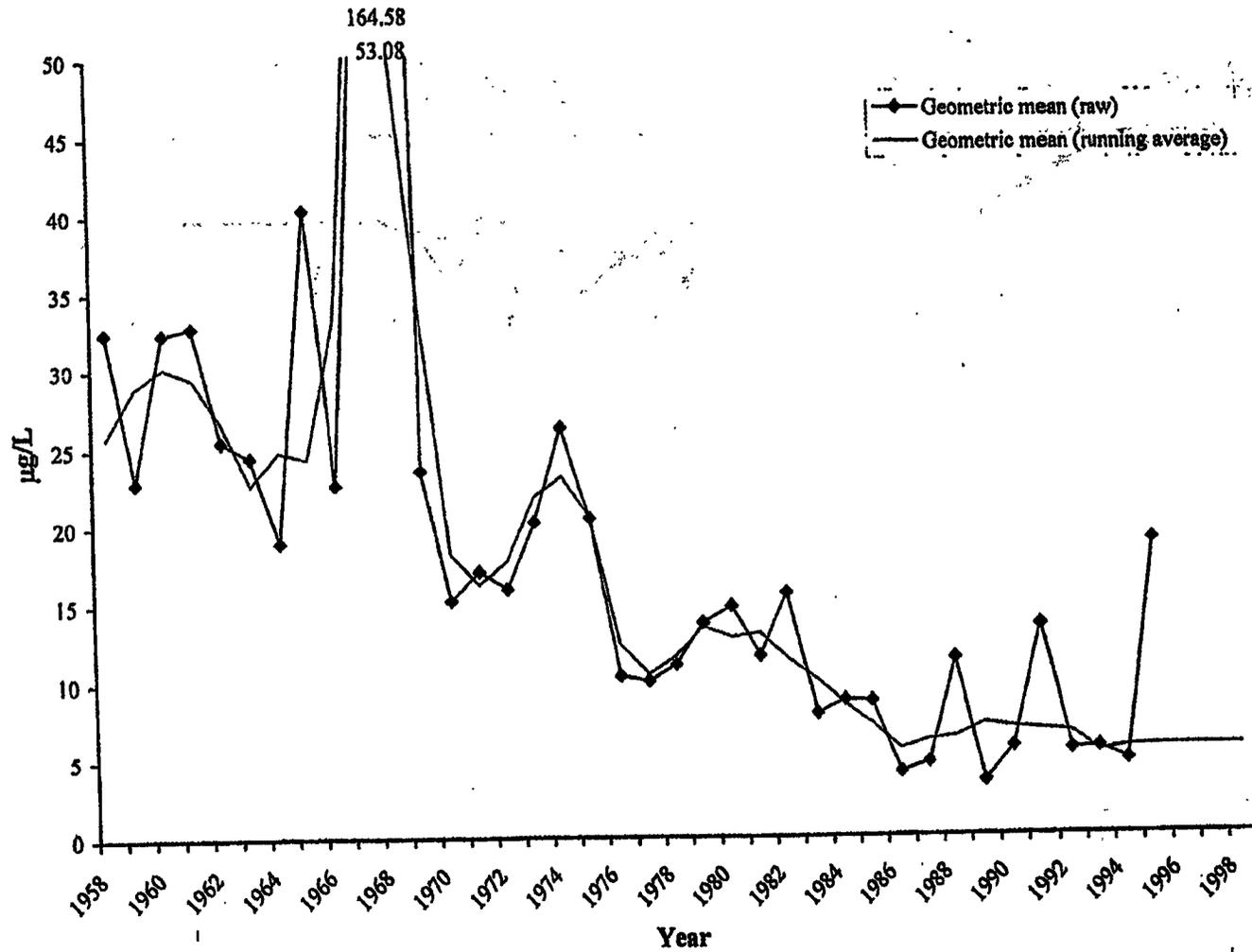
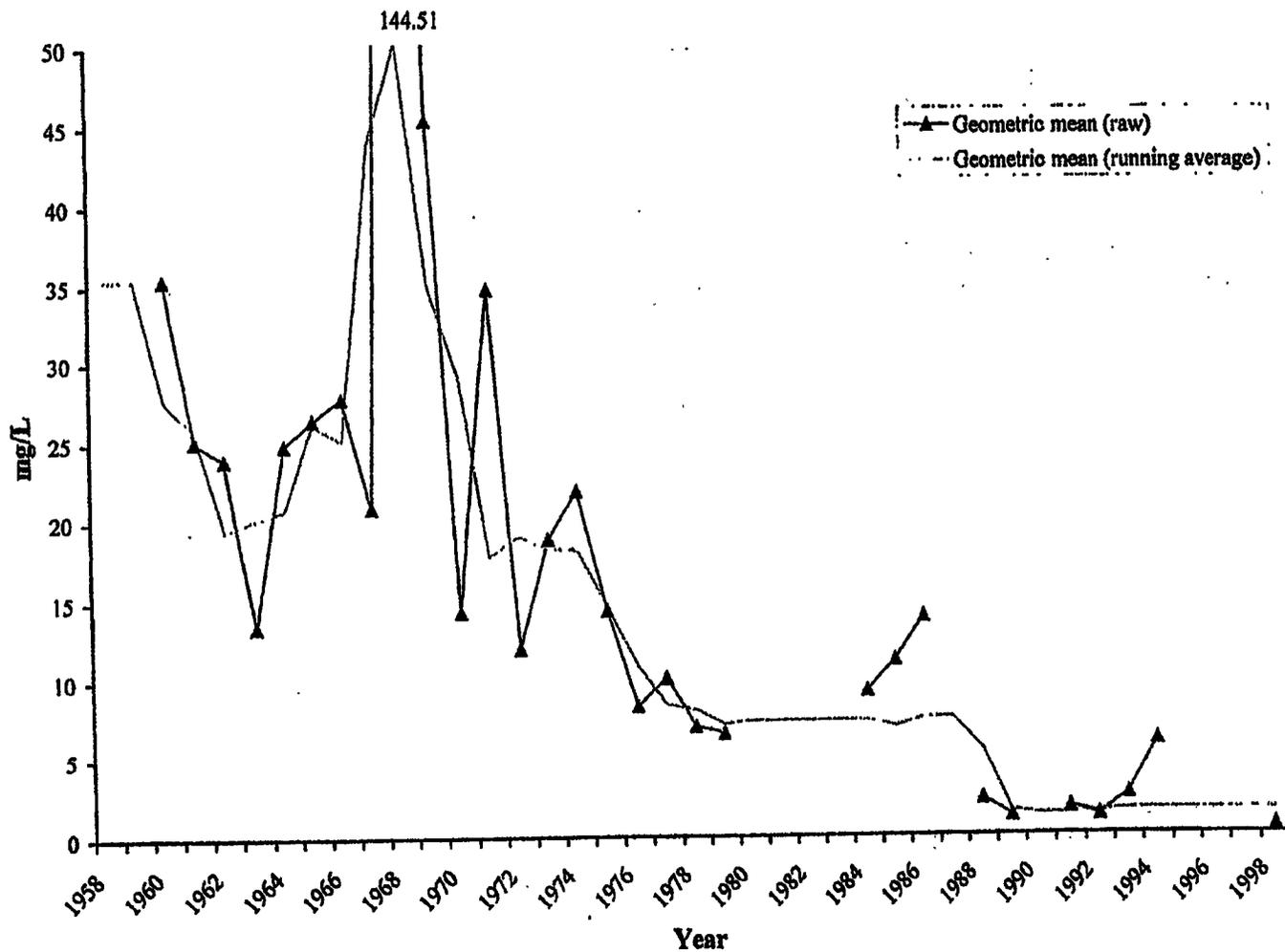


Figure 11: Maintenance Workers & Foremen - Leverkusen



IHF29141

Figure 12: Sulfate Separation & Drying - Leverkusen

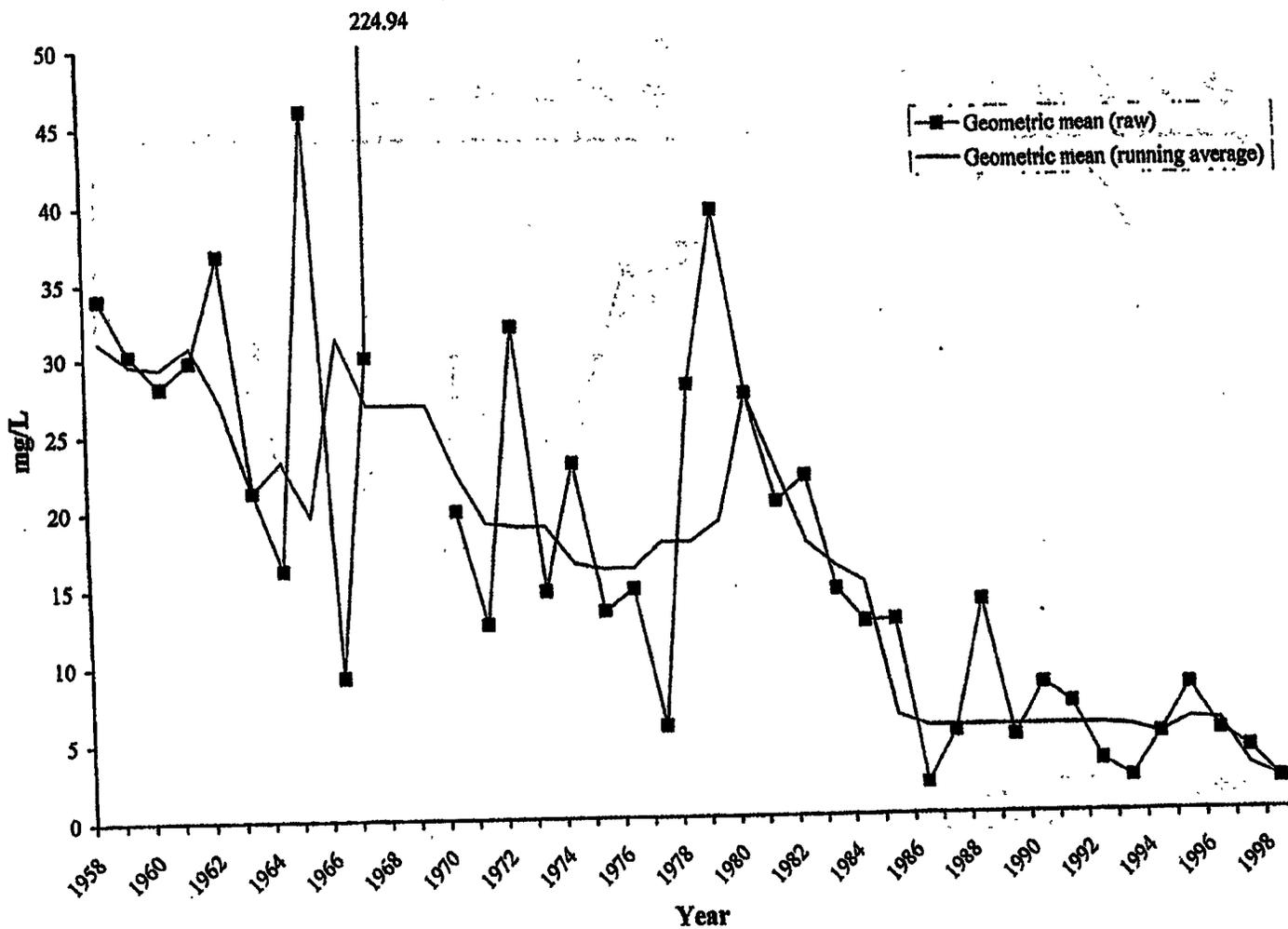
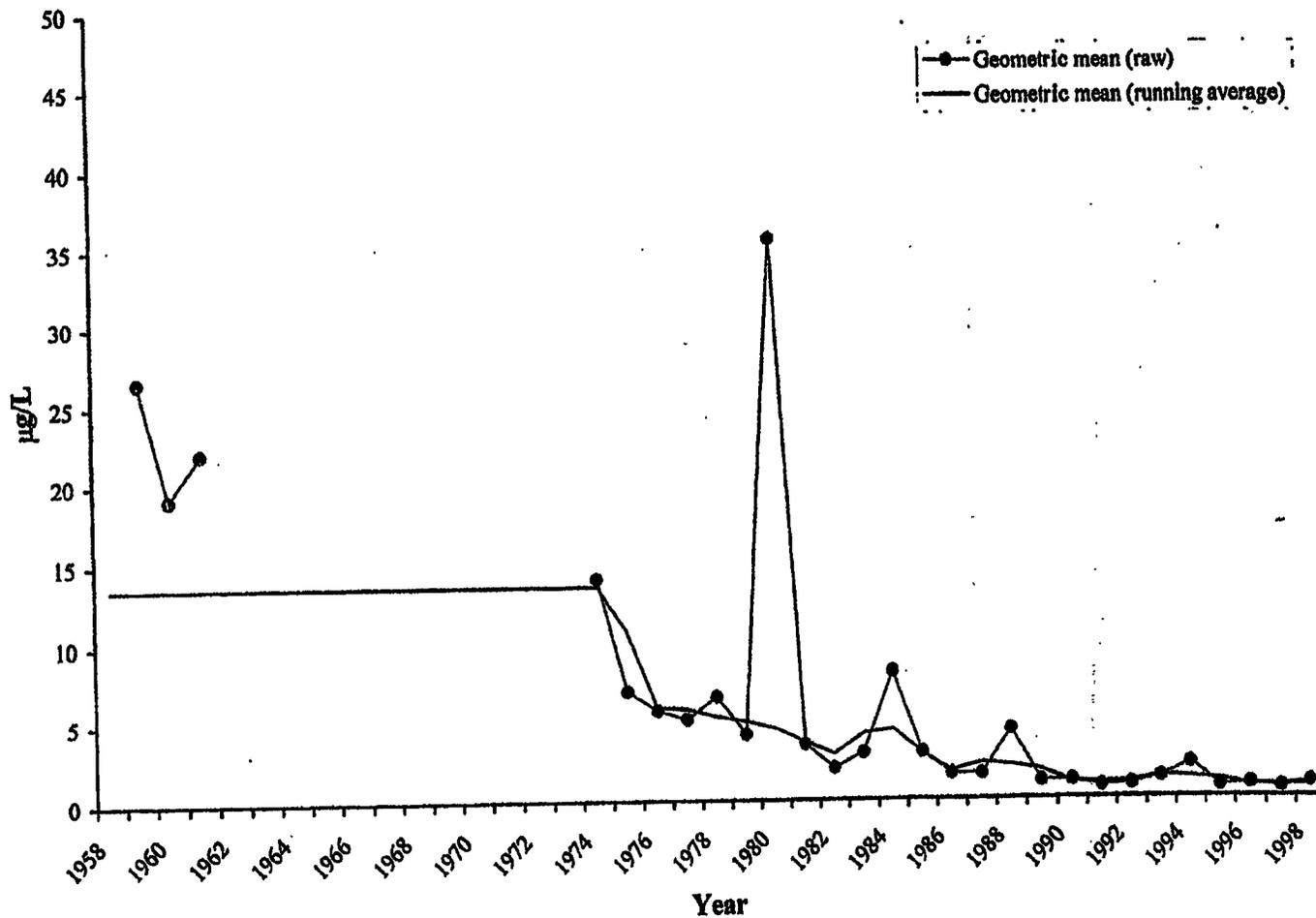


Figure 13: Lab Technicians - Leverkusen



IHF29143

Figure 14: Shipping – Corpus Christi

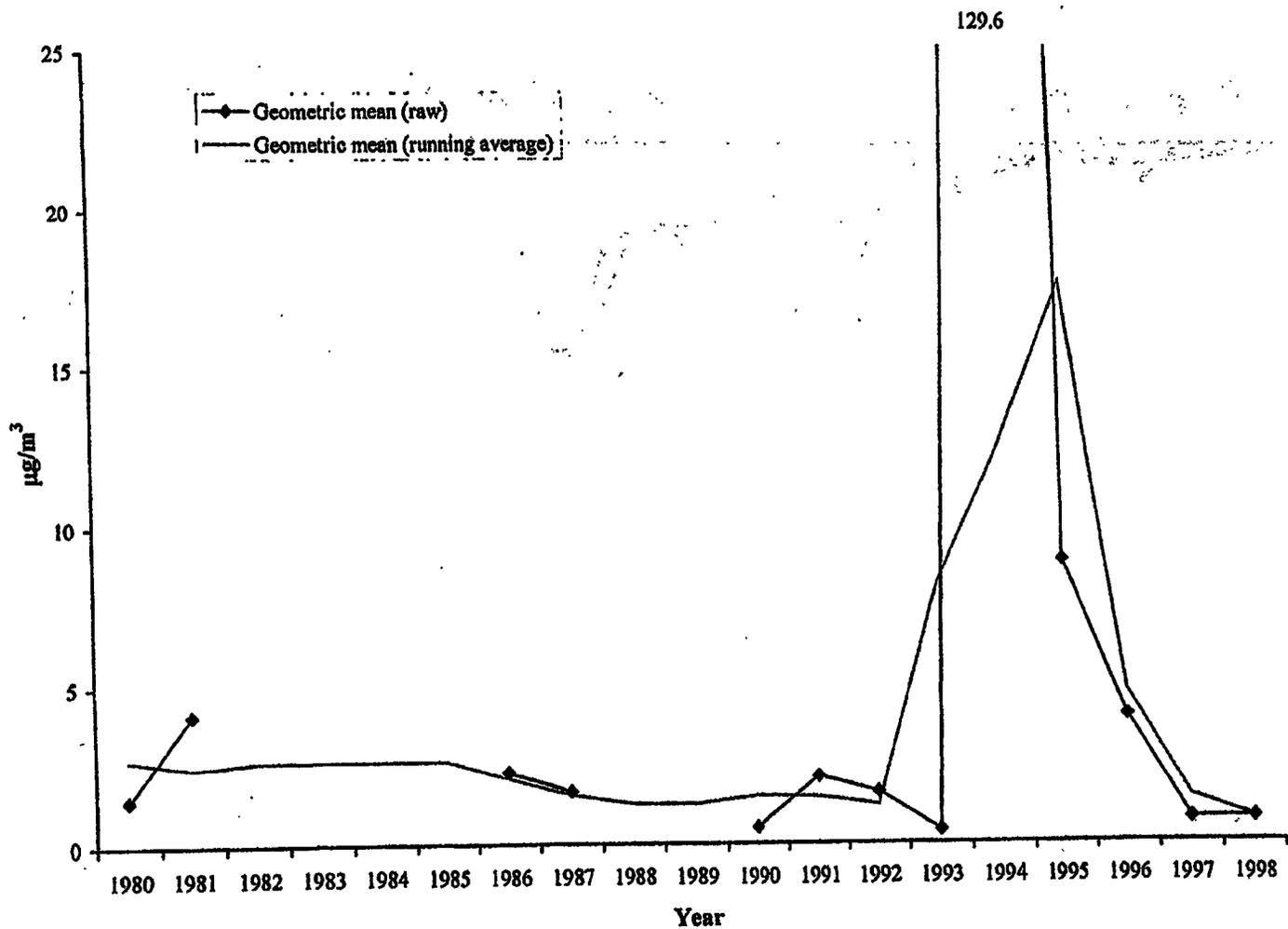
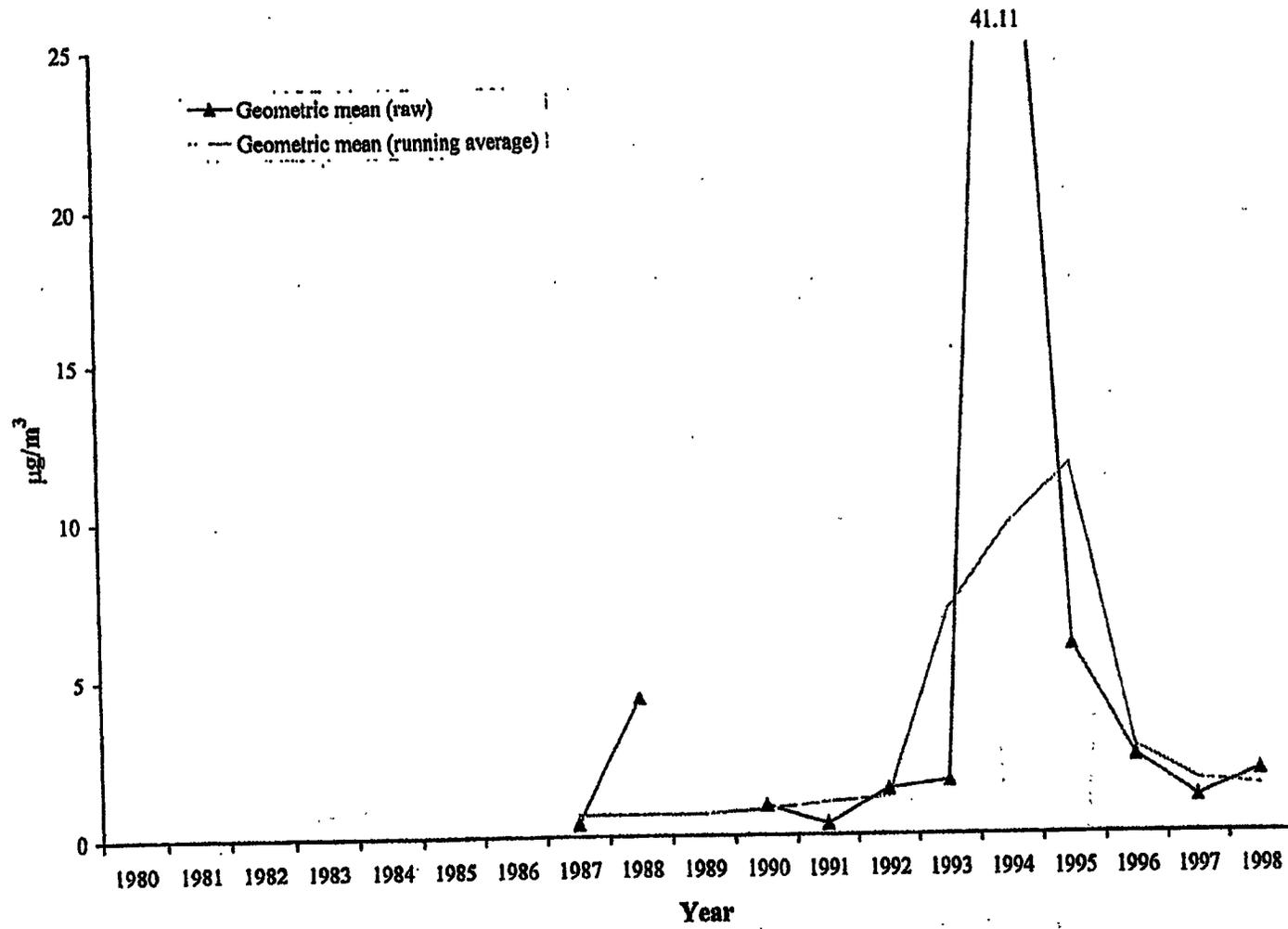


Figure 15: DCS Kiln -- Corpus Christi



IHF29145

Figure 16: DCS Hearth -- Corpus Christi

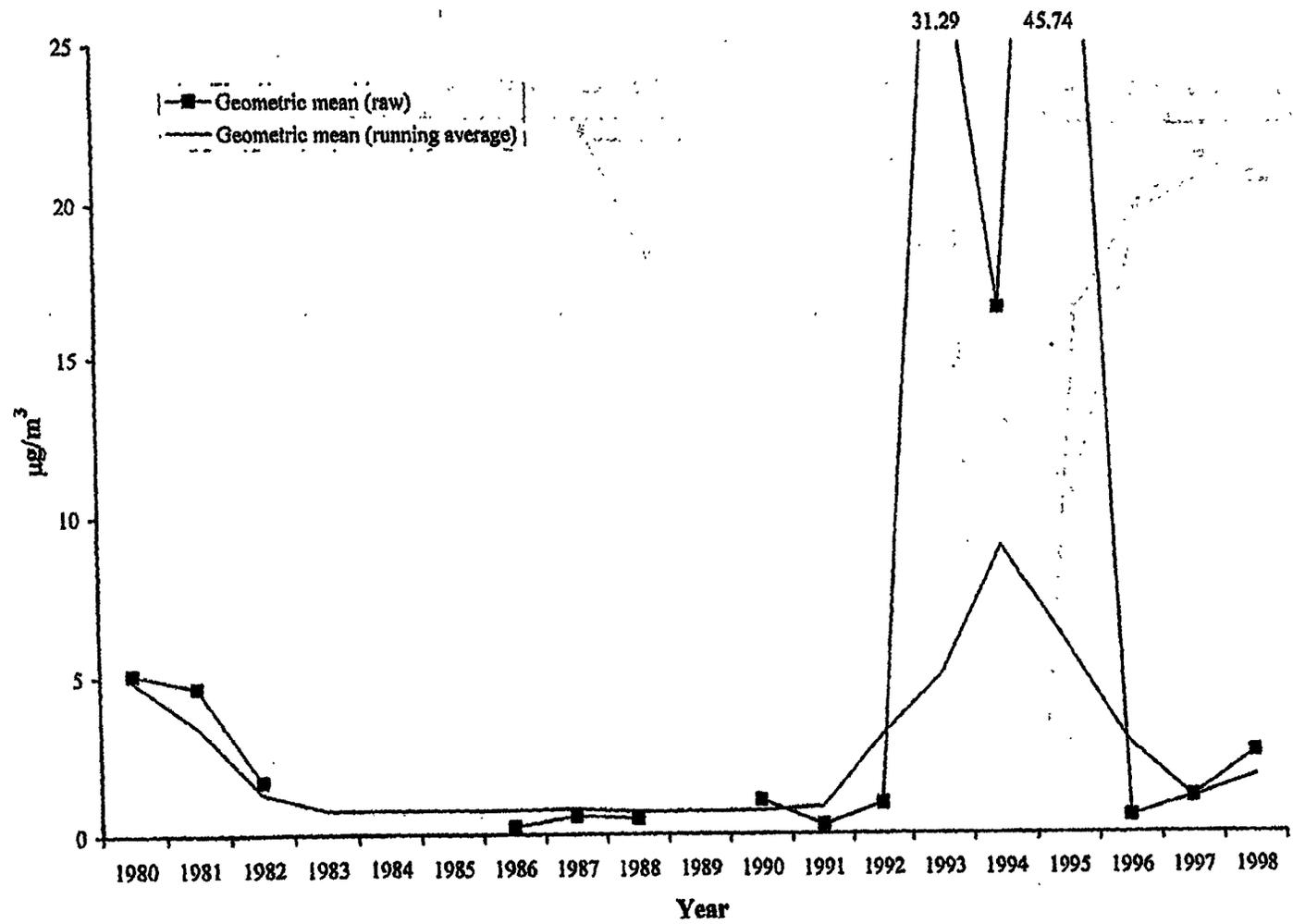
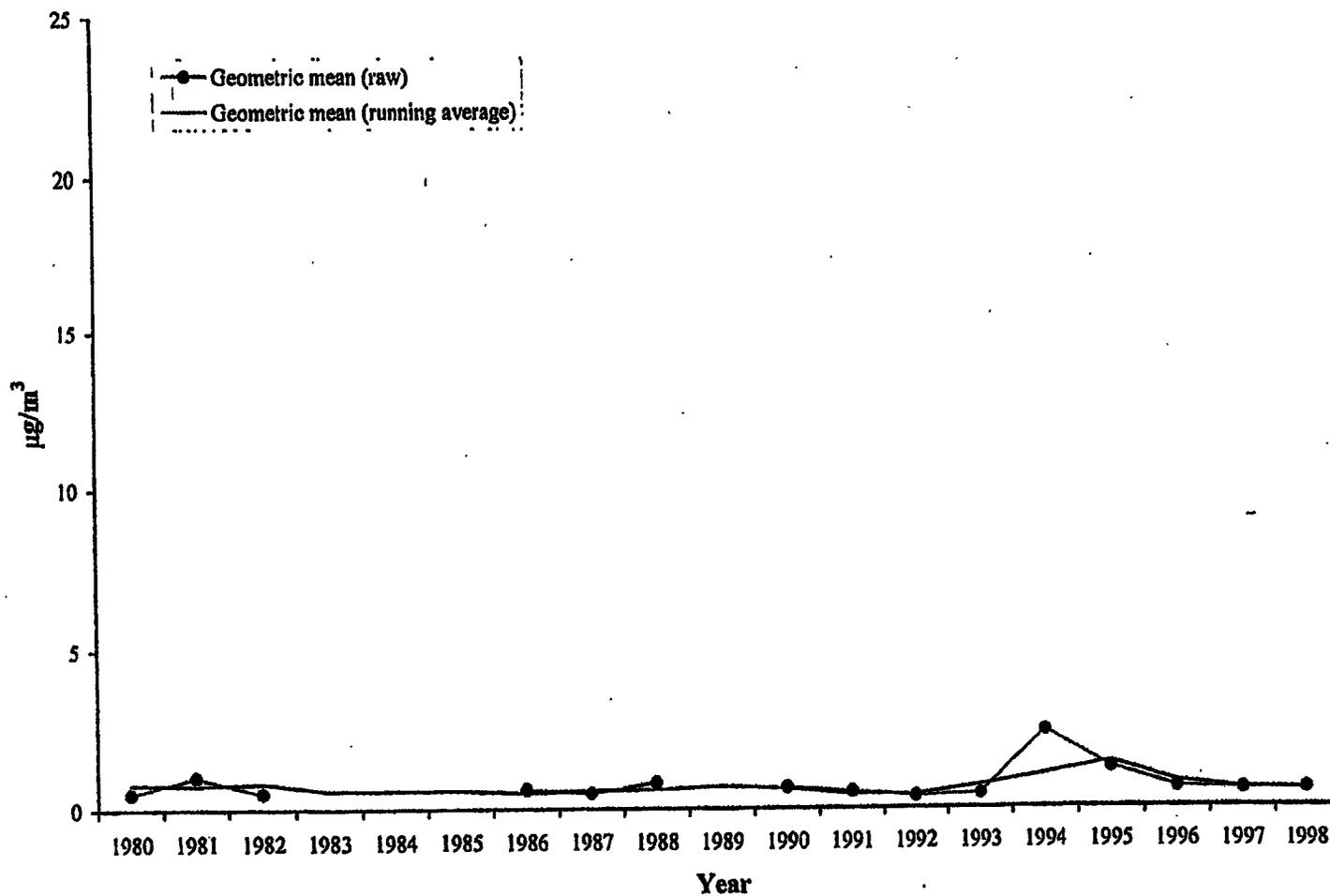


Figure 17: Combined low exposure areas (GM < 1  $\mu\text{g}/\text{m}^3$  over all years) – Corpus Christi



IHF29147

Figure 18: Crystal Packing – Castle Hayne

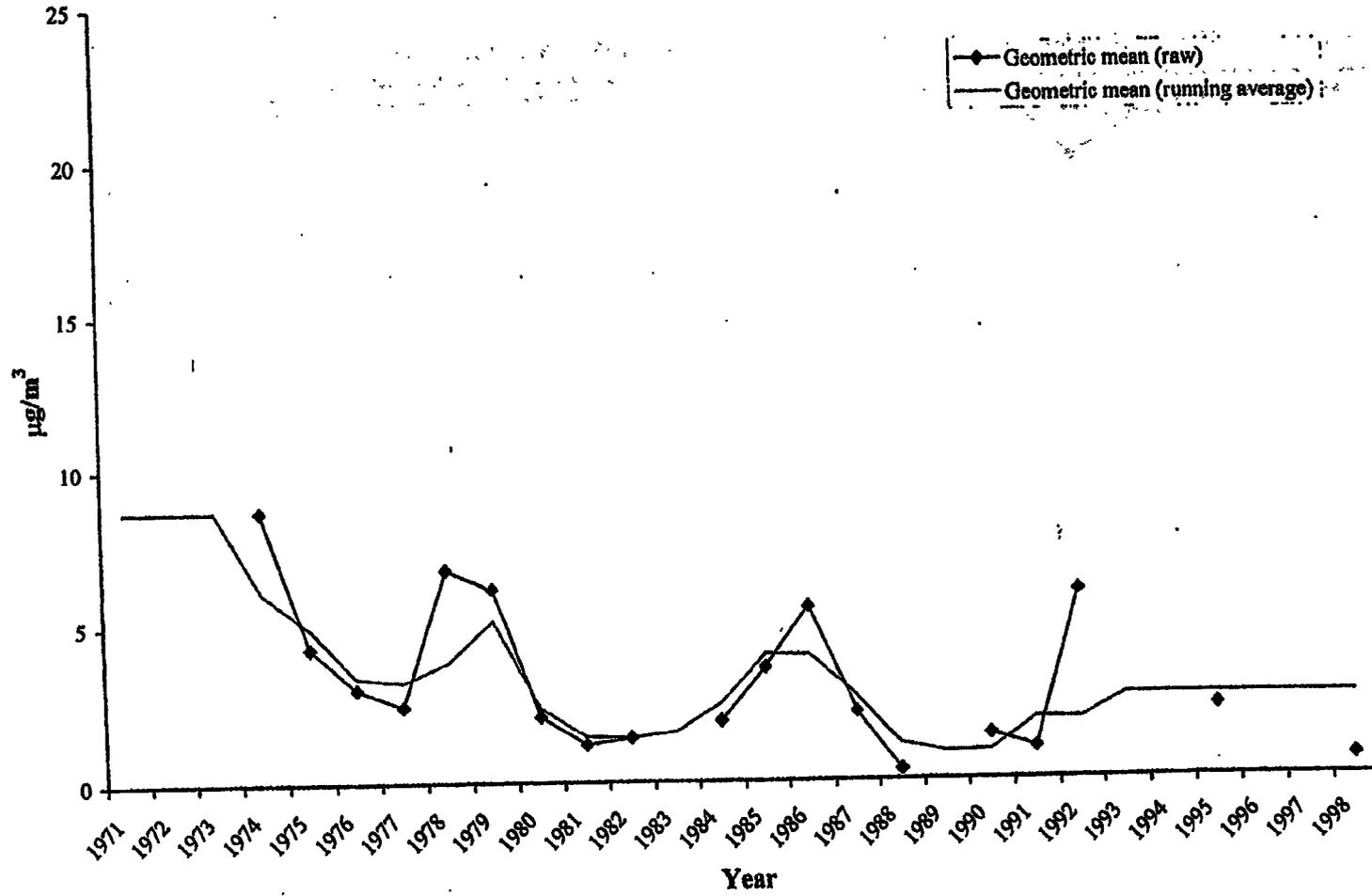
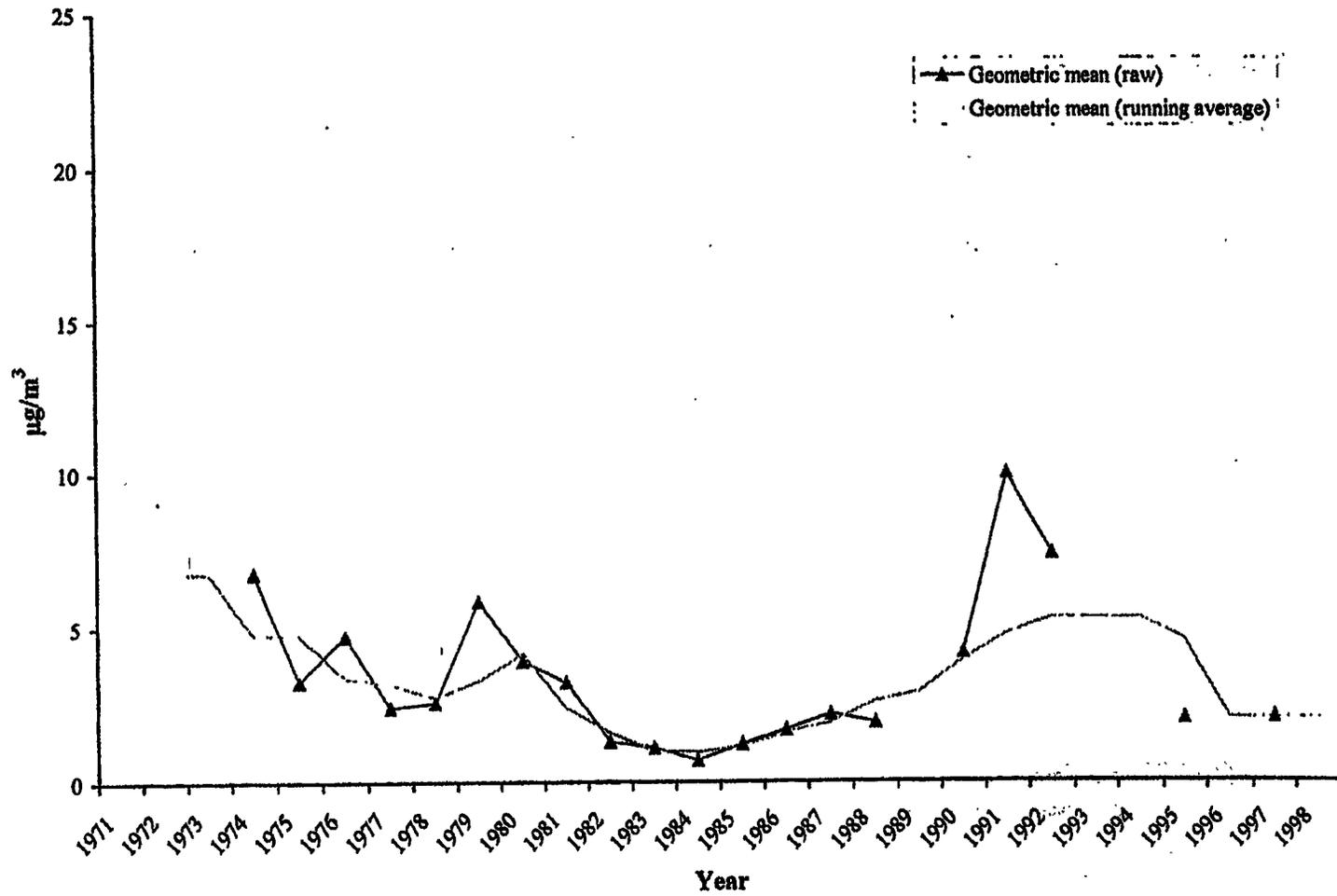


Figure 19: C.A. Packing – Castle Hayne



IHF29149

Figure 20: Chromic Acid – Castle Hayne

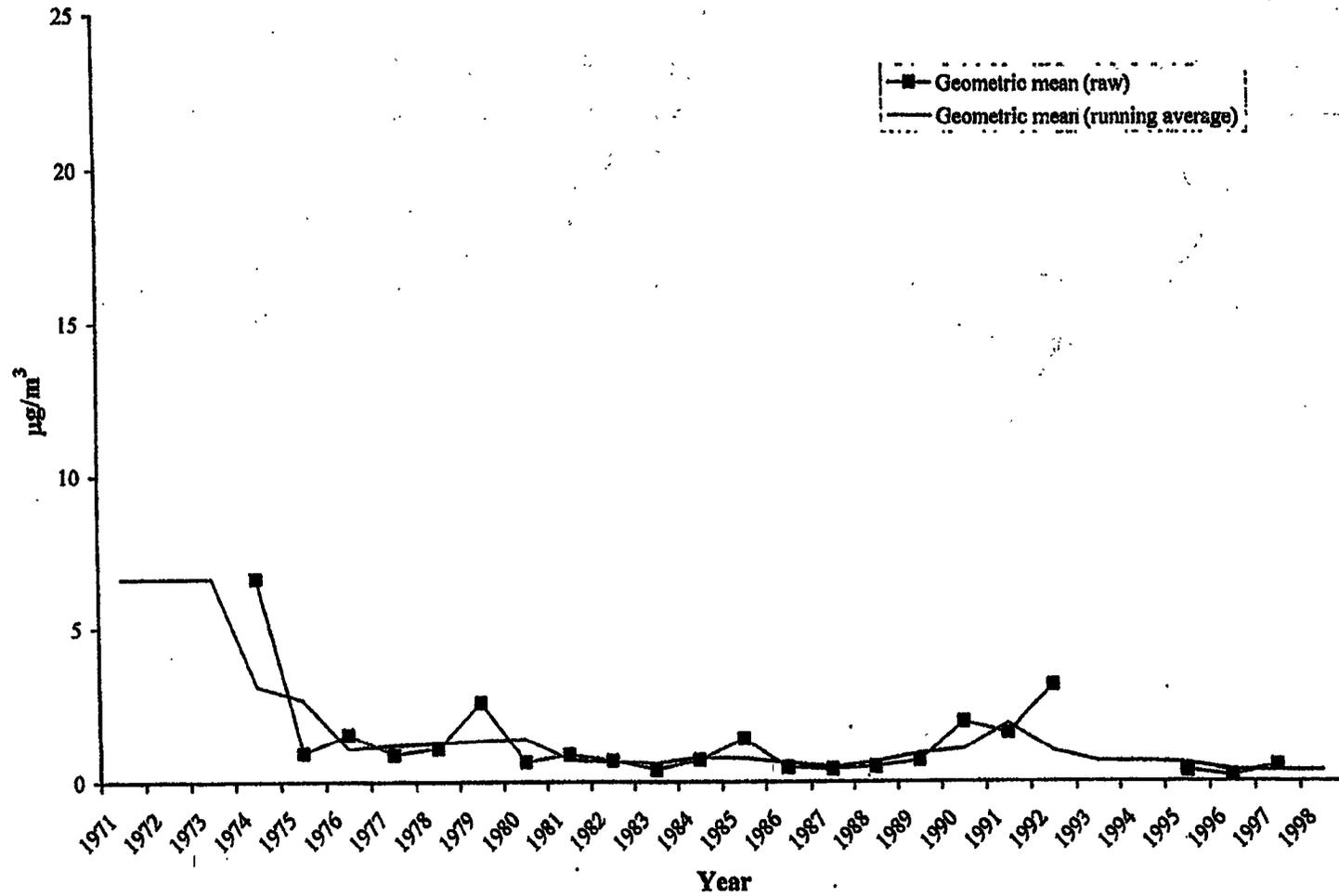
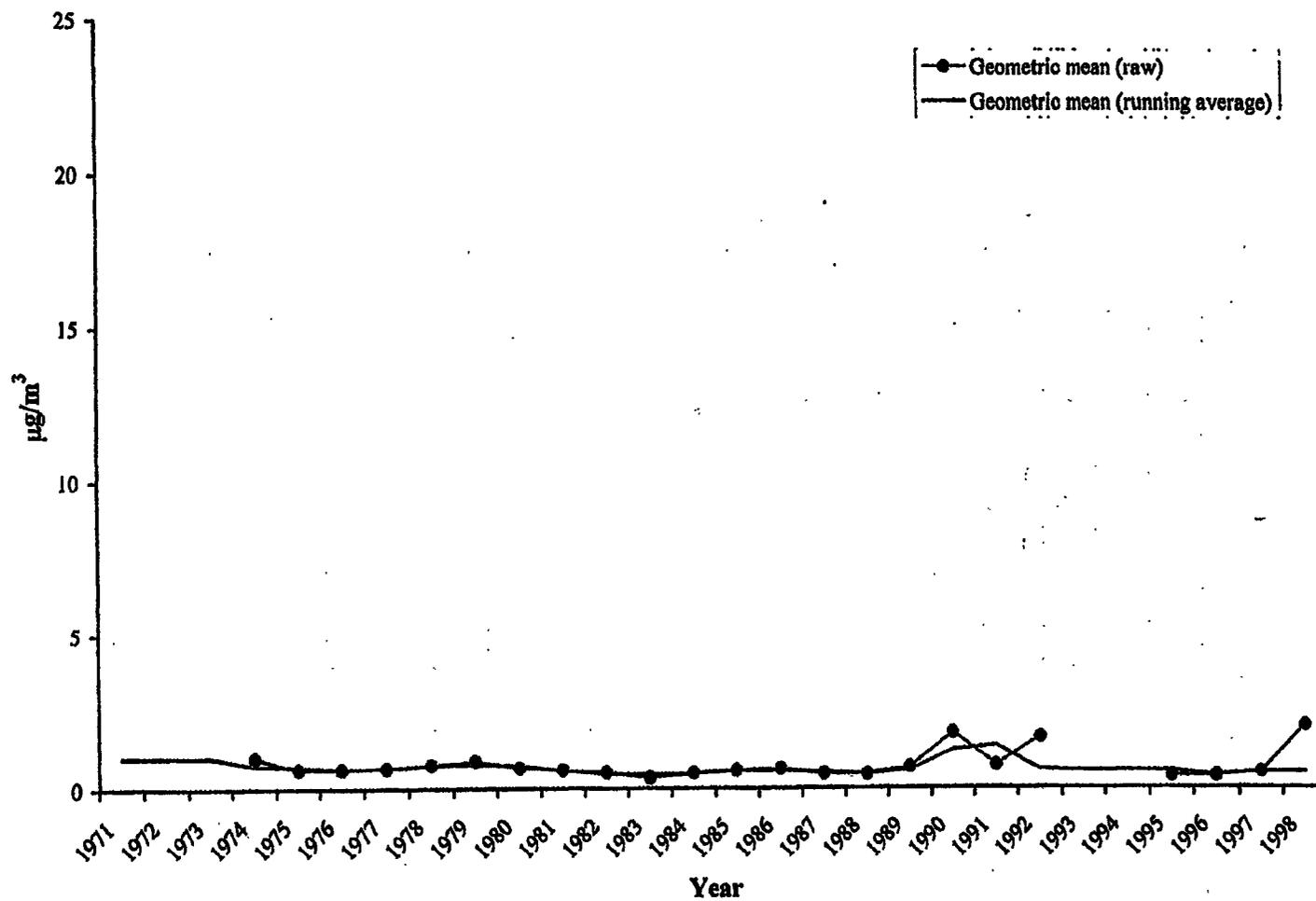


Figure 21: Combined low exposure areas – Castle Hayne



IHF29151

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Figure 22: Scatterplot of peak versus cumulative exposure, cohort (n=1472)

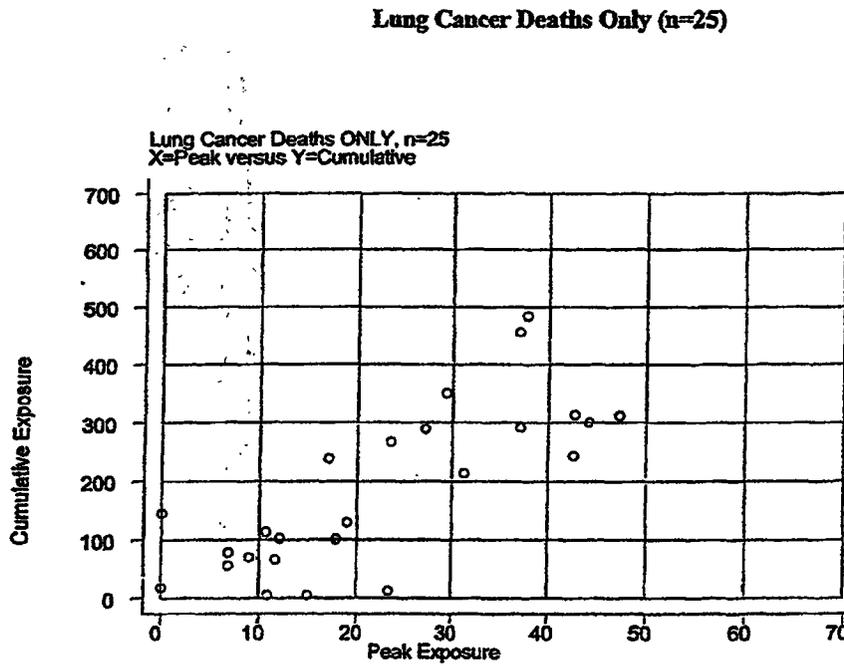
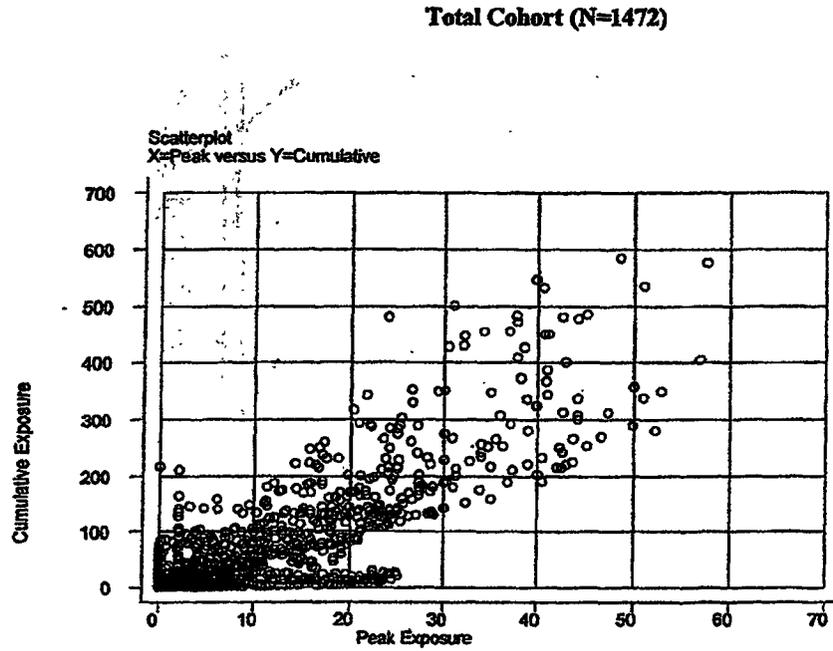
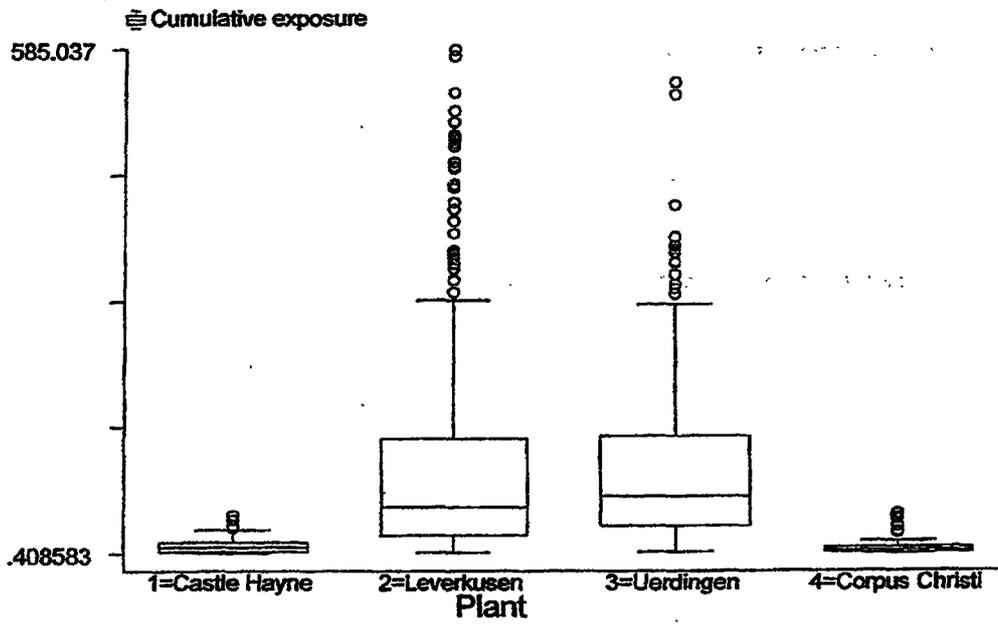
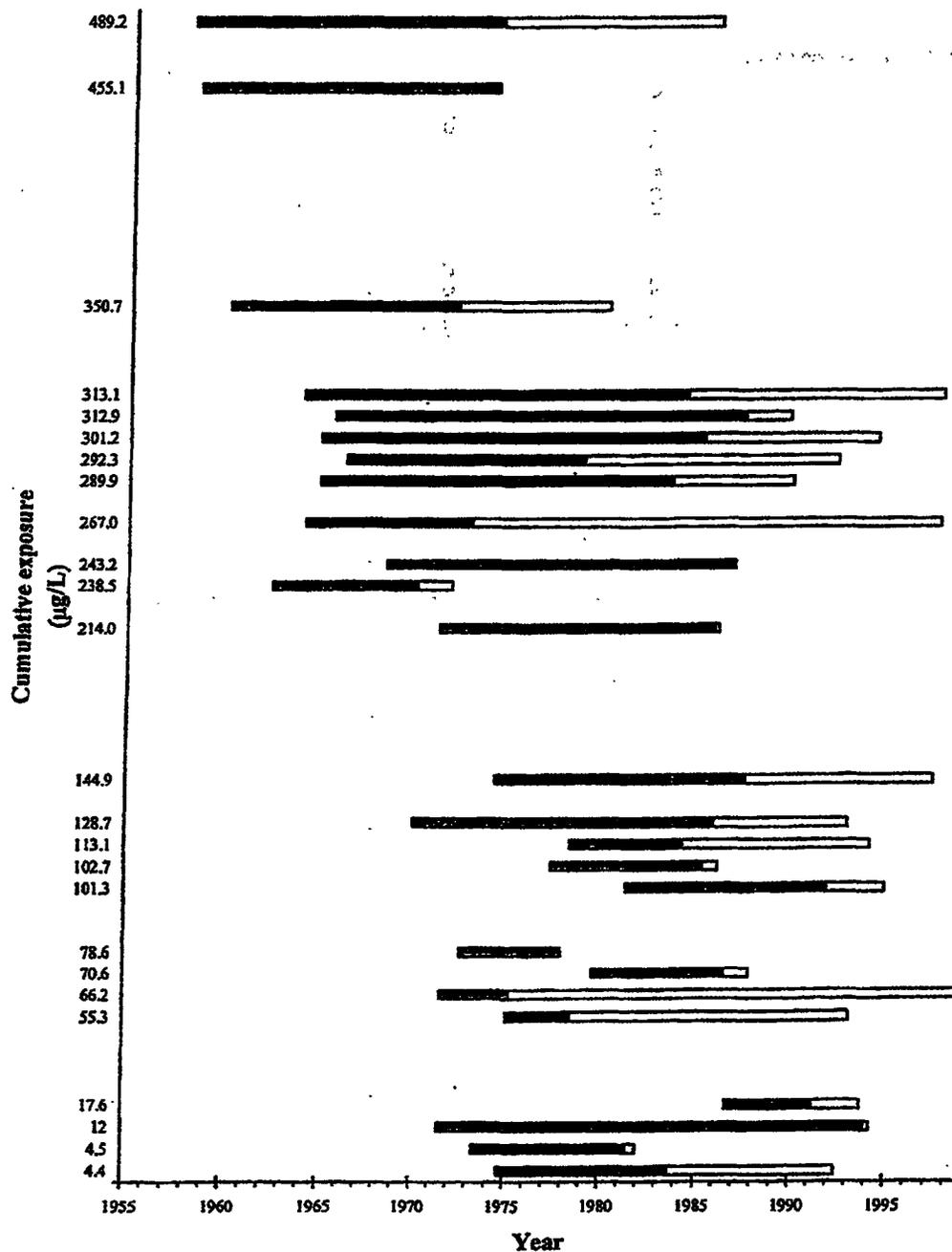


Figure 23: Box and whisker plot of distribution of cumulative exposure by plant



MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

Figure 24: Year of hire, separation and death for 25 lung cancer cases



**Appendix**

## APPENDIX

No.	MAJOR / Minor Category of Death	ICD-9 Codes NIOSH rates 1979-present	ICD-9 Codes German rates 1979-present
Major_01	<b>TUBERCULOSIS</b>		
1	Respiratory Tuberculosis	010-012	001-139
2	Other Tuberculosis	013-018	
Major_02			
3	MN of Lip	140	140
4	MN of Tongue	141	141
5	MN of Other Parts of Buccal Cavity	142-145	142-145
6	MN of Pharynx	146-149	146-149
Major_03	<b>MN OF DIGESTIVE ORGANS AND PERITONEUM</b>		
7	MN of Esophagus	150	150
8	MN of Stomach	151	151
9	MN of Intestine Except Rectum	152-153	152, 153
10	MN of Rectum	154	154
11	MN of Biliary Passages, Liver, and Gall Bladder	155.0, 155.1, 156	155
12	MN of Liver, not Specified	155.2	156
13	MN of Pancreas	157	157
14	MN of Peritoneum and Other and Unspecified of Digestive Organs	158, 159	158, 159
Major_04	<b>MN OF RESPIRATORY SYSTEM</b>		
15	MN of Larynx	161	161
16	MN of Trachea, Bronchus and Lung	162	162
17	MN of Other Parts of Respiratory System	160, 163-165	160, 163-165
Major_05	<b>MN OF BREAST</b>		
18	MN of Breast	174-175	Unused
Major_06	<b>MN OF FEMALE GENITAL ORGANS</b>		
19	MN of Cervix Uteri	180	Unused
20	MN of Other and Unspecified Parts of Uterus	179, 181, 182	Unused
21	MN of Ovary, Fallopian Tube, and Broad Ligament	183	Unused
22	MN of Other Female Genital Organs	184	Unused

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

<b>Major_07</b>	<b>MN OF MALE GENITAL ORGANS</b>		
23	MN of Prostate	185	185
24	MN of Other Male Genital Organs	186, 187	186, 187
<b>Major_08</b>	<b>MN OF URINARY ORGANS</b>		
25	MN of Kidney	189.0-189.2	189
26	MN of Bladder and Urinary Organs	188, 189.3-189.9	188
<b>Major_09</b>	<b>MN OF OTHER AND UNSPECIFIED SITES</b>		
27	MN of Skin	172, 173	172, 173
28	MN of Eye	190	190
29	MN of Brain and Other Parts of Nervous System	191, 192	191, 192
30	MN of Thyroid Gland	193	193
31	MN of Bone	170	170
32	MN of Connective Tissue and Soft Tissue	171	171
33	MN of Other and Unspecified Sites (Minor Category)	194-199	194-199
<b>Major_10</b>	<b>NEOPLASMS OF LYMPHATIC AND HEMATOPOIETIC TISSUE</b>		
34	Lymphosarcoma and Reticulosarcoma	200	200
35	Hodgin's Disease	201	201
36	Leukemia and Aleukemia	204-208	204-208
37	Other Neoplasms of Lymphatic and Hematopoietic Tissue	202, 203	202, 203
<b>Major_11</b>	<b>BENIGN AND UNSPECIFIED NATURE NEOPLASMS</b>		
38	Benign Neoplasms of the Eye, Brain, and Other Parts of Nervous System	224, 225	210-239
39	Neoplasms of Unspecified Nature of Eye, Brain and Other Parts of Nervous System	237.5-237.9, 239.6-239.7	Unused
40	Other Benign and Unspecified Nature Neoplasms	210-223, 226- 237.4, 238.0-239.5, 239.8-239.9	Unused
<b>Major_12</b>	<b>DIABETES MELLITUS</b>		
41	Diabetes Mellitus	250	250

IHF29157

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

<b>Major_13</b>	<b>DISEASES OF THE BLOOD AND BLOOD FORMING ORGANS</b>		
42	Pernicious Anemia	281.0, 281.9	280-289
43	Anemias of Other and Unspecified Type	280, 281.1-281.8, 282-285	Unused
44	Coagulation Defects, Purpura and Other Hemorrhagic Conditions	286, 287	Unused
45	All Other Disease of Blood Forming Organs	288, 289	Unused
<b>Major_14</b>	<b>MENTAL, PSYCHONEUROTIC AND PERSONALITY DISORDERS</b>		
46	Alcoholism	303	303
47	Other Mental Disorders	290-302, 304-319	290-302, 304-319
<b>Major_15</b>	<b>DISEASES OF THE NERVOUS SYSTEM AND SENSE ORGANS</b>		
48	Multiple Sclerosis	340	Unused
49	Other Diseases of the Nervous System and Sense Organs	320-337, 341-389	320-389
<b>Major_16</b>	<b>DISEASES OF THE HEART</b>		
50	Rheumatic Heart Disease, Including Fever	390-398	390-398
51	Ischemic Heart Disease	410-414	410-414
52	Chronic Disease of Endocardium	424	Unused
53	Other Myocardial Degeneration	429.0, 429.1	Unused
54	Hypertension with Heart Disease	402, 404	401-405
55	Other Diseases of the Heart	420-423, 425-428, 429.2-429.9	420-429
<b>Major_17</b>	<b>OTHER DISEASES OF THE CIRCULATORY SYSTEM</b>		
56	Hypertension without Heart Disease	401, 403, 405	Unused
57	Cerebrovascular Disease	430-438	430-438
58	Diseases of the Arteries, Veins & Pulmonary Circulation	415-417, 440-459	415-417, 440-459
<b>Major_18</b>	<b>DISEASES OF THE RESPIRATORY SYSTEM</b>		
59	Acute Respiratory Infections Except Influenza and Pneumonia	460-466	460-466
60	Influenza	487	487
61	Pneumonia (except newborn)	480-486	480-486
62	Chronic and Unspecified Bronchitis	490, 491	490, 491
63	Emphysema	492	492

MULTI-PLANT CHROMATE COHORT MORTALITY STUDY

64	Asthma	493	493
65	Pneumoconioses and Other Respiratory Diseases	470-478, 494-519	470-478, 494-519
Major_19	<b>DISEASES OF THE DIGESTIVE SYSTEM</b>		
66	Diseases of the Stomach and Duodenum	531-537	530-537
67	Hernia and Intestinal Obstruction	550-553, 560	550-553, 560
68	Cirrhosis of the Liver	571	571
69	Other Diseases of the Digestive System	520-530, 540-543, 555-558, 562-570, 572-579	520-529, 538-545, 555-558, 561-570, 572-579
Major_20	<b>DISEASES OF THE GENITOURINARY SYSTEM</b>		
70	Acute Glomerulonephritis Nephrotic Syndrome and Acute Renal Failure	580, 581, 584	580-589
71	Chronic and Unspecified Nephritis and Renal Failure and Other Renal Sclerosis	582, 583, 585-587	590-608
72	Infection of Kidney	590	Unused
73	Calculi of Urinary System	592, 594	Unused
74	Hyperplasia of Prostate	600	Unused
75	Other Diseases of Male Genital Organs	601-608	Unused
76	Diseases of the Breast	610, 611	Unused
77	Diseases of the Female Genital Organs	614-629	Unused
78	Other Genitourinary System Diseases	588, 589, 591, 593, 595-599	Unused
Major_21	<b>DISEASES OF THE SKIN AND SUBCUTANEOUS TISSUE</b>		
79	Infections of the Skin and Subcutaneous Tissue	680-686	680-709
80	Other Diseases of the Skin and Subcutaneous Tissue	690-709	
Major_22			
81	Arthritis and Spondylitis	711-716, 720, 721	710-739
82	Osteomyelitis and Periostitis	730	Unused
83	Other Diseases of MS System	710, 717-719, 722-729, 731-739	Unused