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Characteristics of Worker Populations: Exposure Considerations in the Selection of Study Populations and Their Analysis

Robert M. Park, Michael A. Silverstein, and Franklin E. Mirer
Health and Safety Department, United Auto Workers International Union, 800 Jefferson, Detroit, Michigan 48214

For many chemical exposures, the most appropriate study populations are among the diverse end-users of the materials rather than the large producers or processors. Important exposures often occur in complex process settings that are not easily characterized but which could be epidemiologically evaluated. Industrial hygiene approaches are needed for characterizing process emissions when the relevant constituents are unspecified. Aggregating study populations from plants where there is a mature labor–management dynamic allows access to the collective memory of the plant populations, a major resource in exposure reconstruction. In population-based studies that apply exposure matrices to interview data, the use of interviewers trained in industrial hygiene would help minimize misclassification. Restricting population-based studies to a subset of employers would also facilitate exposure classification. Analyses using internal exposure comparisons are essential to address noncomparability of study and reference populations. Improved statistical efficiency can be achieved through the latency weighting of exposures and the modeling of exposure–mortality associations using external reference rates. Paradoxical dose–response can arise from imprecise exposure classifications if a worker's duration in the exposure is dependent on exposure level. When exposure data are limited, statistically significant excesses showing paradoxical dose–responses should be interpreted as evidence in support of an exposure effect. **Park, R.M.; Silverstein, M.A.; Mirer, F.E.: Characteristics of Worker Populations: Exposure Considerations in the Selection of Study Populations and Their Analysis. Appl. Occup. Environ. Hyg. 6:436–440; 1991.**

Industrial Characteristics of Study Populations

The evaluation of cancer risks for widely used chemicals frequently has taken the form of mortality studies on populations involved in the production of the material, in derivative processing, or in specific large-scale industrial processes utilizing the material. Recent examples are studies of formaldehyde,[1] acrylonitrile,[2] ethylene oxide,[3] and methylene chloride.[4] However, such populations have often had relatively low exposures compared to workers in many downstream manufacturing processes that use these materials (Table I). A substantial proportion of work-attributable malignancies may occur in end-user populations scattered throughout the manufacturing industry, often in small groups. For many materials, these populations may be a more useful source for epidemiological inference than large-scale operations selected for ease of study.

Some exposures are unique to specific process applications which have complex emissions that are not well characterized (Table II). Nevertheless, these processes need to be generically evaluated in terms of disease risks in order to set priorities and design controls and further investigations. For these studies, innovative industrial hygiene is required not only to parameterize and estimate relative "process exposures" but also to enumerate the plausible or conceivable constituents of complex process emissions that are potentially of biological relevance.

Exposure Representation in Population-Based Studies

Population-based studies systematically identify disease cases from the general population as opposed to searching specific plant populations, craft registries, or other selective sources. This approach facilitates case-finding; however, it may suffer from exposure misclassification because of inconsistent process terminology or material descriptions across the industries sampled, across employers within industrial sectors, between individual study participants or their surrogates, and across time. Deriving consistent exposure histories from interviews requires prior characterization of all industrial settings likely to arise and allows for no interaction between respondents that could facilitate standardization. What is a "machine operator," "coolant," or "solvent" in one context might be quite different in another. Worker awareness of some important exposures may be even more variable. For example, the recent National Cancer Institute (NCI) bladder cancer studies which utilized Bureau of the Census industry and job title codes share some of these limitations.[5,6] Therefore, interviewers trained in industrial hygiene may be needed for population-based studies. Compiling study populations from specific industrial sectors, groups of employers, or plant

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TABLE I. Industrial Processes with Higher Exposures to Materials Than in Their Original Production or Processing

- Polymerizing Systems: spray application of polyurethane, epoxy, or other paint and resin systems generating aerosols containing original reactants and reactive intermediates. Isocyanate systems produce isocyanate monomer, free reactive isocyanate groups, and catalysts such as amines. Partition between the particulate and vapor phases is poorly understood.
- Metal Stamping Operations: oil mists from power presses.
- Machining and Grinding Operations: oil and water-based metalworking fluid components.
- Small-Scale, Batch Sterilization Operations: ethylene oxide.
- Foundries: formaldehyde in "hot box" core-making.
- Solvent Cleaning: such as methylene chloride in paint booth cleaning and plastics fabrication, or perchloroethylene and 1,1,1-trichloroethane in small-scale degreasing.
- Diverse Manufacturing: skin absorption of great variety of specialty organic chemicals by workers in fabrication or assembly activities, particularly when solvents are used for clean-up.
- Contract Maintenance in Oil Refinery, Petrochemical, or Chemical Industry: activities not usually included in studies of this industry.

populations (e.g., using hospital cases with a restricted set of group insurance codes or matched against a roster of employer populations) would favor the development of exposure indices that are more consistent within study populations.

Populations with Accessible Exposure Histories

The limitations of industrial hygiene records for exposure reconstruction in most study situations are well known. Considerable thought has been given to methods for enhancing the available historical data by using expert opinions, usually those of industrial hygienists familiar with the processes.[7] Such methods typically seek plant history from knowledgeable plant personnel. Obstacles to this process include 1) insufficient allocation of plant staff or priority to the tasks, 2) subjective judgments that may be responsive to perceived management interests, 3) tedium resulting from systematic approaches that emphasize rigor over efficiency, 4) biased recall by professionals whose personal experience is derived from work assignments on narrow problems or model systems, and 5) recall bias toward exposures with acute health effects.

The authors have pursued a variation on the "expert opinion" approach which consists of meeting with a group of 8 to 20 employees from a single plant. The group includes both hourly and salaried employees (and retirees) with long histories in the plant (often 30 years or more and sometimes dating from the beginning of operations). Both production and maintenance workers are involved, and management is represented by safety, labor relations, and operations personnel including quality control, laboratory, or engineering staff. Using previously generated department and job dictionaries, the group is guided through an intensive review of plant process history, characterizing departments and jobs in terms of the processes and materials likely to have been present. Often, initial disagreement on a particular question yields a consensus after discussion. Additional iterations of meetings and record retrieval may be required to obtain sufficient detail in areas of special interest.

An essential condition for a productive meeting is for at least some of the participants to be committed to advancing the study. Most individuals who have spent several decades in a particular set of environmental conditions acquire a curiosity on potential health effects; such a group includes not only workers but also members of management. Management participants with detailed process knowledge can make vital contributions to an exposure assessment. An additional incentive for their participation is the understanding that the study will go forward with or without their input.

Based on the discussion at the meeting as well as walkthroughs and a compilation of available industrial hygiene records, it is usually possible to map the presence of specific processes in time across the work history dictionaries and, in some cases, to rank particular process features. This approach has been used in several studies involving a total of approximately 15 plants.[8–10] In some machining plants, it was possible to rank major types of cutting fluid exposures into three or four levels.

The ability to perform this type of exposure reconstruction is often facilitated by a unionized workforce with enthusiastic union support for the research objectives. Without such support, it would be difficult to arrange meetings and generate vigorous discussions evoking diverse points of view.

Population Characteristics Due to Employment Selection

Generalized Healthy Worker Effect

The healthy worker effect is commonly said to be limited

TABLE II. Industrial Processes Generating Complex Exposures Not Well Characterized

- Heat Treat Quench Media: oils or water-based solutions of organic materials into which very hot metal parts are dropped for the purpose of controlled rapid cooling; pyrolysis products escape or accumulate in the system.
- Forging Lubricants: similar oil- or water-based liquids sprayed on red-hot metal or on forging dies in hot pressing operations, generating pyrolysis and other air contaminants.
- Metalworking Fluids: oil- and water-based liquids containing multiple components from recirculating central coolant systems in machining and grinding operations; compositions evolve with use and with modifications to control corrosion, bacterial/fungal growth, lubricity, etc.
- Welding: emissions arising from coated metals (oils, cutting fluids, drawing compound, corrosion inhibitors, primers, epoxy or urethane paints, adhesives, etc.).
- Rapid Curing of Polymers: especially in high-volume painting operations using ovens and in fabrication using adhesives such as epoxies or cyanoacrylates ("super-glues") with application of heat.
- Machine Maintenance: skin absorption of process or waste materials by machine cleaners or machine repair/skilled trades workers using solvents; electric motor contact cleaning/degreasing by electricians using chlorinated solvents, sometimes performed on operating equipment, with aerosolization of electric arc- and ozone-transformed organics.
- Industrial Process Wastes Handling: degreaser sludge, paint sludge, chemical reactor residue, still bottoms, etc.

to cardiovascular and respiratory disease risks. Substantial effects of employment selection on the risks for malignancies have been found as well. From mortality studies of industrial cohorts published in five leading journals over the period 1981–1987, Park and co-workers[11] selected all cohorts without clearly demonstrated work-related mortality and with 200 or more deaths. In 109 cohorts, Standardized Mortality Ratios (SMRs) were compared with Relative Standardized Mortality Ratios (RSMRs) (the cause-specific SMR divided by all-cause SMR, a surrogate for the Proportional Mortality Ratio [PMR]) to determine how these estimators of occupational disease performed in populations largely free of work-related disease. The results were similar when 14 of the 109 cohorts with suspected work-related mortality were excluded and if certain industries with potential work-related mortality were excluded (asbestos, smelting, chemical manufacturers). Surprisingly, many all-cancer SMRs were considerably less than 1.0. On average (using log-transformed SMRs to stabilize variance), the SMR for all cancer underestimated risk by 13 percent (using 1.0 as the null value), while the all-cancer RSMR overestimated by 6 percent. A plot of the all-cancer SMRs versus all-nonmalignant disease SMRs showed a clear association (Figure 1) with a least squares slope of 0.70. For lung cancer, the slope was 1.3, indicating that the lung cancer SMR varied faster than that of all nonmalignant disease across the selected cohorts.[11]

These findings imply that SMRs without internal exposure comparisons (sometimes performed prior to a decision on whether to conduct an exposure assessment) should receive a very critical interpretation, especially when all-cause SMRs are less than 0.8. Relying on SMRs could result in missed associations, particularly in subpopulations exposed to carcinogens. PMRs, on the other hand and contrary to much prevailing opinion, offered a less flawed estimate of work-related mortality in aggregate populations for most causes of death.[11]

Confounding by social class, an important determinant of most causes of death, malignant or otherwise, is one explanation for the selection effect observed for malignancies. The importance of social class has been demonstrated in British mortality statistics which are stratified on social class (Table III).[11,12] The occupational cohorts surveyed were largely free of work-related mortality and may have exhibited less than expected cancer mortality as a consequence of those populations typically being drawn from large employers representing a select work force with above-average education, income, and health care. These are the same populations where exposure reconstruction efforts are most likely to be undertaken.

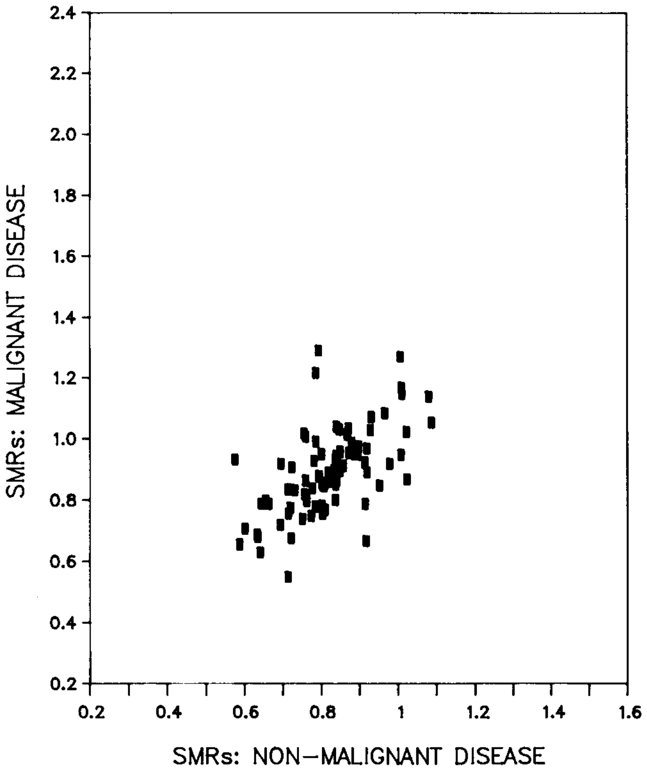

FIGURE 1. All-malignant cause SMRs versus all-nonmalignant cause SMRs for 79 cohorts largely free of work-related mortality and excluding asbestos, smelter, and chemical industries. (Figure from Park *et al.*[11])

Power Optimization and Internal Comparisons

For study populations that are plant-based, issues of statistical power can be critical. Underestimation bias from SMRs is one source of power erosion. Others include 1) limited subpopulations with sufficient exposure, duration, and latency to show increased risk, especially for industrial exposures appearing relatively recently (e.g., formaldehyde in foundries) and 2) the multiple stratification required by traditional analytic methods for concurrently addressing latency, cumulative exposure (or duration),

TABLE III. SMRs for Men in Social Class Strata in England and Wales[A]

Social Class	All Causes	All Cancer	Lung Cancer	Stomach Cancer	Colon Cancer	NMRD[B]
Professional	0.77	0.75	0.53	0.50	1.05	0.37
Managers/ Employers	0.81	0.80	0.68	0.66	1.00	0.53
Skilled, nonmanual	0.99	0.91	0.84	0.79	1.05	0.80
Skilled, manual	1.06	1.13	1.18	1.18	1.06	1.06
Semiskilled	1.14	1.16	1.23	1.25	1.01	1.23
Unskilled workers	1.37	1.31	1.43	1.47	1.09	1.87

[A] From Registrar-General's Report,[12] table taken from Park *et al.*[11]
[B] Nonmalignant Respiratory Diseases.

confounding exposures, and, when using internal comparisons, for control of confounding by age, year, race, and sex. One means to improve statistical power is to compute latency-weighted durations or cumulative exposures using a weighting function defined *a priori* based on biological plausibility.[9,10] This method gives less weight to exposures occurring in the years immediately prior to death than to those in earlier years. In this way, exposure (or duration) and latency are combined in a single variable.

Internal exposure comparisons to control selection-derived noncomparability can be efficiently achieved with mortality odds ratio analyses using a logistic regression model that incorporates the expected odds of a mortality outcome based on stratum-specific rates from a national reference population.[13–15] This method improves the power of the analysis by avoiding expenditure of scarce estimation resources on well understood confounders.

Paradoxical Dose–Response

It is not uncommon to observe statistically significant overall excesses for specific diseases but without trends on the available exposure measures. Sometimes there are paradoxical trends or other nonrandom patterns. The conclusion drawn is typically that little or no evidence of a work-related effect exists. Consider the following examples.

- A SMR study of 1700 deaths in a General Motors foundry by the Chemical Industry Institute of Toxicology found inverted trends for lung cancer with duration of employment for both white and black workers.[16] The authors concluded, without an analysis of exposure histories, that smoking probably accounted for the excesses. The average employment duration in this old foundry was only 6.9 years. This study found a SMR of 1.6 for emphysema in white men, unusually high for an industrial population, but other smoking-related causes of death were depressed (heart disease and bladder, buccal cavity, laryngeal, and pancreatic cancers).
- A study of Bendix asbestos brake-shoe manufacturing workers found substantially elevated cancer mortality for the lung (SMR = 2.1, n = 13), larynx (SMR = 6.6, n = 2), and rectum (SMR = 7.7, n = 5) in the shortest duration workers, many of whom were hired during World War II.[17] It was concluded that the pattern was not consistent with work-related mortality. (Elevated laryngeal cancer risk has been observed in other asbestos brake workers.[18,19])
- A study of lung cancer among meat processing workers in Britain found highest rates among those with shortest duration of employment.[20] The authors tentatively concluded that the excess was work-related, despite the paradoxical duration trends.
- The NCI formaldehyde study found statistically significant excesses of lung cancer, but the highest SMR was in the lowest stratum of cumulative exposure.[1,21] The authors' conclusion—little evidence of lung cancer risk—has stimulated considerable controversy.[22–24]

The possibility that workers with high exposures are leaving their jobs earlier than others is not usually considered. In a re-analysis of the NCI formaldehyde data, limited to the decedent population, duration of employment was found to be essentially independent of lifetime average exposure levels (weighted to account for latency) up to a level of about 0.9 ppm (the average duration was 12 years).[22] Above exposures of 2 ppm, the average duration was less than 1 year. While this pattern is consistent with exposure-driven duration truncation, another explanation is that entry-level jobs have the highest formaldehyde levels; therefore, workers leaving for other reasons after brief employment will have higher average exposures. In the full NCI study population and without an adjustment for latency, the NCI investigators observed negative correlations between average exposure levels and employment duration across the study plants; however, less consistent correlations were observed between average exposure and exposure durations.[25]

In studies where exposure histories are imprecise, it is conceivable that workers leaving employment because of high exposure actually may have higher cumulative exposures than many of those who remain while, based on nominal exposure assignments, they will appear to have lower cumulative exposures. If early termination was also a function of smoking status, there could be profound effects on risk estimates for smoking-related diseases. For example, long-duration, high-exposed workers could represent a low smoking population. This was one conjecture proposed to explain the NCI formaldehyde results.[22,23] In contrast, if nonsmokers were selecting themselves out of the exposure, the high-duration strata would have excess lung disease in the absence of exposure effects.

A Theoretical Model of Exposure-Driven Employment Duration

Exposures may be causing truncated work histories because of acute health effects or because of strongly exposure-associated adverse process conditions such as noise, heat, or other noxious exposures. If the exposure reconstruction is imprecise, then relatively weak exposure-driven duration effects can dominate dose–response relations. Consider an extreme case where the mean duration of employment (or exposure) varies inversely with the worker's (unknown) average exposure level. Then the relation between apparent cumulative exposure (duration) and outcome will be flat, i.e., independent of duration, because workers with different durations on average will have the same cumulative exposures. Suppose, as is more likely, that duration is less strongly affected (than inversely) by exposure, e.g., inverse square root. Then the expected association between apparent cumulative exposure (based on duration) and outcome will be negative! Workers with smaller exposure durations will have higher actual cumulative exposures and higher risks for disease.

This holds for dependencies weaker than inverse linear (Table IV). While the functions chosen for this example may not be the most appropriate (duration is unbounded at zero exposure), they illustrate plausible inverted dose–

TABLE IV. Trends for Risk on Duration with Exposure-Driven Duration Truncation

Duration Dependence of Average Exposure		Actual Cumulative Exposure	Risk of Outcome on Duration
D = f (X)	X = g (D)	XD	R
1. a/X	a/D	(a/D) D = a	ba + c
2. $a/X^{.5}$	$(a/D)^2$	$(a/D)^2$ D = a^2/D	(ba^2/D) + c
3. $a/X^{.33}$	$(a/D)^3$	a^3/D^2	(ba^3/D^2) + c
4. $a/X^{.25}$	$(a/D)^4$	a^4/D^3	(ba^4/D^3) + c

where: X = individual's average exposure
a = constant
D = duration of exposure
C = cumulative exposure = XD = g (D) D; g = f^{-1}, inverse function
R = risk = bC + c; b and c are constants

response trends for the high exposure range. For some study situations, it is entirely reasonable and should even be expected that inverted, dose–response causal relations will occur. When observed in studies with limited exposure information involving noxious exposures, a statistically significant paradoxical dose–response should be interpreted as evidence in support of a health effect.

Analytical methods that address this problem are needed. In one re-analysis of the NCI formaldehyde data, a method was used to correct for exposure truncation caused by the chronic disease itself but not by the antecedent exposures in the early phase.[24] Approaches are needed that can identify when exposure termination is associated with exposure level.

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