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Assessment of Exposure to Chemicals in a Complex Work Environment

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Exposure information was evaluated for two large chemical manufacturing facilities and a research and development center in support of occupational health studies of employees assigned to these facilities. Methodology and rationale underlying the exposure categorization are provided, and descriptive exposure statistics are presented for a sample of 774 employees. Analysis of work patterns and exposure profiles revealed that 1) employee transfers among various production work areas did not follow a predictable pattern, 2) over 41% of the chemicals identified were present in multiple work areas, and 3) individuals exposed to one chemical of toxicologic interest were also likely to be exposed to other similarly toxic materials. The use of both work area and chemical-specific exposure measures is recommended, as each may be helpful in addressing etiologic questions regarding complex work environments.

Key words: **carcinogenesis, case-control methods, occupational epidemiology, chemical manufacture**

INTRODUCTION

One of the more pressing needs in occupational cancer research is for the development of agent-based classifications of exposure [Cole and Merletti, 1980]. Several distinct approaches for obtaining such exposure information have arisen. Investigators who conduct broad population- or disease-based research have developed systems to classify chemical agent exposures using either in-depth interviews coupled with technical review of various industrial workplaces or publicly available environmental data bases [Gérin et al., 1985; Hoar et al., 1985]. Recently, the use of biological markers has been advocated as a means of selectively improving exposure assessments [Perera et al., 1982].

Researchers whose primary focus is the study of specific industries or work environments have most often relied on linkage of company personnel and other records to describe and then categorize employee exposures [Lloyd and Ciocco, 1969; Gamble and Spirtas, 1976; Ott et al., 1975; Corn and Esmen, 1979; Bond et al.,

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1986]. The usual strategy has been to define work areas that are internally homogeneous in regard to exposure profiles and to link specific agent exposures to employees through knowledge of past work assignments and environmental data relevant to each work area.

The present effort concerns a particular chemical manufacturing and research environment that dates back to the 1920s. Our major goal was to develop an exposure classification system that would be applicable to a variety of epidemiologic research projects. Thus, we sought to retain the maximum of detail regarding the specific occupational exposures that had occurred in this workplace over the 50 year period of interest. Using a lowest common denominator approach, we relied primarily on data contained in historical employment and chemical production records. Linkage of exposure information to individual employees was based on determination of the work area assignments of employees and the nature of chemical processing associated with each work area.

In this report we: 1) describe the methodology supporting our categorization of work exposures; 2) present descriptive exposure statistics for 774 male employees included in a nested case-control study of multiple myeloma, non-Hodgkin's lymphoma, and leukemia [Ott et al., 1989]; and 3) discuss the implications of the methodology and the observed exposure profiles on the conduct of etiologic research related to cancer.

METHODS AND MATERIALS

Research Setting

In 1979 a long-term mortality follow-up study of Union Carbide employees in the Kanawha Valley of West Virginia was initiated [Rinsky et al., 1988]. The final study cohort consisted of 29,139 men who had ever worked at one of three selected company locations between January 1, 1940, and December 31, 1978. The facilities at these locations included two large chemical manufacturing complexes (one in South Charleston, West Virginia, and a second in Institute, West Virginia) and a research and development center. There were also 4,579 women employees who had been assigned to these company locations. However, the women worked primarily in salaried classifications (78%) and for short time periods (71% were employed for less than 5 years by the company). Since follow-up was judged to be incomplete, women were excluded from both the prior cohort analyses and the present study.

The complicated nature of these work environments was recognized at the outset of the study. Consequently, efforts were begun in the late 1970s to reconstruct a history of chemical processing at the production facilities. Two retired senior manufacturing personnel were contracted to review available records and prepare chronological listings of substances present in each chemical processing area as well as to describe briefly the processes. The listings were compiled from resources that included production reports, manuals of industrial processes, and engineering records. The reconstruction of process history was approximate because of the size of the task, the necessity of relying on personal recall and judgment in many instances, and because certain operations dated as far back as 1925. Oversight guidance was provided by site industrial hygienists. Over 1,000 chemicals were specifically identified as having been used or produced at some time between 1925 and 1978 within these facilities. The collected materials provided the core information for developing an exposure classification system to reflect the many agent exposures within these work environments.

Although a mortality analysis of the study cohort through 1978 showed fewer observed than expected cancer deaths, there was an increase in lymphosarcoma and reticulosarcoma deaths (48 observed vs. 34.0 expected deaths based on comparison to U.S. white male death rates) and marginal increases in deaths attributed to other lymphatic and hematopoietic tissue cancer (18 observed vs. 16.3 expected deaths) and leukemia (54 observed vs. 49.1 expected deaths) [Rinsky et al., 1988]. Additional analyses based on a regrouping of diagnosis categories to identify separately non-Hodgkin's lymphoma, multiple myeloma, and leukemia indicated a relative increase in standardized mortality ratios with longer employment for each of these categories and supported the need for case-control studies of these diseases. In turn, planning for the case-control studies gave added impetus to completing the exposure classification effort.

Overall Strategy

The recognition of underlying etiologic relationships as occupational in origin is highly dependent on: 1) the degree of heterogeneity of exposure within the examined population; 2) the ability to define indices that reflect the extent of exposure to each causative factor; and 3) sufficiently large numbers of exposed individuals to detect the relationships. Of the above elements, the only one directly under investigator control is the selection of exposure indices. Three measures of exposure were developed for this purpose, one based on identifiable work areas, a second based on specific exposure agents, and a third based on chemical structure groups.

In many respects, these exposure measures complement one another. The classification based on assignment to work areas subdivides all production and nonproduction areas and work activities into mutually exclusive and exhaustive categories, such that every job assignment maps into a single work area. Work areas describe unique exposure settings. However, the chemical exposure profiles within work areas may vary widely in complexity. Single process chemical units can give rise to a rather limited list of agents and exposure conditions, whereas multiprocess and specialty chemical units give rise to variable and difficult to quantify opportunities for exposure. Nevertheless, using this approach, evidence can be developed of work-related disease occurrences that are localized to specific work areas. Clearly, it may not be possible to isolate the offending agent or agents.

Classification based on the presence of specific environmental agents and chemical structure groups allows the grouping of individuals across work areas based on a shared exposure. This increases statistical power with respect to the specific agent at the expense of increased heterogeneity of the exposure milieu. Although it is possible to estimate the extent of exposure to a given agent for individuals assigned to production units, this is not generally the case for nonproduction work assignments (e.g., maintenance, distribution, warehouse, construction, and so forth). In fact, no attempt was made to associate specific substances with employment in these work assignments, other than exposures that are peculiar to a given trade, such as asbestos with the insulation trade. Thus, there is more overall uncertainty although greater specificity for a specific exposure agent versus a work area categorization approach. With the agent classification approach, the critical decision point is the selection of par-

TABLE I. Subdivision of Production and Nonproduction Areas and Activities Into Defined Work Areas in Three UCC Facilities, 1940–1978

Functional activity	No. of distinct work areas
Administrative and business services	4
Construction and maintenance	11
Production support	7
Research and development	6
Production	83
Acid/ester/anhydride units	5
Acrylate units	2
Alcohol/ketone/aldehyde units	7
Amines units	2
Ethylene/propylene-derivative units	4
Hydrocarbons units	18
Miscellaneous chemicals units	10
Oxide-derivative units	14
Specialty/developmental chemicals units	5
Vinylic monomers and polymers units	16
Total	111

ticular chemicals to be evaluated from among the 1,000+ candidates. With the work area approach, the concern is how narrowly or broadly to define work areas.

Definition of Work Areas

There are six major activities within the facilities included in this study: 1) administrative and business services; 2) construction; 3) plant-wide maintenance; 4) production support services; 5) research and development; and 6) production. Employees engaged in administrative and business activities generally worked in office settings separate from the production operations. Employees assigned to construction included tradesmen and laborers who constructed new facilities and expansions of existing facilities. Plant-wide maintenance work was carried out by maintenance tradesmen and laborers who could be assigned duties in central shop areas or throughout the production facilities. Production support encompasses: material transfer and distribution activities; janitorial and groundskeeping work; utilities generation (power plant operation) and distribution; and industrial hygiene, health, security, and safety support. Employees assigned to research and development activities worked in laboratory settings or were active in new plant start-ups throughout the production facilities. Also included in this group were engineering design personnel. Finally, the employees assigned to chemical production included operators, foremen, and some maintenance personnel who were assigned to specific production units.

Work areas were defined within the activity groups, and separately for the Institute and South Charleston plant facilities. The research and development center was treated as part of the South Charleston complex. A detailed subdivision of production work areas was possible and desirable since distinct work areas with relatively homogeneous exposure profiles could be reasonably defined for production units (see Table I). For each employee, duration of assignment in the work area was calculated as an index of exposure to that area.

The potential for occupational exposure to plant materials existed for many maintenance, production support services, and research employees. However, on a historical basis, such exposures were not well defined. This is because either the individual employees have been assigned tasks throughout the plant complex on an ad hoc basis (as in maintenance work) or because the materials being worked with changed frequently (as in a research setting). Thus, for men in nonproduction jobs, fewer, broader work area groupings were defined for analysis purposes. Specific trades groups such as electricians and insulators were separately identified.

Definition of Environmental Agents

Well over 1,000 substances (raw materials, catalysts, intermediates, and products) were initially identified through the agent listings developed for each chemical processing unit. After editing to eliminate synonyms, biologically inert materials, and different formulations of essentially the same products and to replace trade names with generic chemical names when possible, there remained an edited chemical agent file of 1,020 unique substances linked to the various chemical processing units on a year-by-year basis.

With the assistance of chemists and toxicologists, all agents were subcategorized by chemical structure using as a guide the functional classification described by Soderman [1982]. Several chemical groups were formed based on end-use rather than active structure group. For example, antioxidants and catalysts were separately identified. A summary list of the 52 major groups is provided in Table II. A further subdivision of chemical families by size of molecule was not utilized in this study. The present grouping was aimed at separating agents by structures likely to have importance relative to carcinogenesis. The same chemicals could easily be regrouped to reflect other dimensions of toxicity such as absorption, distribution, and excretion characteristics of the molecules, as well as known organ-specific toxicity.

Chemical groups of notable concern from a carcinogenic standpoint included epoxides, halogenated compounds, fused cyclics, nitriles, and vinylics [Soderman, 1982; Fishbein, 1979]. Twenty such groups of particular interest for the case-control study are designated in Table II. An individual was considered positive for exposure to a chemical group based on the presence of any member of that group in a work area to which the employee was assigned. Often, however, multiple members of a chemical group were found in areas in which any one was present. The only index of exposure to a chemical group was the duration of contact (measured in years) with at least one member of that group. Analysis of exposure–response relationships based on assessing exposure to groups of structurally similar chemicals has many limitations in terms of identifying possible adverse health effects. However, this assessment was only considered an adjunct to work-area and chemical-specific analyses.

There were also 21 individual chemicals selected for analysis based on their carcinogenic potential and their use in multiple work areas (see Table III). If a particular substance had been used in only one work area (this was true for 598 of the 1,020 identified environmental agents), essentially all information available relative to that substance was contained within the work area analyses. Therefore, these 598 agents were not considered as candidates for individual analysis. On a selective basis, exposure intensity scores have been developed for individual agents, but have not been used in the present case-control research.

TABLE II. Subdivision of Chemicals by Major Functional Groups at Three UCC Facilities, 1940–1978

Chemical group	No. of chemicals in group	Chemical group	No. of chemicals in group
Acrylates[a]	15	Glycols	18
Alcohols	46	Haloalkanes[a]	16
Aldehydes saturated[a]	25	Haloaryls[a]	8
Aldehydes unsaturated[a]	11	Haloethers[a]	4
Alkanes	15	Halohydrins	3
Alkenes[a]	18	Inorganic irritants	27
Alkyl acids	25	Isocyanates	6
Alkyl esters	30	Ketones	21
Alkyl ethers	16	Lactones	2
Alkyl sulfates[a]	6	Mercaptans	7
Alkylamines	31	Metal salts high tox[a]	42[b]
Alkylene amines[a]	22	Metal salts low tox	73
Amine alcohols	20	Nitriles[a]	11
Amides	5	Peroxides[a]	9
Anhydrides[a]	12	Phthalates[a]	21
Anionic surfactants	6	Poly ethers	71
Antioxidants[a]	12	Pyrans	4
Aromatic amines	12	Pyridines[a]	8
Aromatic esters	2	Resins and latexes	45
Aryl ketones	3	Silicates	7
Aryls[a]	27	Sulfones	3
Carbamates	3	Triols	10
Catalysts	46	Unclassified	90
Cationic surfactants	2	Vinylics[a]	26
Epoxides[a]	15		
Epoxy esters	4		
Fused cyclics[a]	20		
Glycol ethers	39		

[a]Chemical groups selected for emphasis in the case-control study.
[b]Includes cadmium, chrome, cobalt, manganese, mercury, nickel, silver, tin, and vanadium compounds.

Selection of Subjects

The employees included in the case-control study consisted of 129 men with lymphatic or hematopoietic tissue malignancies except Hodgkin's disease and 645 controls selected from the total cohort according to an unmatched incidence density sampling design described by Greenland and Thomas [1982].

Linking Exposure Measures to Employees

Linkage of potential chemical exposures to individual employees required a history of assignments for each employee, an algorithm to map assignments (designated by payroll account numbers) into work areas, and a history of chemical usage associated with each work area. The steps required to complete the linkage are outlined in Figure 1. The record linkage system was dynamic, since both payroll account numbers and chemical usage changed over time. Dates, therefore, had to be part of the link between account numbers and work areas. During their working careers, employees could be assigned to multiple work areas and, consequently, experience exposure to many different chemicals. To determine whether employee

TABLE III. Individual Chemicals Appearing in More Than One Work Area and Selected for Analysis at Three UCC Facilities, 1940–1978

Chemical[a]	No. of work areas
Acetaldehyde	16
Acetonitrile	5
Acrolein	7
Acrylonitrile	10
Allyl alcohol	4
Allyl chloride	3
Benzene	22
Butadiene	10
Butylene oxide	2
Dichloroethyl ether	7
Dioxane	3
Epichlorohydrin	3
Ethylene chlorohydrin	4
Ethylene dichloride	11
Ethylene oxide	29
Formaldehyde	6
Ketene	2
Propylene oxide	17
Styrene	9
Vinyl acetate	10
Vinyl chloride	6

[a]Certain chemicals of interest such as dimethyl sulfate are not included here, since alkyl sulfates are being examined as a group and most members of this group tended to be present in the same work areas.

transfers between work areas followed predictable patterns and whether exposures to any given chemical were independent of exposures to other selected chemicals, correlation analyses were performed.

RESULTS

The combined case-control group of 774 men represents 2.7% of the total cohort of 29,139 employed men. In general, individuals selected for the case-control study had earlier hire dates compared with the overall distribution of employees in the study cohort. For example, 82.9% (642) of the case-control employees had been hired before 1950 compared with 53.8% (15,677) of the total employee cohort. Case-control employees also had longer employment durations than employees in the overall cohort. Thus, whereas 41.7% (12,151) of the men in the total cohort worked for 10+ years in the facilities, 57.8% (447) of the men in the case-control group had worked that long.

Using the algorithm described in Figure 1, the number of men assigned to each work area and to each chemical exposure category was determined based on cumulative work history information. The percentage of the work force ever assigned to each major activity group was 10.1% for administrative and business services, 34.9% for construction, 25.8% for plant-wide maintenance, 38.8% for production support

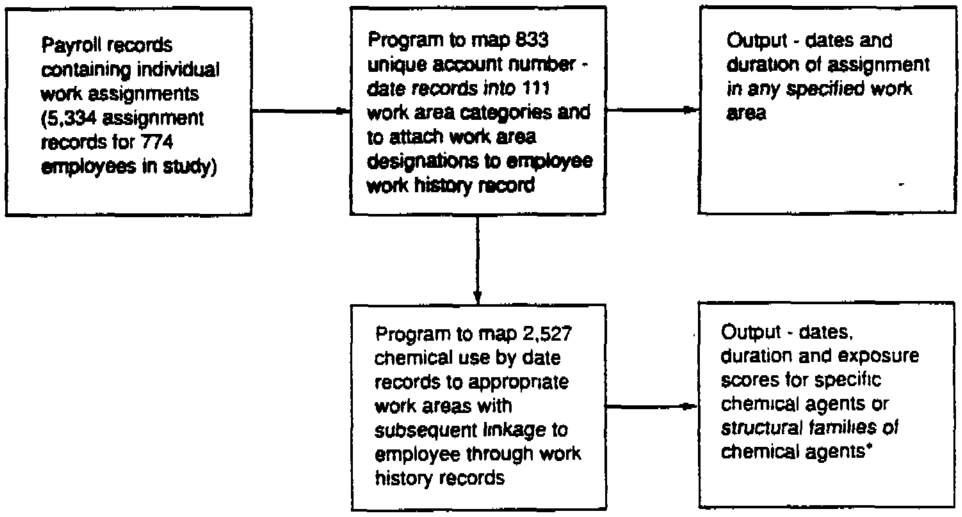

Fig. 1. Outline of job history record processing to obtain exposure measures by employee. *Intensity of exposure scores have been selectively developed for individual chemicals such as ethylene oxide, but were not used in this research.

services, 25.5% for research and development, and 25.8% for production. Assignments in construction and production support services were of relatively short duration, with 47 and 52% of the men, respectively, having worked in these activities for less than 1 year. Maintenance and production assignments were of longer duration, with 45 and 51% of the men, respectively, having worked in these activities for at least 10 years.

In Table IV, the distribution of employees within work areas is given by production status and by employment duration within work area. The nonproduction activity groups accounted for 28 of the 111 work areas. Since these work areas were defined rather broadly, there were far more employees assigned per nonproduction work area than per production work area.

There were 200 men in the case-control group who had ever worked in production areas. Considering all chemicals and cumulative work histories, these production workers came in contact with an average of 58 different chemicals during their assignments in production work areas. For the 52 selected chemical groups, the distribution of employee contact with one or more members of these groups among the 200 production employees in the sample is given in Table V. The percentage of production employees ever exposed ranged from 1.5% for carbamates, cationic surfactants, and epoxy resins to 90% for the unclassified group of chemicals. For more important chemical groups such as vinylics, 78.5% of the production employees had ever worked with one or more of these substances, and 45.5% had worked with these substances for at least 5 years. Thus, at some point during their careers, a high percentage of production employees worked in a production department where vinylics such as vinyl chloride were present. Members of other chemical groups, such as alcohols, inorganic irritants, and metal salts of low toxicity, were also relatively ubiquitous in the production facilities.

TABLE IV. Distribution of 111 Work Areas by Production/Nonproduction Status of Work Area and by Number of Male Employees Assigned to Area

No. of employees	No. of distinct work areas			
	Ever employed in area		Employed 5+ years in area	
	Production[a]	Nonproduction[a]	Production	Nonproduction
0	5	0	28	2
1–4	38	1	46	4
5–9	26	4	6	6
10–24	12	9	3	11
25–74	2	8	0	5
75+	0	6	0	0

[a]There were 83 production and 28 nonproduction work areas in the study.

Similar information is provided in Table VI for 21 individual chemicals. As would be expected, lower percentages of production employees were exposed to individual substances than to chemical groups. Exposure percentages among production employees ranged from 3.5% for butylene oxide to 48.0% for benzene. With a 5 year minimum period of contact, the highest exposure percentage was 26.5% for benzene.

Correlation analyses were performed for men ever assigned to production areas to evaluate the patterns of employee contact with different members of chemical groups, individual chemicals, and work areas. Product moment correlation coefficients were calculated using each employee's total duration of contact with a particular chemical or work area. The distributional properties of the correlation coefficients calculated from exposure durations are unknown. However, the correlation coefficients were only required to serve as simple measures of association in this application. A summarization of all possible pairwise correlation coefficients among chemicals, chemical groups, and work areas is provided in Table VII.

Focusing on the 21 individual chemicals, the distribution of correlations was skewed to the right, with 18.1% of all correlations exceeding 0.5. There were notably high between-chemical correlations for several chemical subgroups. For example, within a subgroup of six chemicals (dichloroethyl ether, dioxane, epichlorohydrin, ethylene chlorohydrin, ethylene dichloride, and ethylene oxide), 13 of the 15 correlation coefficients were greater than 0.5. Vinyl chloride, acrylonitrile, and vinyl acetate were also highly correlated, presumably because these three chemicals were often used concomitantly to produce copolymers. Finally, allyl alcohol, allyl chloride, acrolein, epichlorohydrin, and ketene shared relatively high correlation coefficients with one another.

A somewhat similar pattern of correlations emerged when chemical groups were substituted for individual chemicals in the analyses. However, 89% rather than about 64% of all correlations were positive, indicating more overlap in exposures to broad families of chemicals. Among all 52 chemical groups, pairwise correlation coefficients exceeded 0.5 in 12.8% of the comparisons.

Analyses among the various production work areas revealed a totally different pattern of interrelationships. Among the 52 production work areas with three or more employees having assignments in the area, most pairwise correlations were slightly negative and only five (0.3%) exceeded 0.5. The relative independence of work area

TABLE V. Percent of Employees Exposed to One or More Chemicals Within 52 Chemical Groups Among 200 Production Workers at Three UCC Facilities, 1940–1978

Chemical group	Ever exposed	Exposed 5 + years
Acrylates	22.0 (44)[a]	11.0
Alcohols	86.5 (173)	54.5
Aldehydes saturated	45.0 (90)	21.0
Aldehydes unsaturated	37.0 (74)	16.0
Alkanes	52.5 (105)	29.0
Alkenes	66.5 (133)	39.0
Alkyl acids	53.0 (106)	27.0
Alkyl esters	46.5 (93)	26.0
Alkyl ethers	56.5 (113)	33.0
Alkyl sulfates	15.0 (30)	7.0
Alkylamines	25.0 (50)	11.0
Alkylene amines	21.5 (43)	8.0
Amine alcohols	23.5 (47)	7.5
Amides	11.5 (23)	5.5
Anhydrides	33.5 (67)	16.5
Anionic surfactants	17.0 (34)	5.0
Antioxidants	38.5 (77)	20.0
Aromatic amines	12.5 (25)	4.0
Aromatic esters	4.5 (9)	—
Aryl ketones	8.0 (16)	2.5
Aryls	55.5 (111)	33.0
Carbamates	1.5 (3)	1.0
Catalysts	55.5 (111)	28.0
Cationic surfactants	1.5 (3)	—
Epoxides	45.5 (91)	23.5
Epoxy esters	1.5 (3)	—
Fused cyclics	22.5 (45)	11.5
Glycol ethers	29.5 (59)	13.0
Glycols	38.0 (76)	16.5
Haloalkanes	45.0 (90)	22.0
Haloaryls	10.0 (20)	3.0
Haloethers	23.0 (46)	11.0
Halohydrins	22.0 (44)	12.0
Inorganic irritants	88.0 (176)	59.5
Isocyanates	3.0 (6)	2.0
Ketones	70.5 (141)	44.0
Lactones	2.0 (4)	1.0
Mercaptans	17.0 (34)	4.5
Metal salts, high toxicity	46.5 (93)	21.5
Metal salts, low toxicity	87.0 (174)	58.0
Nitriles	21.5 (43)	11.5
Peroxides	32.0 (64)	14.5
Phthalates	10.5 (21)	2.5
Poly ethers	31.5 (63)	14.5
Pyrans	3.5 (7)	1.5
Pyridines	14.5 (29)	6.0
Resins and latexes	43.0 (86)	23.5
Silicates	7.0 (14)	2.5
Sulfones	7.5 (15)	2.5
Triols	12.0 (24)	5.0
Unclassified	90.0 (180)	56.5
Vinylics	78.5 (157)	45.5

[a]Total number of employees in parentheses.

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TABLE VI. Percent of Employees Ever Exposed to 21 Specified Chemicals Among 200 Production Workers at Three UCC Facilities, 1940–1978

Chemical	Ever exposed	Exposed 5 + years
Acetaldehyde	30.5 (61)[a]	11.5
Acetonitrile	5.0 (10)	2.5
Acrolein	12.5 (25)	3.0
Acrylonitrile	25.0 (50)	9.0
Allyl alcohol	9.0 (18)	3.0
Allyl chloride	10.0 (20)	4.0
Benzene	48.0 (96)	26.5
Butadiene	30.5 (61)	13.5
Butylene oxide	3.5 (7)	2.0
Dichloroethyl ether	22.5 (45)	11.0
Dioxane	10.5 (21)	4.0
Epichlorohydrin	10.5 (21)	4.5
Ethylene chlorohydrin	18.5 (37)	11.0
Ethylene dichloride	22.0 (44)	9.5
Ethylene oxide	35.5 (71)	20.0
Formaldehyde	15.0 (30)	4.5
Ketene	9.0 (18)	3.0
Propylene oxide	28.5 (57)	15.0
Styrene	13.5 (27)	4.5
Vinyl acetate	40.5 (81)	20.5
Vinyl chloride	28.5 (57)	12.0

[a]Total number of employees in parentheses.

TABLE VII. Distribution of Pairwise Correlation Coefficients for 21 Selected Chemicals, 52 Chemical Groups, and 52 Work Areas Among 200 Male Employees Ever Assigned to Production Areas

Correlation coefficient[a]	21 selected chemicals		52 chemical groups		52 work areas with 3+ individuals assigned to area	
	No.	Percent	No.	Percent	No.	Percent
<−0.100	12	5.7	2	0.2	0	0.0
−0.099 to −0.001	64	30.5	136	10.3	1167	88.0
0.0 to 0.099	25	11.9	246	18.5	102	7.7
0.1 to 0.199	22	10.5	254	19.2	20	1.5
0.2 to 0.299	12	5.7	228	17.2	13	1.0
0.3 to 0.499	37	17.6	290	21.9	18	1.4
0.4 to 0.699	20	9.5	125	9.4	3	0.2
0.7+	18	8.6	45	3.4	2	0.1
Total	210		1326		1326	

[a]For each employee, the duration of exposure (measured in years) was determined for all chemicals, chemical groups, and work areas. Then correlation coefficients were computed using the individual employee as the unit of observation.

assignments among employees reflects the mutually exclusive definition of work areas and, by inference, the lack of strong systematic patterns in the way individuals transferred between work areas. Conversely, many of the chemicals used within each

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production work area were interrelated, thus giving rise to an increased likelihood that individuals exposed to one chemical of toxicologic importance would also be exposed to other similar chemicals.

DISCUSSION

The task of linking personnel and other historical records to conduct a retrospective exposure assessment can be quite onerous. Nevertheless, when the targeted health outcomes (e.g., site-specific cancers) become manifest only many years after initial exposure, this approach appears to make optimal use of admittedly imprecise exposure information, but information that is specific to the relevant exposure period. From an epidemiologic perspective, the lack of precision in the exposure estimates is of concern. Nondifferential misclassification may bias relative risk estimates toward the null, reduce power, and have unpredictable effects on tests of trend in subgroup analyses [Flegal et al., 1986]. In particular, our ability to be specific in associating exposure agents only with production job assignments is a study limitation. In essence, we have presumed that having daily assignments in specific production work areas will lead to greater average exposure opportunities to a given agent than having been assigned to production support or maintenance activities on a plant-wide basis. There is some evidence in other records to support this presumption. For example, review of medical visits related to acute ethylene oxide exposures revealed far higher visit rates among ethylene oxide production personnel than for maintenance personnel, who were only intermittently working in these units. The supplemental work area classification is a partial, but incomplete, solution to the problem of having different levels of knowledge regarding exposure potential within the various work activities. Better tracking of the exposures of nonproduction personnel is needed to support occupational health research. An additional limitation of the exposure assessment is our inability to account for differences in personal work practices that may lead to widely disparate exposures. There is no easy remedy for this limitation.

There are other biologic and statistical impediments to detecting etiologic relationships in complex work environments. An important biologic impediment may be our lack of understanding of the mechanisms of cancer causation, particularly as they relate to low level or intermittent exposures and to the effects of direct-acting carcinogens versus agents that may promote or influence the progress of cancer. Toxicological studies of animals have generally been directed at determining the effects of high intensity exposure to specific agents and have not yet been particularly helpful in addressing the multiple exposure issue.

While genotoxic agents may be of concern at relatively low exposure intensities, the promotional activities of a much broader class of agents may occur only with high intensity exposures, which are less likely in work environments with active industrial hygiene programs. Thus, the mix of complete carcinogens or genotoxic agents and agents capable of promotion could be an important determinant of the overall impact of a work environment on its subject employee population, with genotoxicity playing a dominant role.

A number of large cohort mortality studies have examined cancer mortality rates among persons employed by U.S. chemical, petroleum, and rubber manufacturing companies [Andjelkovic et al., 1976; Delzell and Monson, 1981; Divine et al., 1985; Hanis et al., 1985; Kaplan, 1986; Wen et al., 1983; Wong et al., 1986; Austin and

Schnatter, 1983; Bond et al., 1985; O'Berg et al., 1987; Ott et al., 1985; Ott, 1982; Pifer et al., 1986]. Overall, cancer mortality has generally been found to be less than that of the corresponding U.S. population. Although there are important methodologic concerns regarding these studies (see Savitz and Moure [1984] for a discussion of the petroleum industry studies), the findings argue against exposures to the many different chemicals used in these work settings having substantial independent or multiplicative carcinogenic effects. These findings support a practical epidemiologic strategy emphasizing detection and control of complete carcinogens that would be expected to represent a small fraction of the substances in use in these industries. Of the 21 likely carcinogenic agents noted in multiple work areas of the present work environment, 11 were recognized to be mutagenic, four were negative in mutagenicity studies, and information was incomplete for the six remaining substances. Our exposure assessment strategy does provide for epidemiologic investigation of these substances, and the list of targeted substances can be readily adjusted to accommodate advances in toxicologic knowledge.

For reasons cited by Savitz and Moure [1984], the large cohort study findings do not preclude the possibility of small risk elevations for relatively large segments of the exposed workforce. Such a possibility is difficult to evaluate epidemiologically. Furthermore, if there are many indirect pathways through which low level exposures to a broad group of toxicants influence the risk of cancer, then all but the most direct relationships with individual substances would be hard to identify. The multiple exposure question is particularly difficult to evaluate because of all the possible combinations of exposure. We have attempted to simplify this issue by subcategorizing chemical substances according to structure, thereby reducing the combinations of exposure circumstances to be considered.

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