

Use of exposure data in occupational reproductive studies¹

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LEMASTERS GK, SELEVAN SG. Use of exposure data in occupational reproductive studies. *Scand j work environ health* 10 (1984) 1—6. Accurately characterizing worker exposure presents some unique problems in occupational reproductive studies. The latency period between exposure and the adverse event may be relatively brief — days, weeks, or months. Inaccurately identifying the specific exposure period which initiated the adverse event may then contribute to sizeable misclassification errors. This paper discusses different types of exposure models that can be used to help reduce misclassification and delineate the exposure-effect relationships more accurately. The advantages and disadvantages of exposure data sources are also discussed.

Key terms: occupational exposure, pregnancy, reproduction.

One of the most critical problems in occupational research is the accurate characterization of worker exposure. Some of the pitfalls encountered in assigning exposure categories in epidemiologic studies have been described by others (4, 11). Enterline (4) described the hazards of analyzing overlapping exposure and follow-up periods. For example, in mortality studies, high exposure (calculated as duration times level of exposure) and death tend to be incompatible; the longer workers are exposed, the longer they have lived. Recently, Samuels & Lemasters (12) noted a similar problem in assessing the association between exposure during a pregnancy and a preterm delivery. If sufficient numbers of women work late in pregnancy, the largest cumulative gestational exposure may be artifactually associated with the oldest gestational ages. Misclassification of the worker's exposure due to some of these inherent problems may seriously dilute the degree of association between the exposure and the outcome variable (3, 5).

In occupational reproductive studies the obstacles met in accurately assigning exposure status include

those already mentioned plus others unique to the study of reproduction. For most chronic diseases, such as cancer or coronary heart disease, the latency period between exposure and onset of symptoms may be decades. Therefore, identifying the specific exposure period that "triggered" the event is often impossible. In reproductive research adverse outcomes may be associated with relatively brief exposures followed by even shorter latency periods — days, weeks, or months. The time-span between exposure and the expression of an event is relatively narrow, eg, less than 20 weeks for a fetal loss or 74 d for a spermatogenic cycle. Therefore the accurate identification of the specific exposure period which initiated the event is important to minimize errors in exposure status assessment, but it may be very difficult. The present paper discusses the development of exposure models and the advantages and disadvantages of different sources of exposure data for use in occupational reproductive studies.

Chronic versus acute exposure models

Workers generally experience a range of exposures from "long-term and chronic" to "very brief, but critically high." Adverse reproductive responses may result from either chronic, prolonged, and repeated exposures or brief but acute exposures. Although there may be considerable overlap, biological responses may depend on the type of exposure.

Chronic exposure to a toxicant which causes adverse effects may be associated with either (i) damage attributed to a bioaccumulation of the toxicant or (ii) repeated cellular insult resulting in the accumulation of injury (2). Effects of chronic exposure are likely to

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consist of histopathological alterations which produce physiological or biochemical disruptions (14). The experience of male workers with exposure to dibromochloropropane provides an instructive example of the adverse reproductive effects associated with chronic exposure. Sperm count was inversely related to years of employment (total duration of exposure) in a plant producing this pesticide (17). Histological examinations from testicular biopsies showed a loss of spermatogenic cells and a decrease in the amount of cellularity within the seminiferous tubules (18).

An acute exposure model, on the other hand, assumes that it is not duration of exposure that is important but the timing and dose of exposure during a brief period. Wilson's principle of teratogenesis (19) aptly demonstrates this point; according to it expression of a particular type of birth defect depends on a critical period or specific days of gestational exposure. Therefore, using the total duration of exposure when assessing birth defects in offspring of pregnant workers might then actually mask effects that might otherwise have been apparent if only the exposure during the pregnancy or the first trimester had been considered. Some reproductive effects associated with the exposure of males might be better identified with an acute exposure model. For many of

the compounds examined to date (20), the sperm morphological abnormalities induced by mutagenic agents were also time specific. The period of maximum sensitivity occurred during late spermiogenesis. When the outcomes of pregnancy for the wife of an exposed worker are being assessed, the period prior to the conception, perhaps the preceding four months, may be the focus for classifying the worker's exposure. Hence, for many reproductive outcomes, it is not a worker's total person-years of exposure that is important, but the exposure which occurred relative to a specific period of reproductive development.

In view of these considerations, it is not surprising that Townsend et al (16), in a recent survey of pregnancy outcomes among wives of employees exposed to chlorinated dioxins, found no increase in spontaneous abortions, stillbirths, and infant deaths. An employee was considered exposed if he had been assigned to a chlorophenol process for at least one month. Duration of exposure was categorized as less than or more than 12 months. However, no attempt was made to link each pregnancy with specific exposures.

The prudent investigator, in most instances, would not use either a chronic or an acute exposure model — but both. Any single exposure of a chronically exposed worker might precipitate an adverse response, but attempting to isolate the critical period when an exposure initiated the effect could be difficult. Conversely, workers who frequently rotate jobs may also have frequent changes in exposure; if exposure is based only on a worker's "typical" exposure or total duration of exposure, misclassification can occur because there is no linkage of exposure to the event.

Level of exposure

Clinical toxicology assumes that the greatest effects are exhibited in the group with the highest exposure level; however, this assumption is not always accurate in reproductive research. Wilson (19) states, as a principle of teratology, that the manifestation of deviant development increases as the level of exposure increases. In respect to the *observable* human condition, however, this principle might not be apparent. For example high exposure to an agent causing severe damage to the conceptus might end in a very early fetal loss, unrecognizable to a woman and not identified as a miscarriage. Consequently the results of a comparison of reported congenital malformations or spontaneous abortions in a highly exposed group versus a reference group would not appear as statistically significant; the exposed group might even appear healthier. In this example the analysis of periods of subfecundity or menstrual disorders among female workers might have been more appropriate. There are at least two potential solutions to this problem. The first requires an examination of a broad spectra

Table 1. Effects of chemical exposures on males.

Direct effect	Possible end points
Central nervous system or endocrine disorders	Reduced libido Reduced fertility
Testicular atrophy	Reduced fertility
Disruption of biochemical milieu/balance	Reduced fertility Disruption of the functional properties of the sperm
Germ cell damage	Reduced fertility
Chromosomal damage	Fetal loss
Morphological changes	Congenital anomalies
Impaired protein synthesis	
Reduced cell number	
Toxins in seminal fluid	Impaired sperm motility Female systemic absorption or direct action on uterus or fetus

Table 2. Effects of chemical exposures on females.

Direct effect	Possible end points
Central nervous system or endocrine disorders	Reduced libido Menstrual disorders Reduced fertility
Germ cell damage	Reduced fertility
Chromosomal damage	Fetal loss
Atresia	Congenital anomalies Childhood cancers
Fetal cell death or dysfunction	Fetal disorders or death
Breast milk alterations	Neonatal disorders

of outcomes. Though the toxicology literature might provide some clues towards identifying appropriate end points, differences in exposure levels or mechanisms at various stages in the male and female are varied and require a comprehensive assessment of reproductive impairment. Tables 1 and 2 list some of the primary end points that might be assessed after the male or female worker has experienced similar direct effects (1, 7, 10, 15). These tables demonstrate that insult at a specific site may cause a number of different adverse outcomes and, moreover, any one type of adverse response may result from several types of insult.

The second solution suggests the examination of workers at different exposure levels. Inclusion of workers exposed at several levels helps differentiate possible outcomes and elucidate the effective dose. This procedure also helps to identify inverted-U dose-response relationships for specific outcomes, the result being, as mentioned earlier, a shift in the outcome observed, eg, from fetal loss to subfecundity.

Determining the worker's level of exposure can be difficult. During each spermatogenic cycle a male worker may change his absolute level of exposure. Neither will a pregnant worker stay in a well-defined exposure chamber during a particular part of her pregnancy; she moves in and out of exposure as her work schedule and duties change. Not only will the absolute presence or absence of an exposure change within a 24-h period, but levels of exposure and the specific chemical that a worker is exposed to may fluctuate. Workers do not experience constant or equal risk during their reproductive cycles. Therefore, particularly when an acute exposure model is being applied, the classification of exposure status must reflect the fluctuations that occur in level of exposure over relatively narrow time frames.

Sources of exposure data

There are basically two types of data, quantitative measurement data and qualitative data, each of

which has advantages and disadvantages for characterizing exposure (table 3). The first, quantitative or numerical measurement information, includes biological or industrial hygiene data. The second type, qualitative data, is more commonly used for dividing groups into broad exposure categories. Company personnel records, union records, and interview data are examples of the latter.

Measurement exposure information

Biological measures of exposure may include levels of compounds found in samples of blood, urine, hair, saliva, menstrual fluid, or semen. Though semen has generally been collected to measure spermatotoxic outcomes, it could also be an important measure of exposure, particularly to fat-soluble compounds and certain metals. The major advantage of using biological measurements for assessing exposure is that they provide an internal measure of exposure specific to individuals. Hence these data allow for individual variation in exposure and response. In addition, when outcomes associated with maternal exposures are being considered, biological measures may allow for the estimation of fetal exposure. However, the decision to use a biological index of exposure requires an understanding of the toxicokinetic properties of the compound. The stability of this index should also be assessed so that its value for estimating exposure levels for intervals between measures can be determined.

Except for studies that measure concurrent outcomes such as suppressed libido, estrous cycles, or spermatotoxic or cytotoxic effects, biological measurement may, in actuality, have limited usefulness. Even if biological exposure data were collected historically by the company, it is unlikely that values would be available for all times of interest in an individual's reproductive life-span. Exposure data gathered prospectively is both expensive and difficult to collect. Although very desirable, it is difficult, at best, to collect blood or urine samples routinely from workers throughout their reproductively active life-span.

Table 3. Advantages and disadvantages of exposure data sources.

Type of exposure data	Advantages	Disadvantages
<i>Measurement sources</i>		
Biological monitoring	Specific to each individual Estimates fetal levels	Often incomplete Invasive, costly, time-consuming
Industrial hygiene measurements	Quantifies environment Gives magnitude of exposure Not dependent on individual participation	Independent of biologic absorption, distribution, or excretion
<i>Categorical sources</i>		
Company and union work histories	More accurate dates Effective when used with industrial hygiene data	Incomplete Nonspecific job titles: "laborer" Data reduction costly, time-consuming
Interview work records	Linkage with events of interest All jobs obtained Nonoccupational exposures	Problems with recall

Another source of exposure information is industrial hygiene measurements which quantify the environment and provide data on magnitude of exposure. Industrial hygiene data are easier to collect than biological data and are not dependent on individual participation. These exposure values may be collected concurrently or may have been collected historically by the company on a few workers and used to estimate the exposure of all workers in particular job categories. Adverse reproductive events caused by exposure to a toxicant may, however, be associated with individual idiosyncracies in absorption, metabolism, distribution, and excretion that would not be reflected by ambient exposure measurements. Characterizing exposure with industrial hygiene measurements may have therefore the limitation of being considerably nonspecific to a particular reproductive event, eg, a pregnancy, and, unless the monitoring is frequent, may create gaps in the assignment of exposure doses during crucial periods of reproduction. Quantitative measures can be used either to form exposure categories or to create individual "doses" for use in regression equations and allow for the construction of a variety of models — maximum, minimum, critical-period, and cumulative exposure.

Categorical exposure information

Qualitative exposure data for occupational studies are commonly obtained from three sources, company work records, union work records, and interviews of workers. Company work histories generally have the more accurately recorded job titles and dates when compared to histories obtained from either union records or interviews. After work records have been abstracted and the exposed jobs identified, job titles are then classified into broad categories of exposure. Greenberg & Tamburro (6) have described a system using work histories of employees in combination with rank-order job exposure categories to characterize exposure. These indices were validated by the procedure of using industry-related cases of liver angiosarcoma to determine if cases would have been identified as highly exposed if their system was in use. This approach was originally used to establish surveillance methods for carcinogenic agents but could also be applied in reproductive studies. The authors estimated that the cost to characterize exposure prospectively was only two to three dollars per employee. The use of company work histories to characterize exposure may therefore be a fairly comprehensive, valid, and cost-efficient approach.

The disadvantages of company or union work histories are that they may be incomplete or nonspecific. Frequently job classifications reflect pay scale, not job function or exposure. For instance, it is not uncommon to find nondescriptive job titles like "laborer" or "utility worker" used to classify workers performing numerous functions. These generalizations

make the proper classification of exposure for a given reproductive period impossible. Other problems associated with the use of these data include the vast numbers of job titles often found within a plant and the changing of nomenclature over time (9). In addition it is extremely time-consuming to collect, code, and edit data to make it compatible with other information such as industrial hygiene measurements or reproductive histories.

Interviews of workers have the unique advantage of providing information on all employment and all exposures, both occupational and nonoccupational. In addition, if unusual exposures or spills have occurred, the worker may be the only source for this information. The respondent can also assist in the linkage of pregnancies with job history. For example, if work histories are obtained by interview, the worker can be asked if a pregnancy occurred while the worker held a particular job. Dates of pregnancies can then be cross-checked with these responses during the interview. This method of cross-referencing pregnancy information with work histories during the interview aids in the reduction of misclassification errors.

The disadvantages of interview data are well known. These data may be incomplete or inaccurate and hard to validate. Lemasters (8), in a reproductive study of female workers in the plastics industry, assessed the reliability of work histories obtained in an interview by reinterviewing a random sample of workers six months later. Seventy-six percent of the workers agreed exactly on the two interviews as to total number of jobs held at a specific company, and 62 % reported job titles in the exact sequence in both interviews. Only 40 % of the cohort agreed, however, in the two interviews on the month and year of hire, and only 55 % agreed on the date of termination within plus or minus three months.

Lemasters (8) also assessed the validity of work histories obtained during interviews by comparing the results with company data. Fifty-three percent of the workers agreed with company information on exact date of hire, and 70 % agreed within six months. Agreement was similar for termination date of employment. Only 16 % of the workers' information agreed exactly, however, with company records on both dates of hire and termination. These findings on the validity of company records versus worker's reports are similar to those presented elsewhere (13).

If proxy reporting is used to obtain a spouse's exposure history, even more problems exist. Selevan (13) compared a husband's self-reported work history to his wife's proxy report and found that, although there was 73 % agreement on the presence or absence of an exposure, there was only 50 % agreement on dates of hire within one year and 63 % agreement on the last year of employment.

Because of the well-known problems with recall of dates, a sample of work history data should, whenever possible, be validated against company informa-

tion to estimate the extent of error. Company records, or work records kept by unions, should be used as independent criteria for validating the interview data only when the probable level of accuracy of the records is high.

Another problem with interview data is biased recall of the work-related events and adverse reproductive outcomes. To reduce the potential for biased prompting by the interviewer, different interviewers should, ideally, collect exposure information and reproductive histories. When two interviewers cannot be used, the order of collection of exposure data and reproductive data should be planned carefully to minimize the potential for bias. The collection of either type of data first may result in biased prompting of the respondent by the interviewer while obtaining the other data. The order of collection of these data items in the interview may be affected by, for instance, the particular outcomes selected or the sex of the workers studied; eg, the "better" order may be different for interviews of male workers than it would be for interviews of female workers. Respondent fatigue must also be considered in the planning of the order of data collection in interviews. If a questionnaire is lengthy, the data which are more difficult to recall, such as work history, may be of poorer quality if left to the end of the interview.

Recommendations

No one type of exposure model or source of information is perfect. An optimum approach in occupational reproductive studies would include an examination of several outcomes from multiple sources of exposure information and several exposure models. If, for example, fetal loss is the primary suspected adverse outcome, both infertility and menstrual disorders should be considered, if possible; periods of subfecundity or irregular menses could also indicate embryo lethality. In an ideal study, detailed company or union records should first be abstracted. If these data are only partly informative, the employees could be asked for more-detailed data on dated and/or specific job functions. Either specific supplementary questions could be asked, or an independent report of the work history could be obtained by interview. Next, if industrial hygiene or biological measurements are available, level of exposure could be estimated. Analysis of the data would proceed from the assessment of outcomes with the use of gross exposure categories (no, low, high) to analyses with estimated doses. Caution must be exercised when exposure is examined as a continuous variable, since a traditional, increasing dose-response relationship may not be a good model for a specific outcome. In addition, each outcome would be assessed with the assumption of both acute and chronic exposure models. Selection of the appropriate study outcomes,

linking exposure information with the reproductive event, and determination of the relevant time period of exposure make occupational reproductive research extremely difficult and time consuming, and they may be subject to considerable error.

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