

Epidemiologic design for field studies

Occupational neurotoxicity

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MELIUS JM, SCHULTE PA. Epidemiologic design for field studies: Occupational neurotoxicity. *Scand j work environ health* 7 (1981): suppl 4, 34—39. Assessing the neurotoxic effects of occupational exposures has become increasingly sophisticated in the past decade with the application of neurophysiological and neurobehavioral research techniques to occupational disease problems. With a good epidemiologic study design and the careful application of these techniques, occupational field studies of neurotoxic effects are possible. Three examples from recent health hazard evaluations of the National Institute for Occupational Safety and Health (NIOSH) illustrate some of the problems in performing these studies and methods to overcome these problems.

Key terms: epidemiologic study design, methyl alcohol, neurobehavioral tests, neurotoxic, organ-risk index, pesticides.

With the application of neurophysiological and neurobehavioral research techniques to occupational disease problems, the assessment of the neurotoxic effects of occupational exposures has become increasingly sensitive and sophisticated in the past decade. This work has included the development and application of new techniques to evaluate neurotoxic effects (6). With the use of these techniques, the potential neurotoxic effects of occupational exposures to solvents, many organic chemicals, metals, and even combinations of chemicals have been evaluated. Several of the other papers presented in this supplement will illustrate these advances in both human and animal studies.

My presentation focuses on some of the problems encountered with epidemiologic study design in studies of human neuro-

toxicity in workplace settings (as opposed to experimental or laboratory settings). While techniques for assessing human neurotoxicity have improved over the past decade, the nature of occupational neurotoxic effects and of many of the techniques being used to assess them makes proper epidemiologic study design crucial. A review of some study design problems is presented, followed by illustrations from recent health hazard evaluations done by the National Institute for Occupational Safety and Health (NIOSH).

Cross-sectional study design

The design of cross-sectional epidemiologic studies poses many problems in occupational settings. Two main variables are evaluated and hopefully correlated, exposure and response. Several important problems must be overcome when cross-sectional medical studies are being designed to correlate neurotoxic exposures and effects. Some of these problems are common to most occupational cross-sectional studies, but others present special difficulties when neurotoxic effects are to be evaluated.

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Exposure measurements

Measuring exposure is often difficult in occupational studies. The lack of past industrial hygiene measurements often requires that past exposures be estimated or substitutes for exposure measurements such as job classification or work station be used. Even present exposure may be difficult to evaluate accurately because of the daily or weekly variation in exposures and the personal differences in exposure for workers in similar jobs. Furthermore, many workers are exposed, or have been exposed, to several potentially neurotoxic agents, and thus the separation of individual effects is difficult.

Response measurements

Most neurotoxic exposures do not lead to gross clinical effects (eg, paralysis). The major advances in assessing neurotoxic effects are the result of improvement in the ability to evaluate more subtle neurobehavioral and neurophysiological effects (6, 7). These new methods are often very sensitive to application techniques. Also, they are often specific for certain types of neurobehavioral effects (eg, visual vs auditory memory). Hence, a careful selection of these tests is required for field surveys. Consideration must also be given to other possible influencing factors such as age, alcohol intake, and education. Sometimes it may be necessary to use a battery of tests to screen workers for the effects of a neurotoxic substance(s). This battery should be specific enough to measure functions related to any known effects of the substance(s), and heterogeneous enough to cover a variety of neurobehavioral functions. This latter requirement is important since the full range of neurological and behavioral effects of a toxic substance is rarely known (7).

Time frame of exposure and response measurements

Neurotoxic effects may be acute, chronic, and/or delayed. Thus, study design must use the proper exposure time frame and the proper response time frame for the situation being evaluated. An obvious example would be a search for chronic effects in a chronically exposed popula-

tion. However, the situation may become more complicated with neurotoxic exposures. For example, solvent exposure just prior to testing may interfere with performance tests for chronic neurotoxic effects.

Reference group selection

Proper reference group selection is often the most difficult problem in cross-sectional study design. Locating a nonexposed group of workers which is in other ways similar to the exposed group may be difficult in field studies. This group must not have, or have had, exposure to the substance in question or significant exposure to any substance(s) known to have similar neurotoxic effects. Confounding factors such as age, sex, education, etc, which may affect the response variables must also be addressed. The reference group must be chosen with these factors in mind, and then, either through later statistical adjustment or through a matching technique, these confounding factors must be controlled in the analysis of the study results.

Another common approach to study design is to compare groups with different levels of exposure. This procedure has the advantage of possibly establishing a dose-response relationship for the substance in question. However, in some situations, the neurotoxic effects of exposure may be masked by comparison with a low exposure group rather than a nonexposed group.

Several illustrations from recent health hazard evaluations will help clarify these study design considerations.

Example 1 — Acute symptoms

A relatively direct evaluation of neurotoxic effects was recently done by NIOSH for a public school system in the state of Washington (1). This evaluation concerned teachers and teachers' aides exposed to methyl alcohol while operating spirit duplicator machines at work. These machines use a duplicating fluid composed almost entirely of methyl alcohol. The duplicators are often located in small, inadequately ventilated rooms, and industrial hygiene

measurements had indicated a substantial exposure to methyl alcohol during machine operation or during the collation of incompletely dried copies from the machines. Although the original health complaints which prompted the evaluation were unrelated to the methanol exposure, a high level of concern and anxiety existed among the school personnel due to the many symptoms (headaches, dizziness, etc) reported by operators of the machines. In order to evaluate these symptoms, NIOSH conducted a questionnaire survey of two groups using the machines, a highly exposed group — the teachers' aides, and a reasonably similar but less frequently exposed group — the teachers. The response variables were a list of symptoms experienced the month prior to the investigation. These symptoms included some which might be expected from methyl alcohol exposure, some unrelated to it, and some unrelated to methyl alcohol exposure, but about which there was concern among the workers. [Limiting the time frame of response is important when acute neurotoxic symptoms (eg, headaches) which the average person might occasionally experience are being evaluated.] For this study, symptoms occurring in the month prior to the exposure were used. Expanding the time frame to 1 a could have led to serious problems with recall bias and, thus, created meaningless results. Timing of the actual administration of a questionnaire is also important, especially when one is dealing with relatively common symptoms likely to be reported in an emotionally charged environment. In this study, care was taken so that the respondents did not have an opportunity to discuss the questionnaire among themselves.

Table 1. Spirit duplicator exposure: Prevalence of symptoms in exposed workers (%).

Symptom	Teachers (N = 66)	Aides (N = 66)
Blurred vision	1.5	22.7
Dizziness	1.5	30.3
Headache	18.1	34.8
Skin problems	1.5	10.6
Nausea	6.0	18.0
Eye irritation	12.1	25.7

The teachers' aides, when compared with the teachers, were found to have a substantial excess of symptoms consistent with methyl alcohol exposure. These symptoms included headache, dizziness/light headedness, burning eyes, blurred vision, and skin problems (table 1). The differences were statistically significant and occurred in most age groups. The lack of difference between the two groups for symptoms unrelated to methyl alcohol exposure makes it unlikely that greater anxiety among the teachers' aides accounted for the other differences found.

This study illustrates some of the care that needs to be taken in study design even when acute effects of exposure to a solvent are being evaluated.

Example 2 — Psychological effects of pesticide exposure

A much more difficult methodological problem is illustrated by a recent hazard evaluation of the possible psychological sequelae of exposure to pesticides at a pesticide warehouse fire 6 a earlier (5). Approximately 80 fire fighters and other safety personnel had potentially heavy pesticide exposure (including toxaphene, chlordane, malathion, 2,4,5-trichlorophenoxy acid, and lindane) while fighting this long and very smoky fire. At least 17 of the fire fighters required acute medical care, including some for suspected organophosphorous pesticide poisoning. Many men reported symptoms such as nausea, dizziness, and headache while fighting the fire. During the years subsequent to the fire, and particularly in 1979, many members of the fire department experienced feelings of mental distress, depression, anger, violence, suicide, and memory dysfunction. The possible relationship of these complaints to the fire prompted the fire fighters' union to request an evaluation from NIOSH.

The exposed group for the study included about 90 % of the personnel at the scene of the fire. Three separate groups were identified: full-time fire fighters, volunteer fire fighters, and other safety personnel at the scene. Due to the vagueness of the complaints and the expected difficulties in evaluating what prevalence of these

complaints is abnormal, a reference group of fire fighters was chosen from a city of similar size in the same region. This reference group was similar to the exposed fire fighters, except for the exposure to a pesticide fire.

The response variables included many questions about health status, symptoms, and medical care. In addition, a standard psychological questionnaire, the Profile of Mood States (POMS), was used (3).

A comparison between these groups and the reference group revealed many differences. Repeated memory loss, nervousness, and loss of concentration were more common in the exposed groups. The POMS revealed only a few fire fighters with abnormal scores for any of the six mood variables on that questionnaire. However, the standard reference group for POMS is college students. When the scores of the exposed fire fighter personnel were compared with the fire fighter reference group, several significant differences were found between the two groups (table 2). This situation illustrates the difficulties encountered when standard clinical reference groups are used for many of these neurobehavioral tests.

Much more marked differences between the exposed and reference groups were found when the exposed group was limited to those reporting acute symptoms at the time of the fire (table 2). This latter group may be used as a substitute for a highly exposed group under the assumption that the acute health effects were due to higher exposures. This "highly exposed" subgroup demonstrated consistently increased problems on the POMS and medical ques-

tionnaire. Although not conclusive evidence of a psychological effect from the fire, these findings do suggest subsequent problems due to this exposure.

Example 3 — Chemical plant

In 1977, NIOSH and the Division of Occupational Medicine at Cook County Hospital (under the direction of Dr S Conibear) conducted a health hazard evaluation at a chemical plant in Michigan (2). The workers at this plant had been intermittently exposed to a variety of potentially neurotoxic agents including benzene, bromine, carbon tetrachloride, dichlorodiphenyltrichloroethane (DDT), ethylene dichloride, tetra-bromo-bisphenol, iodine, lead, methanol, methyl bromide, and polybrominated biphenyls. Many of these exposures were limited to certain parts of the plant. However, there was considerable job mobility, and much of the work force was in the maintenance department and, thus, exposed throughout the plant. Available environmental monitoring data did not allow for a clear separation of high versus low exposure throughout the plant. The study design problems included selection of methods with which to evaluate the effects of these multiple, potentially neurotoxic exposures and choice of a comparison or reference group. No outside comparison group was readily available. Two approaches have been used to evaluate this effort.

The initial approach chosen was to use past and present job type as a substitute for actual exposure measurements. This parameter was then combined with an

Table 2. Pesticide fire-exposed fighters: Test scores for psychological conditions.

State (assessed with the Profile of Mood States)	Full-time fire fighters		Reference group (N = 24)
	Health effects at fire (N = 13)	No health effects at fire (N = 12)	
Tension	15.1 *	11.3	7.8
Depression	13.1 *	9.2	5.8
Anger	10.9	7.2	6.5
Vigor	13.3 *	16.2	19.4
Fatigue	12.2 *	7.9	5.9
Confusion	9.7 *	7.2	4.2

* $p < 0.05$ by chi-square analysis.

estimate of the organ-specific toxicity of the exposures to produce an organ-risk index score for each worker. First, an inventory was made of all chemical exposures by plant department. Twenty-seven chemicals felt to pose significant health risk at the plant were included in this department inventory. An assessment of the degree of exposure for each worker in the department was also made. From the personnel records of the plant, each worker's duration of employment in each department was obtained. A "risk-of-exposure" index was then calculated for each worker

for each chemical. This calculation was done by summing the total number of months the worker was in each department by a weighting factor for the degree of exposure for that particular chemical in that department.

Next, an "organ-risk index" for each target-organ system was prepared for each individual. For it, the previously computed risk-of-exposure index for each chemical toxic to the organ system was summed for each worker. This procedure resulted in a continuous independent variable which assessed the type of exposure, the duration and multiplicity of exposure, and the likely target-organ system. Frequency distributions for each of the various organ-risk indices were developed. These distributions could then be used to divide the population into a high- and low-exposure group for each organ system. The mean organ-risk index value was used as the dividing line. Examination results for the high- and low-risk groups could then be compared, other variables being taken into account as necessary.

The response variables used to assess neurotoxicity in this study included symptom review, neurological examination, and a battery of neurobehavioral tests (Santa Anna Dexterity Test, Block Design, and Neisser Letter Search) for all workers, plus a more-detailed battery for a subgroup of workers.

Table 3 shows the Santa Anna Dexterity Test scores for the low and high neurological risk groups. An analysis of variance of the data accounting for age (divided at age 35) revealed a significant effect for both age and the neurological risk index, the older workers with higher risk showing the greatest deficit.

Table 4 shows a similar analysis for the Block Design score with a statistically significant age effect, but an insignificant neurological risk index effect.

This approach to exposure estimate has the advantage of allowing evaluation of the effect of multiple exposures on the individual worker. However, it is not as helpful in the evaluation of neurotoxic effects of a particular substance in that environment. Modifications of this approach, to include different weighting systems and regression or discriminant func-

Table 3. Chemical plant: Santa Anna Dexterity Test score (sum of number correct in four trials with one hand).

Age (a)	Neurological risk	
	Low	High
≤ 35	97.04	97.71
> 35	91.17	80.21
Analysis of variance:	Neurological risk	p < 0.01
	Age	p < 0.01
	Interaction	p < 0.01

Table 4. Chemical plant: Block Design score.

Age (a)	Neurological risk	
	Low	High
≤ 35	33.97	32.88
> 35	30.61	28.39
Analysis of variance:	Neurological risk	p > 0.25
	Age	p < 0.01
	Interaction	p > 0.70

Table 5. Chemical plant: Absent deep tendon reflexes in both ankles. (HANES = Health and Nutrition Examination Survey)

	Chemical plant workers	White blue-collar males examined by the HANES
Absent reflexes	8	6
Total number of workers	160	1,023

p < 0.01, by the chi-square test (age-adjusted).

tion analysis, may improve the usefulness of this method.

Another approach to study design used in this study was not as helpful, but may be useful in other situations. The National Center for Health Statistics periodically conducts the Health and Nutrition Examination Survey (HANES) (4). In the last round of this survey, detailed examinations (including medical history, physical examination, laboratory testing, pulmonary function testing, etc) were conducted on over 7,000 adults in the United States. This sample was carefully chosen to be a relatively representative sample of adults in this country and not to be biased in participation by past medical history. Unpublished data indicate that a comparison of the demographic characteristics of the examined group with United States census data and other information confirmed the representativeness of the sample. The HANES sample can be further divided into working and nonworking groups, and these working groups divided into white- and blue-collar groups by age, sex, and race.

For comparison with the workers at this chemical plant, the white, male, blue-collar group was the most appropriate reference group. Unfortunately, the HANES physical examination was very limited. The only similar neurological examination item included in both surveys was ankle deep tendon reflexes. Table 5 compares the exposed group with the HANES group for absent deep tendon reflexes in one or both ankles. This age-adjusted comparison shows a much higher prevalence of absent deep tendon reflexes in the chemical worker group. However, the absence of confirming data from other neurological examination items limits the usefulness of this comparison.

Although limited in this application, the HANES data do provide a useful comparison group for other occupational evaluations. The medical history and symptom data have been effectively utilized in other

studies in which small sample sizes or other constraints precluded the use of another reference group.

Discussion

This presentation has been a brief review of some of the epidemiologic design problems encountered in field evaluations of the neurotoxic effects of occupational exposures. The examples, in one sense, represent extremes of difficulty in that they were requested evaluations of specific work situations. However, with careful study design and analysis, important data on neurotoxic effects were obtained. Often, many of these problems could be avoided by a careful preselection of the cohorts for study. Other studies at NIOSH and in Finland have overcome many of these difficulties to produce interesting and valuable research in this important facet of occupational safety and health.

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