OCCUPATIONAL EXPOSURES AND BIRTH DEFECTS

Final Performance Report

Grant Number: 1 R01 OH02598-~~01A1~~ 02

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Date: May 28, 1992

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	PB93-118628

4. Title and Subtitle: Occupational Exposures and Birth Defects

5. Report Date: 1992/05/28

6.

7. Author(s): Mitchell, A. A., and C. Louik

8. Performing Organization Rept. No.

9. Performing Organization Name and Address: Slone Epidemiology Unit, Boston University School of Medicine, Brookline, Massachusetts

10. Project/Task/Work Unit No.

11. Contract (C) or Grant(G) No.
(C)
(G) R01-OH-02598

12. Sponsoring Organization Name and Address

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words): The utility of the job exposure matrix (JEM) of NIOSH in occupational teratogen research was assessed. Information was taken from the Slone Epidemiology Unit Birth Defects Study (BDS). The JEM was used to assign specific workplace exposures to the mothers and fathers of the 11,000 malformed infants in the BDS data file. BDS job title/industry codes were translated into codes compatible with the JEM. Computer software was developed to produce tabulations which provided frequencies of each listed exposure in each birth defect category as well as comparisons to the remaining categories of defects. A detailed exploration of certain aspects of the data was conducted, involving the testing of a specific hypothesis. Neither the absolute attribution of exposure nor the assessment of exposure probability by the JEM provided a credible measure of exposure. The authors conclude that the NIOSH JEM cannot be usefully applied to the BDS data base to assess risks of occupational exposures in relation to birth defects.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms: NIOSH-Publication, NIOSH-Grant, Grant-Number-R01-OH-02598, End-Date-02-29-1992, Reproductive-system-disorders, Reproductive-hazards, Risk-analysis, Epidemiology, Occupational-exposure

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages 48
	22. Security Class (This Page)	22. Price

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List of Abbreviations

BDS	Birth Defects Study
C.I.	Confidence Interval
JEM	Job Exposure Matrix
NIOSH	National Institute of Occupational Safety and Health
OR	Odds Ratio
PCB	Polychlorinated Biphenyl

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Significant Findings

As described in the Specific Guidelines on Sections of the Final Performance Report, NIOSH is interested in "knowledge for prevention of workplace diseases and injuries" as it specifically concerns the public health implications of our research. The nature of this project was primarily methodological, and we developed no new knowledge that has practical application for the prevention of workplace diseases and injuries.

Abstract

In the last few decades, we have become increasingly aware that environmental agents can cause birth defects in humans. Among occupational exposures, there are many suspected but few confirmed teratogens. In fact, the study of occupational teratogenesis is characterized by profoundly inadequate data. This project provided a unique opportunity to pursue such needed research. By applying the NIOSH Job Exposure Matrix (JEM) to the Slone Epidemiology Unit's Birth Defects Study (BDS) data base, we sought to assess the utility of the JEM in occupational teratogen research.

Information was drawn from the BDS, which has data on over 11,000 infants with a wide variety of birth defects. For each malformed infant, the BDS data base contains information on maternal and paternal occupation and industry. The parents' specific occupational exposures were ascertained by applying the JEM to these data.

This research effort consisted of three phases. In the first phase, we used the JEM to assign specific workplace exposures to the mothers and fathers of the 11,000 malformed infants within the BDS data file. For each of these almost 22,000 mothers and fathers, we developed a profile based on the JEM that identified a) all agents to which each parent might have been exposed and b) for each of those agents, the probability of exposure. To produce this profile, the current BDS job title/industry codes were first translated into codes compatible with the JEM. By the conclusion of this phase, we were able to determine the maximum number of study parents with any exposure to a specific occupational agent.

In phase two, we developed the computer software necessary to produce tabulations that provide frequencies of each listed exposure in each birth defect category as well as comparisons to the remaining categories of defects. This series of tables served as the primary tool for subsequent testing and generation of hypotheses regarding occupational exposures and birth defects.

The final phase involved detailed exploration of certain aspects of the data. We selected a specific hypothesis for investigation (benzene exposure in relation to kidney malformations), and in the course of that analysis we attempted to verify the JEM exposure assignments and probability levels.

We found that neither the absolute attribution of exposure nor the assessment of exposure probability by the JEM provided a credible measure of exposure. Because of the nature of our analysis, it is not clear whether this is due to limitations of the JEM or to problems inherent in attempting to infer occupational exposures from job titles. Whichever the case, we must conclude that the NIOSH JEM cannot be usefully applied to the BDS data base to assess risks of occupational exposures in relation to birth defects.

I. Background

In recent years, scientific and public concern over reproductive health has grown substantially. Various outcomes have been studied, including paternal factors (e.g., sperm count and motility) and maternal factors (e.g., fertility and miscarriage rates). However, of all adverse reproductive outcomes, the birth of a malformed child is the most dramatic and has the most serious impact, both from the narrow perspective of the affected family and from the broad perspective of society as a whole. According to the Centers for Disease Control, congenital anomalies are the fifth leading cause of years of potential life lost before age 65(1). Thus, the costs of birth defects, in both suffering and dollars, are considerable.

In the last few decades we have become increasingly aware that environmental agents can cause birth defects in humans. Major categories of known human teratogens include infections (such as rubella), drugs (such as thalidomide), and physical factors (such as radiation). The category of chemicals, which includes most occupational exposures, contains many suspected but few confirmed teratogens. In fact, the study of occupational teratogenesis is characterized by profoundly inadequate data. Four occupational exposures have been identified for which there is a high level of certainty regarding human teratogenicity: methylmercury, polychlorinated biphenyls (PCBs), laboratory work (involving solvent exposure), and ionizing radiation.

Mercury exposure occurs in a wide range of industrial settings, including the manufacture of pharmaceuticals, paints, chemicals, paper and pulp, mining, and agriculture. Its teratogenicity has been well-established(2,3); exposed children developed defects of the central nervous system, including microcephaly. PCBs were used extensively from the 1930s through the 1970s in capacitors and transformers, and as plasticizers, hydraulic fluids, and heat-transfer fluids. Evidence of teratogenicity comes from an industrial accident in Japan in 1968 in which rice oil was contaminated with a commercial PCB(4,5,6). Affected children had dark brown skin pigmentation, gingival hyperplasia, growth retardation, and possible alterations in calcium metabolism. Several reports have suggested that laboratory work is associated with fetal abnormalities(7-11). Swedish studies have found increased rates of malformations for university laboratory staff, laboratory workers in the pharmaceutical industry, and laboratory workers in the paper and pulp industry. The increases were largely accounted for by excess numbers of infants with oral clefts and gut atresias. The teratogenic potential of ionizing radiation has been recognized since the nuclear bomb explosions in Japan in 1945. Affected children have microcephaly and mental retardation following high-dose in utero exposure(12,13). There is greater uncertainty regarding the teratogenic effects of low-dose radiation exposure.

It is widely agreed that these four confirmed teratogenic exposures in the workplace are far outnumbered by exposures for which human teratogenicity is suspected but not confirmed, and even further outnumbered by exposures for which data are simply not available. It was in this setting that we proposed to evaluate methods for the systematic study of occupational exposures in relation to specific malformations.

II. Specific Aims

Specifically, our goal under this grant was to assess the utility of a job exposure matrix in the context of a large-scale, epidemiologic data base that might be used to facilitate study of specific birth defects in relation to occupational exposures. Data were derived from the Birth Defects Study (BDS) of the Slone Epidemiology Unit. This case-control surveillance program was initiated in 1976, and has accumulated interviews of approximately 12,000 mothers of infants with a wide variety of birth defects; subjects were drawn from participating hospitals in the metropolitan areas of Boston, Philadelphia, and Toronto and one-third of the state of Iowa. Mothers were interviewed by trained pediatric nurses in the subject's home. For each malformed infant, the BDS data base contains information on maternal and paternal occupation and industry. Our primary objective was to derive the parents' specific occupational exposures from the NIOSH Job Exposure Matrix (JEM), and to assess the utility of the JEM in this context.

III. Methods

This project was carried out in three phases, each of which is detailed below. In phase I, the JEM was used to assign specific workplace exposures to BDS parents; in phase II, tables were developed comparing exposure frequencies in each birth defect category against all other defect categories; and in phase III, we conducted preliminary explorations of an hypothesis within this new data set.

Phase I. The goal of phase I was to convert all existing industry/occupation codes in the BDS to Census codes which are compatible with the NIOSH Job Exposure Matrix. This conversion procedure would allow us to use the information contained in the JEM to assign to each BDS parent a) exposures related to specific agents and b) probabilities for those exposures.

Occupations in the BDS are coded using an industry/occupation dictionary which was derived from the system developed by Hoar(14). This system uses a two digit industry code based on the Standard Industrial Classification and a three digit occupation code based on the U.S. Dictionary of Occupational Titles. (We had expanded the industry codes to three digits and the occupation codes to five digits to allow greater specificity in coding.)

To translate job codes, we determined those industry/occupation labels which could be converted directly from the BDS coding scheme to the Census codes by means of a simple computer algorithm, which we developed in the following way: for each existing BDS code, we searched the alphabetic list of Census occupation codes for an exact match with the BDS job title. If such a match was found and an associated industry was identified in the Census codes, that industry was assigned. If many industries were identified in the Census codes, the detailed Census information was reviewed to select that industry which was deemed most appropriate. In cases where our codes were less specific than Census codes, we chose the most general code available. For example, waitresses in the food industry were translated by finding "waitress" in the Alphabetic Index of Industry and Occupation and finding associated industries to be "railroads," "eating and drinking places," "private households," and

"hotels and motels"; we selected "eating and drinking places" to be the most appropriate industry. If no exact match for the occupation was found, we searched for similar titles. In situations where we were unfamiliar with the job title, we consulted the Dictionary of Occupational Titles to obtain an explanation.

For those job titles that could not be translated by direct algorithm, either because the job title did not readily correspond to a title in the Census codes or because it was too broad to translate to a single code, individual BDS records were examined and the literals (i.e., the job description obtained at interview) were coded directly into the Census codes. Approximately 5% of the BDS parents had job titles that fell into this category. These included such job titles as "education, nos" and "investigator" in the industry "few chemical exposures"; "quality control" in the "food" industry; "engine mechanic" in the "machinery" industry; and "materials handler" in the "automobile" industry. All coding was done by a single research assistant and reviewed by the project epidemiologist.

Our consultants participated in the validation of this translation process in the initial stages of the project. To this end, we selected a test sample based on the frequency distribution of jobs within the BDS data and including jobs chosen at random from the most common job titles and jobs which, based on our previous coding experience, were likely to present particular difficulty. We then provided our three consultants with the literals for these cases and asked them to assign Census codes. The consultants carried out this task independently of each other and our staff, and then compared their results. Through this procedure, they devised a system for evaluating disagreement, including evaluating the impact of disagreement on exposure assessment. The consultants then compared their consensus results to the job title translations performed by the research assistant and again evaluated the magnitude and effect of any disagreement.

The results of the consultants assessment are presented in Figure 1. Of the 60 charts selected for this comparison, 46 (77%) were judged to have been translated appropriately by means of our computer algorithm. Among the remaining 14, 10 were judged to be identifiable in advance as problematic codes that would require individual review, leaving four codes (7%) that were judged to have been misclassified by the translation scheme. We believe that this 7% rate, while not ideal, represents an acceptable level of misclassification. Based on the results of this evaluation, we concluded that our translation process was satisfactory.

When the algorithm-based translation of BDS job titles had been completed, each consultant was sent a list of the original BDS titles and the newly-assigned Census codes, which they reviewed for appropriateness. Although the vast majority of our translations were considered satisfactory, some changes were suggested. For example, we had coded "alarm installer" as "miscellaneous hand working occupations" in the "watches, clocks, and clockwork operated devices" industry, but one consultant suggested "electrician" in the "security and protective services" industry, and this change was made. On the basis of these reviews, we concluded that our code translations were both coherent and reasonable.

NIOSH also reviewed our code translations. We provided a 5% random sample of the job descriptions as they appear in our completed BDS questionnaires, along with the 1980 Census codes which we had assigned. NIOSH coders then assigned Census codes to these jobs according to standard Census procedures. Since the process by which we assigned Census codes under this grant did not entail examining the literals for each subject but rather consisted largely of translating job titles, we expected the NIOSH coding approach to identify discrepancies, and it did. However, none of the errors reported to us by NIOSH appeared to have a significant impact on exposures. For example, we had assigned a lawyer who worked for the state to the Census industry "legal services" rather than "justice, public order, and safety." (In our original codes, all lawyers were assigned to an industry called "few chemical exposures" and they were all subsequently converted to lawyers in "legal services.") Although the fact that this individual worked for the state has been lost by our coding process, the effect on exposures should be nil. For the same reason, we had assigned an accountant who worked in a bank to the industry "accounting, auditing, and bookkeeping services" rather than "banking"; again, this error should have virtually no effect on exposure assignments. We encountered no assignment errors which were likely to result in appreciable misclassification of exposures.

NIOSH also examined our translated codes for possible inconsistencies in the industry-occupation combinations we assigned. This process revealed some inaccuracies on our part, particularly with regard to sales workers in wholesale versus retail sales, and the assignment of some sales workers to manufacturing industries. In conflict with Census coding procedures, we assigned physical education teachers to the industry "elementary and secondary schools," while the correct procedure would allow them only in the industry "colleges and universities." Again, these errors would have little if any impact on exposure assignments.

The errors identified by the NIOSH review can be classified into three categories. First, there were some clear errors on our part, such as the misclassification of sales workers, that were not detected in our own internal review. These were of course corrected. The second category consisted of problems that we would identify when we encountered industry-occupation pairings which we assigned that do not exist in the JEM. Our assignment of "physical education teacher" is an example of this problem. The third group of errors involved codes which, after investigation on our part, still appear to be consistent with codes given in the Index of Industries and Occupations. While these may be incorrect based on Census coding details of which we are not aware, we believe that errors of this type are unlikely to have an appreciable impact on exposures.

The objective of the code translation procedures of phase I was to yield a set of JEM-derived exposures which could then be used to produce joint distributions of specific exposures and birth defects. The discrepancies identified by NIOSH through the examination of literals and by using the i/o edit resulted largely from differences in the coding approach used by us and that used by NIOSH, together with the fact that we did not strictly follow Census procedure. However, the critical issue with regard to our objective was not whether there are discrepancies, but rather whether the discrepancies would

have a meaningful impact on exposures. In our review of the information provided us by NIOSH, we found no evidence that the coding discrepancies would have an appreciable impact on the exposure assignments made in phase II. Nonetheless, we were concerned about the possibility of spurious results due to errors in coding. Therefore, for any hypothesis which we examined in depth, we incorporated into our analytic plans a review of the literals of all presumed exposed cases and a sample of other study infants. If significant errors were found, we would correct them and repeat the analysis with the appropriate changes.

Apart from the systematic approach described above, our work with the Census codes also made us aware of some apparent inconsistencies in the JEM. Examples include: 1) The industry "insurance" includes the occupation "investigators and adjusters, except insurance." 2) The occupation "groundskeepers and gardeners, except farm" is listed in 39 industries. For 14 of these, "soil" is identified as an exposure, but for the remaining 25, it is not. 3) Within the JEM, the occupation "farmers, except horticultural" is listed only in the industry "radio and television broadcasting."

In addition to these inconsistencies, we found that many of the codes which we had assigned to BDS parents were not included in the JEM. Among these were some very common jobs, such as elementary and secondary school teachers (n=891), computer operators (n=301), computer systems analysts (n=299), lawyers (n=248), policemen (n=196), and dental laboratory technicians (n=103).

At the conclusion of phase I, we were able to generate sets of figures similar to those described in our original grant proposal. These included 1) frequency distributions of exposures to each substance included in the JEM, 2) a probability matrix which provides, for each industry and occupation combination, the probability of exposure to a given substance (as defined in the JEM), and, 3) for each substance, the distribution of probabilities of exposure among parents in the BDS. Because of the extremely large number of substances contained in the JEM as well as the large number of industry-occupation pairs assigned to BDS parents, we restricted our initial investigations to the 50 most common exposures among mothers and fathers. In addition, since effects of exposure may differ according to whether the exposure is maternal or paternal, we considered maternal and paternal exposures separately.

Examination of these tables (previously submitted) revealed that probabilities of exposures were generally low, rarely exceeding 10%. To insure that we had interpreted the JEM data accurately, we requested and received confirmation from Karl Sieber at NIOSH that our assigned probabilities were correct.

Based on our validation process, the examination of code translations by our experts, the review of a sample of literals by NIOSH, the results of the NIOSH i/o edit, and our proposed validation procedure for hypotheses under investigation, we concluded that the results of the code translation and subsequent assignment of exposures to BDS parents warranted proceeding to the second phase of the project.

Phase II. The objective of phase II was to produce joint distributions of exposures and birth defects to determine whether our data a) appeared credible and b) revealed associations of sufficient interest and statistical power to warrant further exploration. These joint distributions were produced in the following way: for each specific birth defect or birth defect class and each JEM-derived exposure, we generated tables which included the total number of BDS subjects exposed, the total number of cases (infants with specified defects), the number of exposed cases, and an odds ratio adjusted for geography and year of interview, with the corresponding level of statistical significance. For this initial crosstabulation (or "screening") of exposures and outcomes, the exposure probabilities assigned by JEM were disregarded and each exposure was considered to be either present or absent. Again, because of the large number of exposures and outcomes involved, we restricted attention to defects and defect categories with at least 100 cases (it is unlikely that we would have sufficient statistical power to either detect or rule out effects for those defects with fewer than 100 subjects), and we similarly restricted consideration to the 25 most common exposures and an additional 12 exposures of particular interest (benzene, ethylene glycol, styrene, toluene, xylene, several forms of lead and mercury, and ionizing radiation). In reviewing these data, we considered three questions: 1) do our data replicate known associations between specific hazards and birth defects? 2) do presumably safe agents appear to be safe? and 3) do we see other associations between exposures and outcomes, and, if so, do we have sufficient statistical power to pursue them? We will consider each of these questions in turn:

1) Do the data replicate known associations?
As mentioned above, mercury is a known teratogen that has been associated with various central nervous system abnormalities(11,12). In our screens, we found associations between paternal mercury exposure and several brain malformations (anencephaly, hydrocephaly, ventriculomegaly), and between maternal mercury oxide exposure and the general category of brain anomalies (Table 1). Although our numbers are small, the relative risks are significantly elevated and these associations are clearly consistent with previous findings. There are too few exposed cases to allow a full, detailed analysis of this association. However, our occupational experts reviewed the jobs of the exposed cases and confirmed that mercury exposure was in fact likely.

Among mothers, reports have linked organic solvents with a variety of malformations including genitourinary system defects(15) and ventricular (cardiac) defects(16). Our data are consistent with these reports (Table 1) in that we observed elevated risks for benzene in relation to anomalies of the kidney, the ureter, and other genital organs. For xylene, we observed associations with anomalies of the female genitalia and conotruncal (cardiac) defects.

Among fathers, work with organic solvents has been reported to be associated with central nervous system defects(17). Again, our data show similar associations: xylene and toluene exposure both show elevated risks for spina bifida, and benzene is associated with an increased risk for anencephaly and spina bifida (Table 2).

2) Do presumably safe agents appear to be safe?
Another indirect measure of the validity of our data would be the lack of positive associations with agents which one might reasonably expect to be safe. We considered mineral oil to be such an agent, and in fact when we examined our screens for associations with mineral oil, we found very few (a small number would be expected by chance alone because of the large number of comparisons involved in the screening process). Those which were present in the data were of modest magnitude and generally involved non-specific and unrelated categories of defects, suggesting random fluctuations (sampling variation).

3) Do we see other associations between exposures and outcomes?
We found a number of previously unidentified associations in our data which might warrant further detailed investigation, pending confirmation of the validity of the data. These included both maternal and paternal exposures, with maternal exposures being primarily associated with genitourinary defects and paternal exposures with cardiovascular defects.

Based on the above assessments, we and NIOSH believed it was appropriate to proceed to the third and final phase of the project.

Phase III. The goal of phase III was to explore certain aspects of the data in detail to provide estimates of the real and potential utility of applying the JEM to the BDS data base. To achieve this goal we sought to conduct detailed analyses of known associations observed within our data. Based on the results of our phase II screens, we selected maternal exposures to benzene in relation to kidney malformations as our initial hypothesis for investigation; a second hypothesis for potential investigation was maternal xylene exposure in relation to selected genito-urinary malformations.

Analysis of Hypothesis: maternal exposure to benzene in relation to kidney malformations:
The results of this analysis are presented in Table 3. When exposure was defined strictly according to JEM attributions without regard to probability of exposure, the odds ratio was 2.7, with a 95% confidence interval of 1.4-5.1. When adjusted for potential confounding by maternal age, maternal education, parity, religion, calendar time, maternal smoking, paternal smoking, geographic region, and baby's sex, the odds ratio increased to 3.2 (95% confidence interval 1.5-6.8).

Validation of Analysis: Code Translations. We assessed concerns that our method of code translation may have resulted in some inaccuracies, and hence misclassification of exposure status. Two consultants (H.F., M.E.) reviewed the job descriptions of all exposed cases and a 1% sample of the remaining study subjects and coded them using 1980 Census codes. When the consultants' codes were compared to ours, we found three instances (4%) in which the code assigned by both consultants resulted in a change in exposure status. The details of these situations were as follows: 1) A nurse in a urologist's office was coded by us as a nurse in a hospital (considered by the JEM to be exposed to benzene) and by both consultants as a nurse in a physician's office (considered by the JEM to have no benzene exposure). This was clearly an error on our part which resulted from the fact that the original BDS job codes did not distinguish between these two jobs. 2) A home care nurse was coded by us

as a hospital nurse; one consultant coded her as a nurse in personnel supply services and the other as a nurse in health services n.e.c. 3) A press worker making rubber car parts was coded by us as a laborer in "other rubber products," which the JEM considers to be benzene-exposed; one consultant coded her as a pressing machine operator in the "motor vehicle and motor vehicle equipment" industry; the other consultant coded her as an extruding and forming machine operator in "other rubber products;" according to the JEM, neither of these jobs is exposed to benzene. There were 11 other instances of coding discrepancies in which the consultants disagreed with each other in terms of exposure in their code assignments; since in these cases one consultant agreed with our assignment, we retained our exposure assignment.

When the data were reanalyzed according to the consultants' revisions, the crude odds ratio dropped to 2.1 (95% confidence interval 1.0-4.2). Control of confounding had no material effect (OR=2.1, 95% C.I. 1.0-4.3).

Exposure Attribution. We next examined the data to determine the source of the benzene exposures. The occupation of over 85% of the mothers classified as benzene-exposed was "registered nurse" in "hospital." The remainder of the exposures derived largely from various occupations in the printing industry. To validate these exposures, we asked our consultants to review all the industry-occupation pairs which the JEM considers to reflect benzene exposure. At the same time, because of our potential interest in xylene, they also reviewed the JEM industry-occupation pairs which reflect xylene exposure. Agreement between the two consultants was only fair; for the 67 benzene-exposed jobs (not individuals) represented in the BDS data, both consultants agreed that the job would include benzene exposure in 46 cases (69%). For 19 jobs (28%), only one consultant classified them as benzene-exposed. For 2 jobs (3%), they agreed that these jobs were not benzene-exposed. One of these was "managers and administrators" in "miscellaneous manufacturing industries"; the other was "registered nurse" in "hospitals." The poor agreement between the JEM and our consultants, the fact that 85% of benzene-exposed mothers in our data were "registered nurses" in "hospitals," and our finding that most jobs in the JEM carried very low probabilities of exposure, prompted us to examine the JEM probabilities more closely.

Exposure Agreement According to Probability Level. The JEM-assigned probability of exposure to benzene among hospital-based registered nurses is quite low--0.015. If this estimate is correct, such a low probability of exposure could explain why neither consultant considered the job to be benzene-exposed. We hypothesized that agreement between the JEM-assigned exposures and our experts would increase as the probability of exposure increases. We therefore examined agreement between the JEM and our experts according to exposure probability for both benzene and xylene. The results are presented in Tables 4 and 5. Although the percentage of jobs for which both reviewers agreed with the JEM exposure increased as the JEM-assigned probability level increased, for benzene, the number of jobs with probabilities greater than 0.5 was quite small (six). For xylene, agreement with JEM exposure increased with probability level, but the percentage of cases in which the experts agreed that the job was not exposed also increased with probability level, including three jobs with JEM-assigned probability of 1.0.

Exposure Probabilities. The credibility of the probability assignments in the JEM is of critical importance for the analysis of our data. Although in our initial investigation we chose to consider any probability level to constitute exposure, one could reasonably postulate that jobs with low probabilities of exposure to the substance of interest (e.g., 0.1) actually provide no information and should be excluded from analysis. From a theoretical standpoint, one must first be assured that the probability estimates supplied by the JEM are reliable. Such assurance is particularly relevant from a practical standpoint, since the vast majority of exposures have very low probabilities for most jobs and therefore exclusions of this type would involve large amounts of data. We therefore investigated these probability assignments in greater detail.

We had already become aware of the fact that most of the jobs held by BDS parents were associated with very low probabilities. (We have previously provided figures showing the distribution of probabilities of exposure for the most common exposures among BDS parents; Figures 2-12 in this report provide these distributions for substances discussed in this report.) To investigate further, we selected three exposures for more detailed consideration: propylene glycol, amorphous fused silica, and dichlorodifluoromethane. These were chosen because a) our phase I analysis revealed each of them to include at least some jobs with high probabilities of exposure, b) our consultants felt that they were sufficiently knowledgeable about these exposures to make valid assessments, and c) they were of potential interest in future analyses. For each of these agents, we: 1) investigated the probability of exposure for BDS parents by geographic area, to assess whether the JEM might be more useful in some regions than in others; 2) asked two of our consultants (H.F., M.E.) to rate each job held by BDS parents according to four levels of exposure--none, low (probability greater than 0 but less than 1/3), medium (probability between 1/3 and 2/3), and high (probability greater than 2/3); and 3) explored the data on which the JEM exposure probabilities were based.

1) Geographic variation. The results of the investigation of probabilities according to geographic area are presented in Tables 6-11. For each exposure, the distributions were similar. This was true for both mothers and fathers. We found no evidence of geographic variation in occupational exposures within our data.

2) Probability ratings. The ratings of our consultants according to our four-point scale showed fair agreement with each other (67%, 72%, and 79% for dichlorodifluoromethane, propylene glycol, and silica, respectively), but when compared to the JEM ratings, agreement was very poor (20%, 3%, and 2% respectively). In fact, most of the agreement between consultants resulted from their both rating JEM-defined exposed jobs as not exposed. Even jobs to which the JEM assigned a probability level of 1.0 were, in many cases, rated by both consultants as not exposed. Among these were dichlorodifluoromethane exposure among "cashiers" at "gasoline service stations" and "managers and administrators" in "banking," and silica exposure among supervisors and proprietors in the retail florist industry.

3) How the JEM assigns exposure probabilities. We also investigated the manner in which the probabilities were derived within the JEM itself. The JEM

provides, for each industry-occupation pair, a) the number of workers surveyed, and, b) for each exposure, the number of workers in that industry-occupation who were observed to have that exposure. A measure of probability is calculated by dividing b by a. For each of the three exposures which we considered in detail, we grouped industry-occupation pair according to JEM-assigned probability level and examined the numbers on which these probabilities were based. For each decile of probability, we calculated the mean and median number of observations for each industry-occupation pair within that decile. Figures 13-15 plot these mean and median numbers according to probability level.

This analysis revealed a curious inverse relation between the probability level and the number of observations on which that probability was based. As noted above, we were already aware of the fact that for most jobs within the BDS data set and for most exposures, the probabilities were quite low. It now appears that this distribution of occupations is also true within the JEM itself. To a large extent, this is to be expected: In order to obtain a probability of less than 0.01, one must observe more than 100 people in that job. It is also the case that one would expect that many jobs would involve exposures to substances at very low probabilities, but only a few would have exposures at high probabilities. Nonetheless, we found it disturbing that the number of observations on which these high probabilities were based were so small--in many cases, fewer than five observations.

Although these high probabilities are quite unstable, it remains possible that they may accurately reflect the likelihood that a particular job is associated with a specific exposure. Based on the exposures which we have considered, this does not appear to be the case. For example, the JEM considered banking managers to have a 100% probability of exposure to xylene, but a 0% probability of exposure to paper. Laborers in the bus and urban transit industry were assigned a 100% probability of exposure to soap, but cooks in eating and drinking places have only a 0.7% probability of soap exposure (although janitors in eating and drinking places were assigned a 10% probability). Though substances such as paper, soap, and water may not be agents intended for evaluation by the JEM, their exposure probabilities were defined in a similarly standardized way, raising questions about the appropriateness of these procedures and methods.

These findings, together with the other problems we have noted, cast serious doubt on the value of the probability assignments in the JEM. Low probability levels (which involve the greatest numbers of people) are of little value because people with these occupations cannot realistically be considered exposed (nor, in fact, can they be considered non-exposed). On the other hand, high probability levels are, at best, very unstable because they are based on so few observations; further, they do not appear to reflect absolute exposure any more reliably than low probabilities.

If the probability levels in the JEM are of doubtful utility, can one apply JEM-based exposures independent of these probabilities? As we have documented in our analysis of benzene and kidney malformations, it is not reasonable to assume that any probability level implies exposure. In that example, virtually all of the benzene exposures derived from nurses, who do not represent a

credible source of exposure. Defining a probability level above which an occupation will be considered exposed and below which occupations must be excluded might seem to be a logical alternative approach, except for two considerations. First, as documented above, the fact that the high levels of probabilities are unstable and of questionable validity suggests that an appropriate level of probability would be difficult to define. Second, the fact that the vast majority of study subjects have occupations with low probabilities presents serious practical problems in attempting to conduct such an analysis. This was clearly a problem for the BDS data, and may well prove problematic in other data sets, since the distribution of job titles among BDS mothers is remarkably similar to that observed in a representative sample of childbearing U.S. women who were surveyed as part of the National Natality and National Fetal Mortality Survey(18).

Conclusions

Our objective in this research project was to evaluate the utility of the NIOSH JEM as a tool for investigating potential associations between workplace exposures and birth defects. The concept of a matrix such as the JEM is attractive as an alternative to the expensive and time-consuming task of expert review of individual job descriptions to assign exposures. By providing a mechanism that systematically links a job title with workplace exposures, a matrix would allow us to impute parental exposures which were not directly measured. The NIOSH JEM appeared to be particularly promising because it is based on direct observation of a large number of workplaces and is thus built on a large body of empirical exposure data, and it also provides the probability of exposure to a given substance for each industry-occupation pairing.

Unfortunately, our experience with the JEM has been disappointing. The mechanics of assigning codes to parents in the BDS data base and translating these into workplace exposures presented no insurmountable problems. The most serious difficulties we encountered in the translation process resulted from the fact that some of the BDS job descriptions were not specific enough to allow reliable assignment of codes; on the other hand, many common occupations were not included in the JEM, resulting in substantial loss of information. However, the larger problem centered on the validity of the exposure assignments within the JEM itself, and especially the probabilities of exposure.

One could ignore the levels of probability associated with each exposure and industry-occupation pairing; however, this approach would, under the best of circumstances, result in a high degree of misclassification. To assign every person who holds a job with any probability of exposure, no matter how low, to an exposed category is not reasonable since most people with those jobs are likely not to be exposed. On the other hand, this same category of workers cannot be considered unexposed. To select a level of probability above which exposure is considered to be plausible assumes that the JEM-assigned probabilities provide an accurate measure of the likelihood of exposure. Based on the assessments of our occupational and industrial health consultants, this does not appear to be the case.

One might consider ignoring probability-based exposure assignments in favor of expert review of job titles to identify exposures. Unfortunately, reviews by our consultants of the job titles of BDS parents, independent of the JEM, did not result in a satisfactory degree of agreement concerning exposure to selected substances. Although we investigated only a limited number of exposures in this way, the validity of this approach also seems questionable.

Given the nature of our analysis, we cannot determine whether the problems we identified are unique to the JEM or are related to more global limitations inherent in making job-exposure inferences. It may be that the information contained in an industry-occupation pair is simply not sufficient to allow valid inference of chemical and physical exposures, whether by means of a matrix or by means of expert review. It is certainly true that almost any single industry or occupation code listed in the Census codes encompasses a large number of diverse titles, and such heterogeneity would itself create difficulty in assigning exposures. Our experience with the Hoar linkage system also supports this theory. We rejected the Hoar system because of the large number of invalid exposure assignments which we discovered, but we had hoped that the inclusion of a measure of probability of exposure (as contained in the JEM) would reduce this problem. This was not our experience, and we must therefore conclude that application of the NIOSH JEM to the BDS data base does not provide a reliable means of assessing occupational exposures in relation to birth defects.

The fact that our screening process replicated several previously reported associations does not change this conclusion. It is well known that random misclassification will alter the observed odds ratio in the direction of the null value. It is also true that risks of large magnitude are the most readily identified. In a relatively unexplored area of investigation such as occupational exposures in relation to birth defects, it is reasonable to assume that the few associations already reported would be large, and therefore detectable despite substantial misclassification. However, for the detection of previously unreported associations which are likely to be of lesser magnitude, such misclassification would render the data uninformative.

Alternative Approaches. One alternative approach which we have not investigated, but which might prove useful, would be to focus on a relatively small number of exposures which are of potential interest and have experts review job descriptions rather than job titles to determine exposure status. This would enable researchers to focus on a subset of industries and occupations and ask more directed questions when gathering occupation information in the course of an interview, thus insuring that the relevant information is available to make exposure assessments. It is of interest to note that Siemiatycki, in a comparison of several methods of determining exposure status, found that an approach similar to this was most cost-effective in spite of its high absolute cost(19).

FIGURE 1

PHASE 1

VALIDATION OF COMPUTER-BASED TRANSLATION

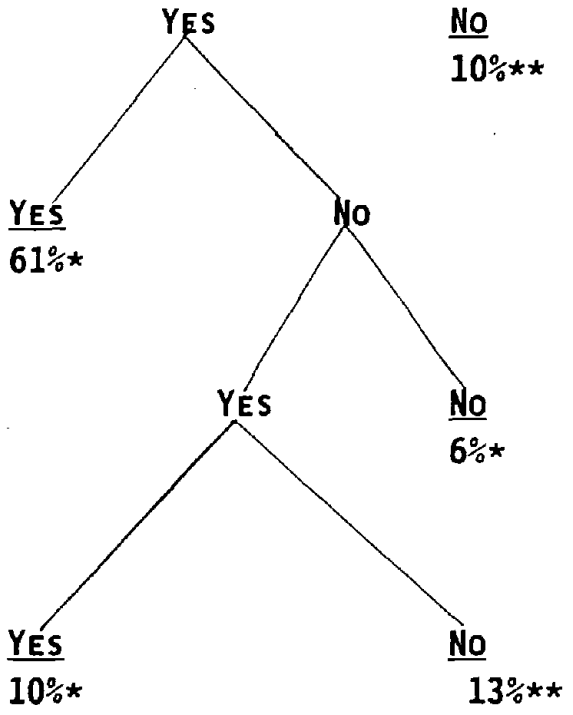
IN A SAMPLE OF DATA (N=60), COMPARE DIRECT CODING WITH COMPUTER TRANSLATION

DO EXPERTS AGREE AMONG THEMSELVES?

DO EXPERTS AGREE WITH COMPUTER-BASED TRANSLATION

IF THEY DISAGREE, IS THE DIFFERENCE IMPORTANT?

IF THE DIFFERENCES ARE IMPORTANT, WOULD THEY BE CORRECTED BY EXPERT REVIEW OF TRANSLATION ALGORITHMS?



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*METHOD PRODUCES VALID TRANSLATION: 77%

**METHOD DID NOT PRODUCE VALID TRANSLATION: 23%

ERRORS IDENTIFIABLE AND CORRECTABLE THROUGH REVIEW OF "HIGH RISK CODES": 16%

ERRORS IDENTIFIABLE AND CORRECTABLE ONLY THROUGH UNIVERSAL CHART REVIEW: 7%

Figure 2

Distribution of Exposure Probabilities
Propylene Glycol

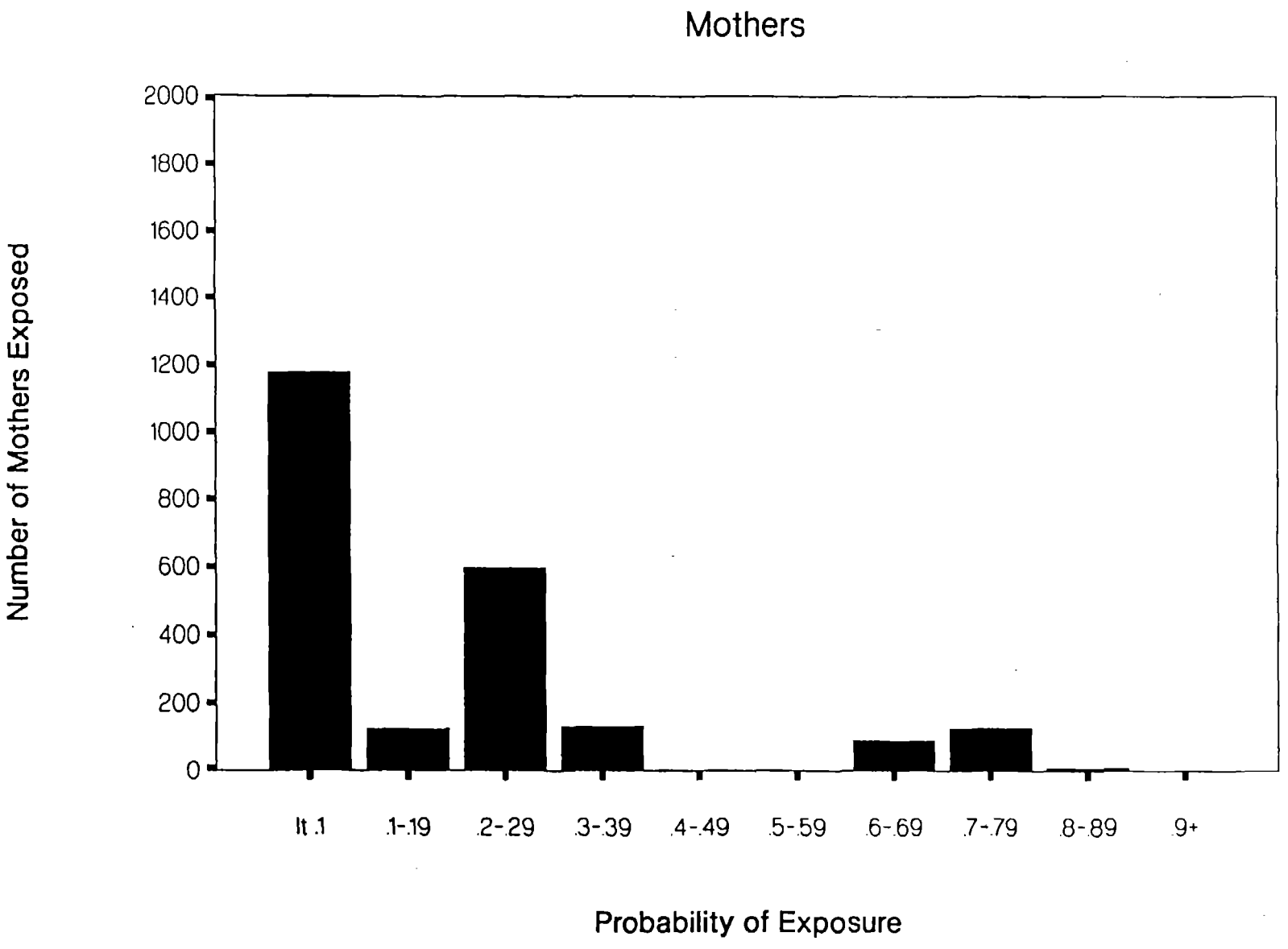

Figure 3

Distribution of Exposure Probabilities
Propylene Glycol

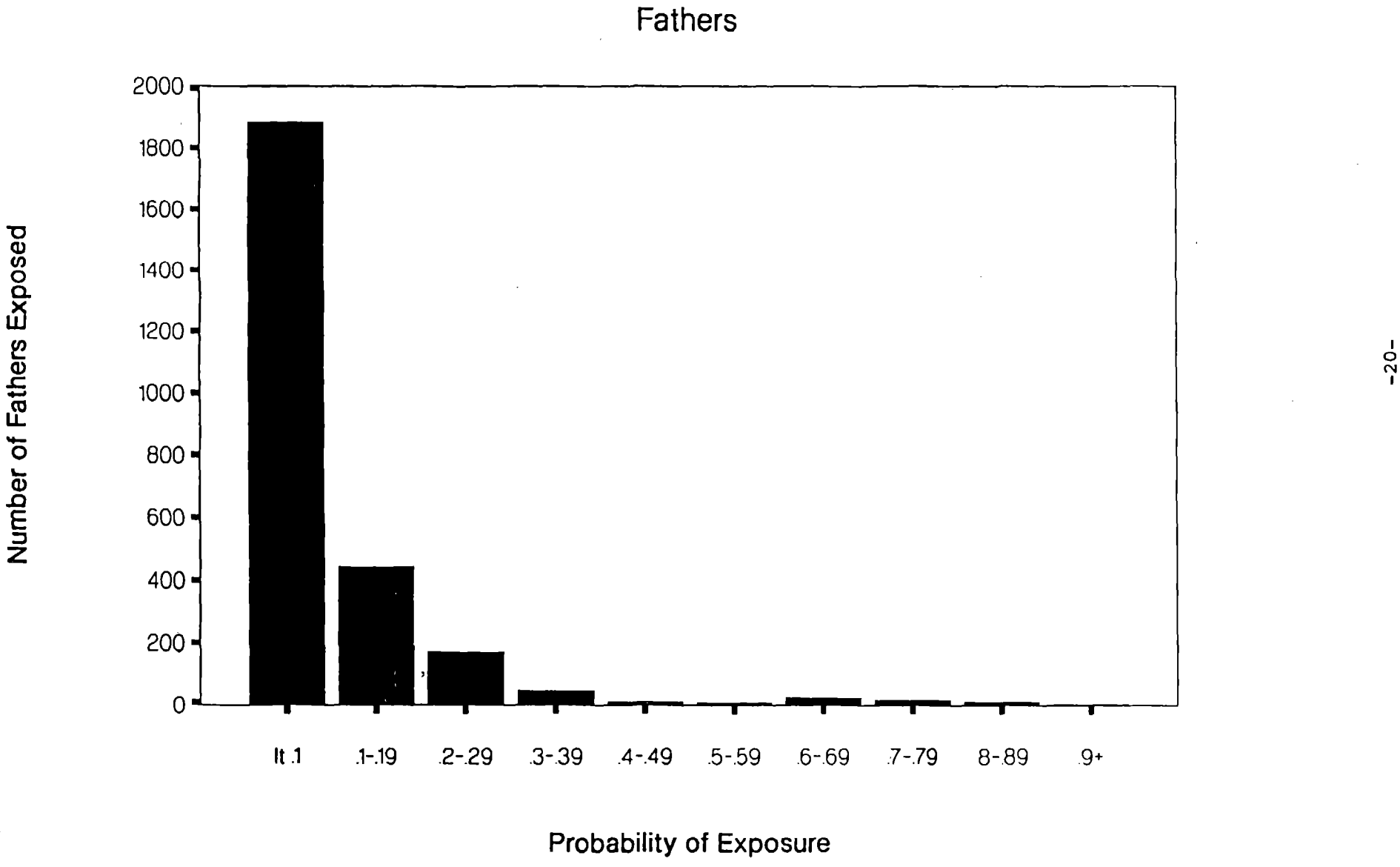

Figure 4

Distribution of Exposure Probabilities
Silica, Amorphous Fused

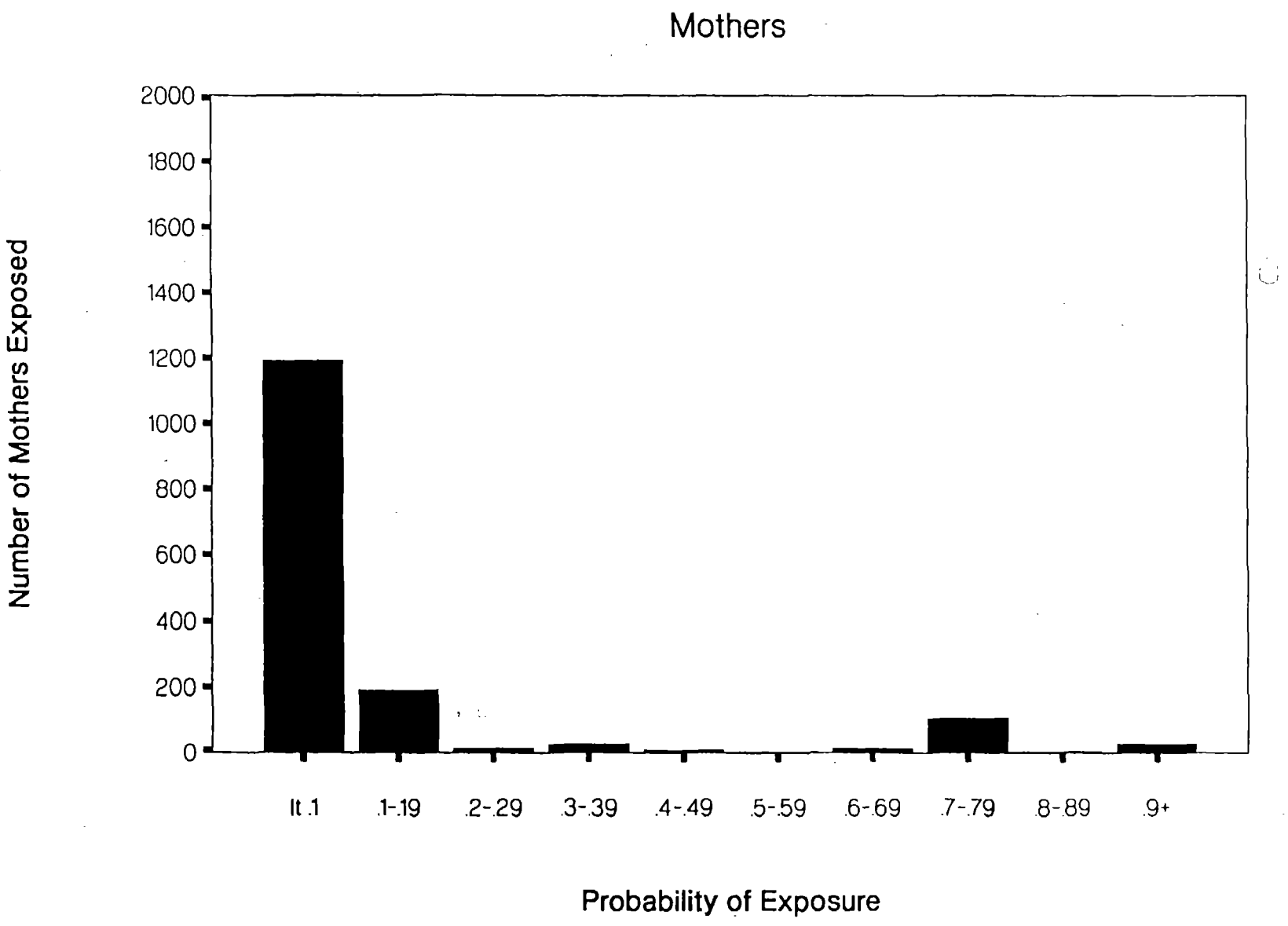

Figure 5

Distribution of Exposure Probabilities
Silica, Amorphous Fused

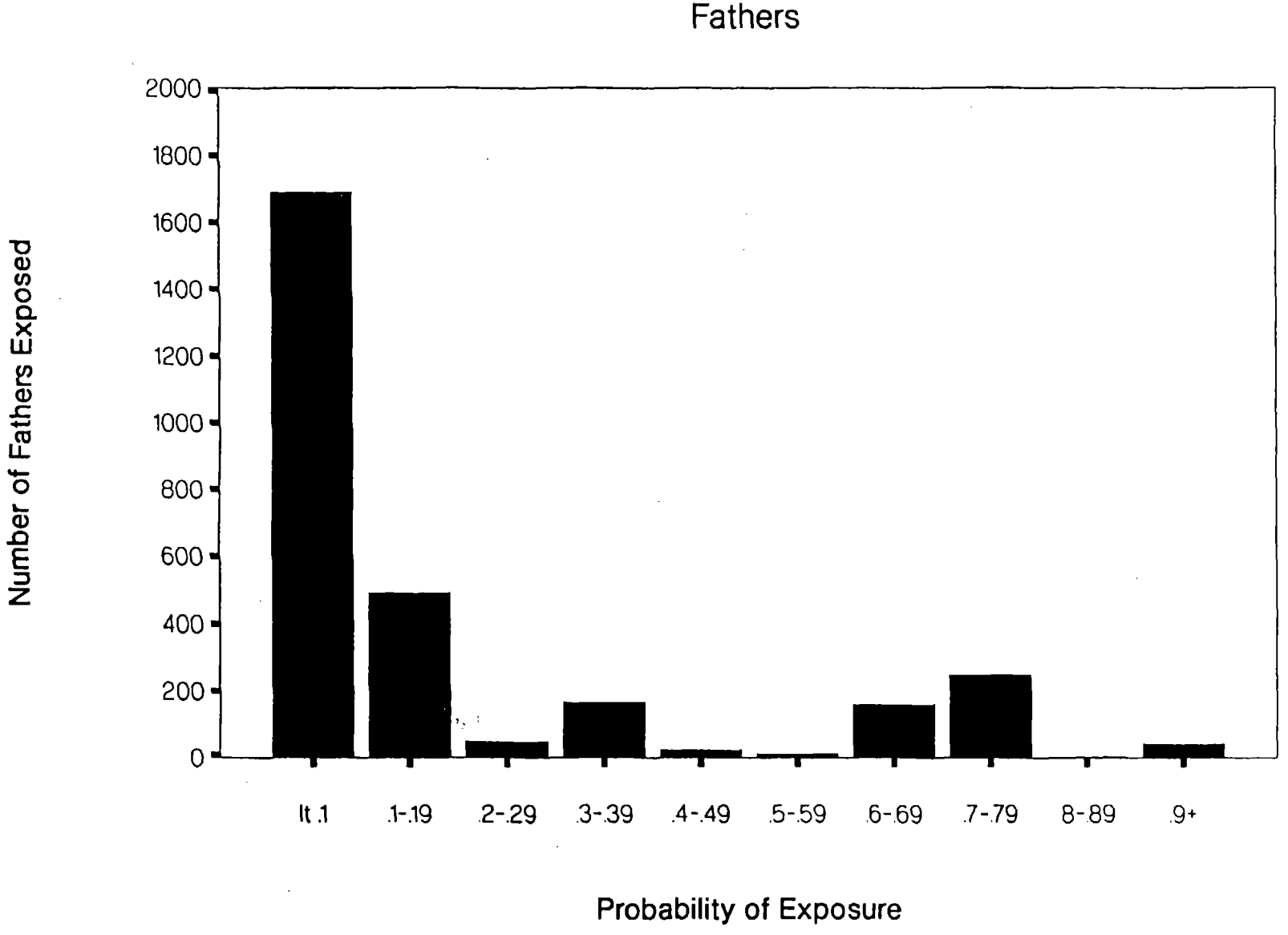

Figure 6

Distribution of Exposure Probabilities
Dichlorodifluoromethane

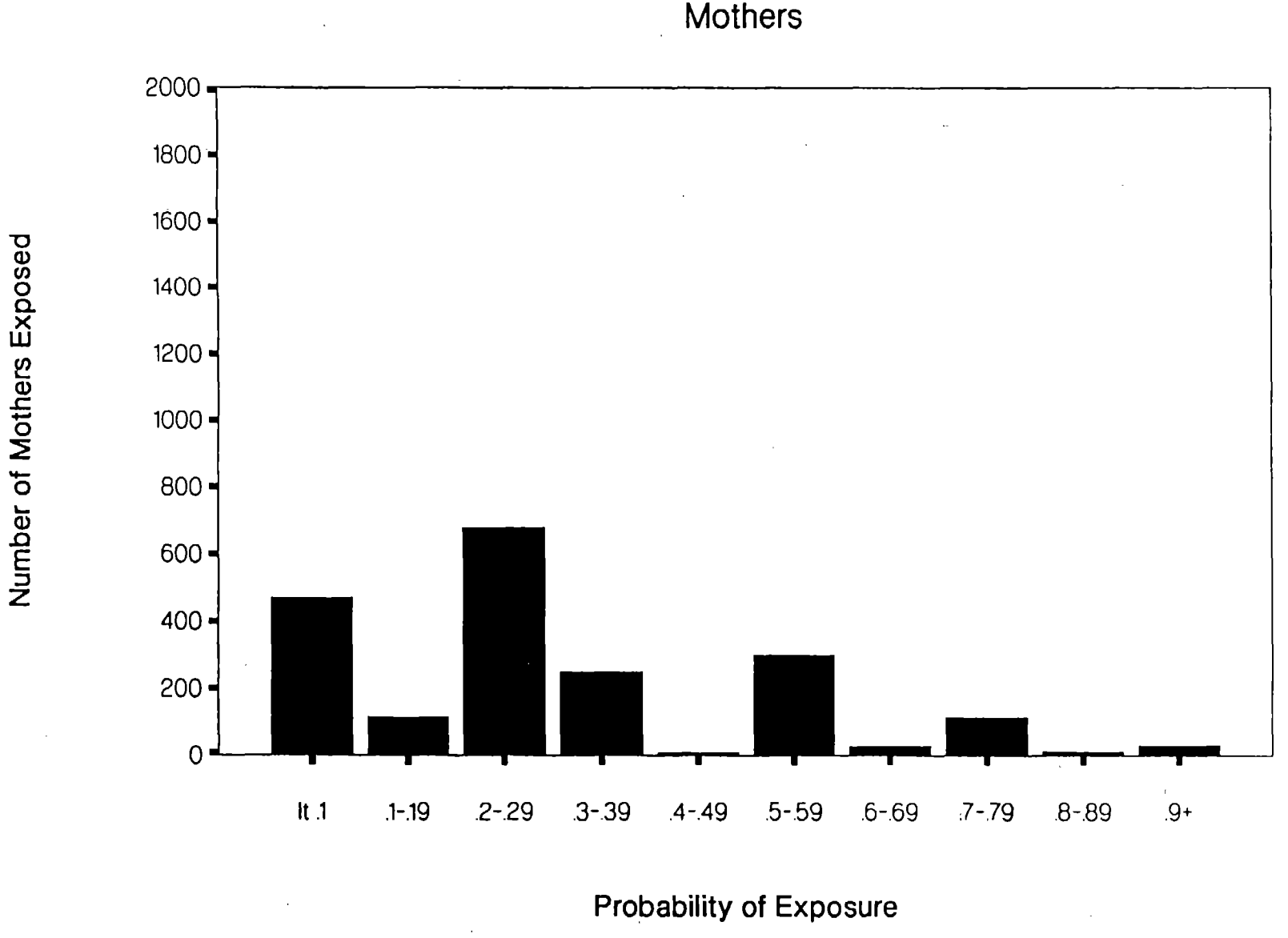

Figure 7

Distribution of Exposure Probabilities
Dichlorodifluoromethane

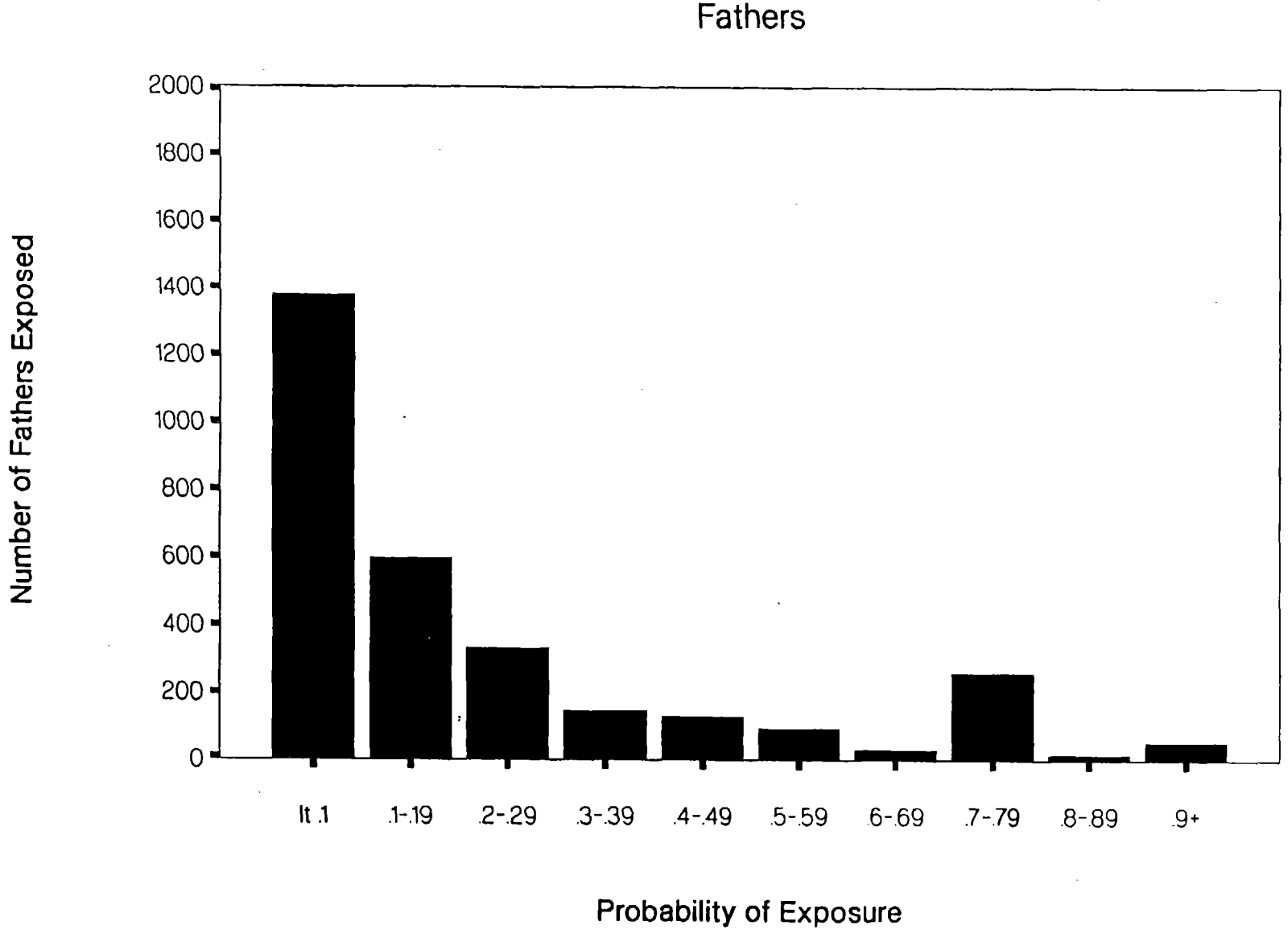

Figure 8

Distribution of Exposure Probabilities
Water

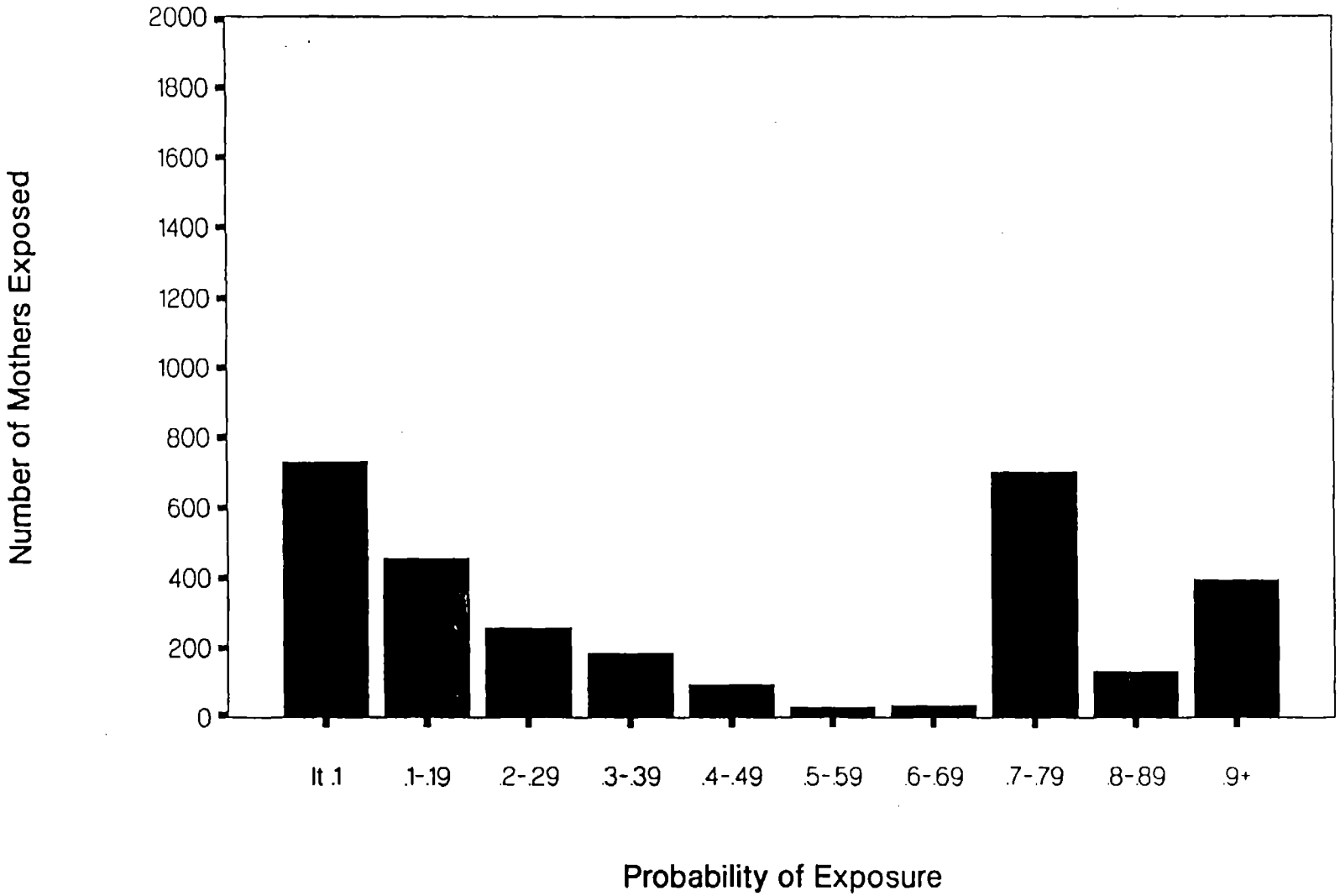

Figure 9

Distribution of Exposure Probabilities
Water

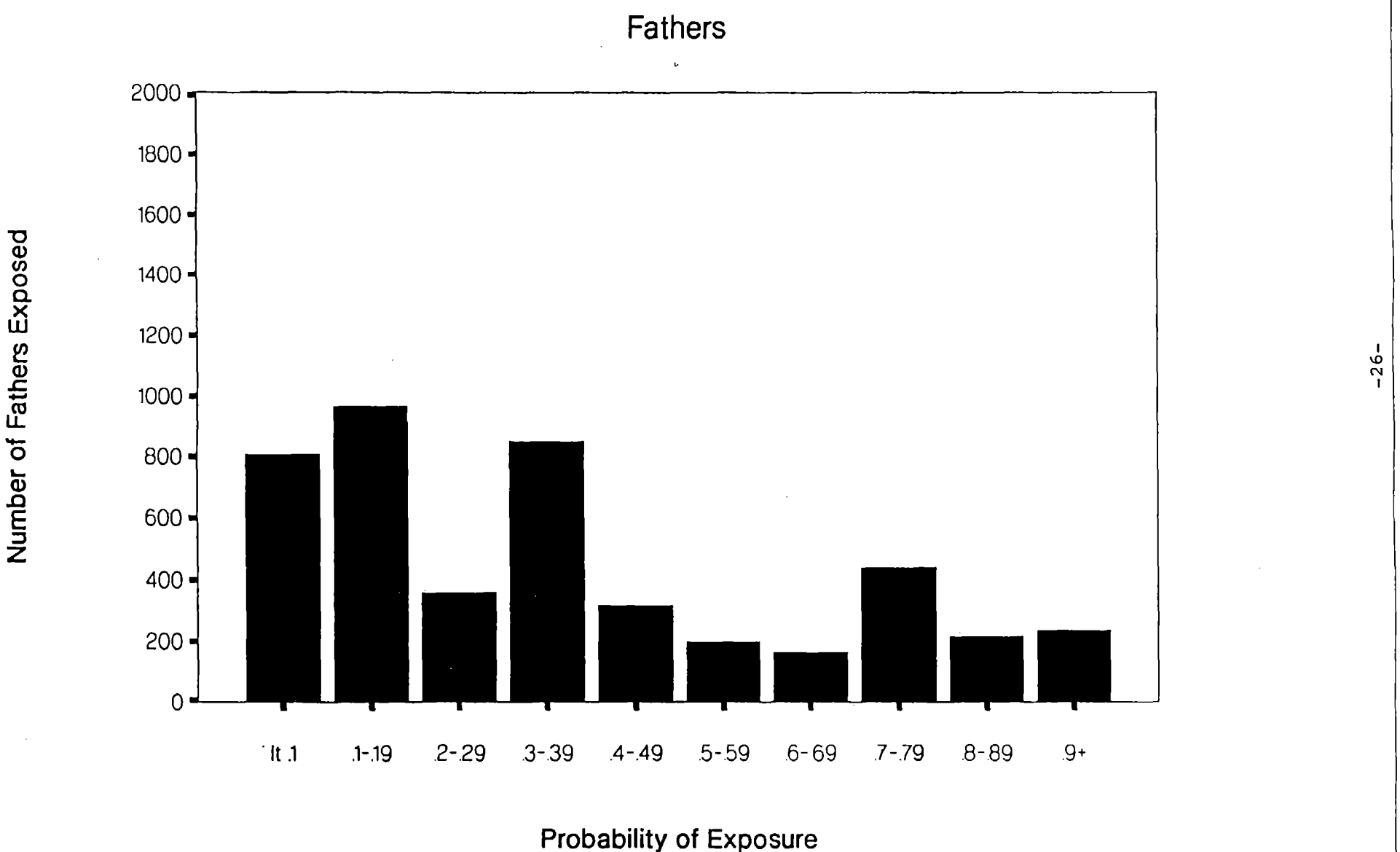

Figure 10

Distribution of Exposure Probabilities
Xylene

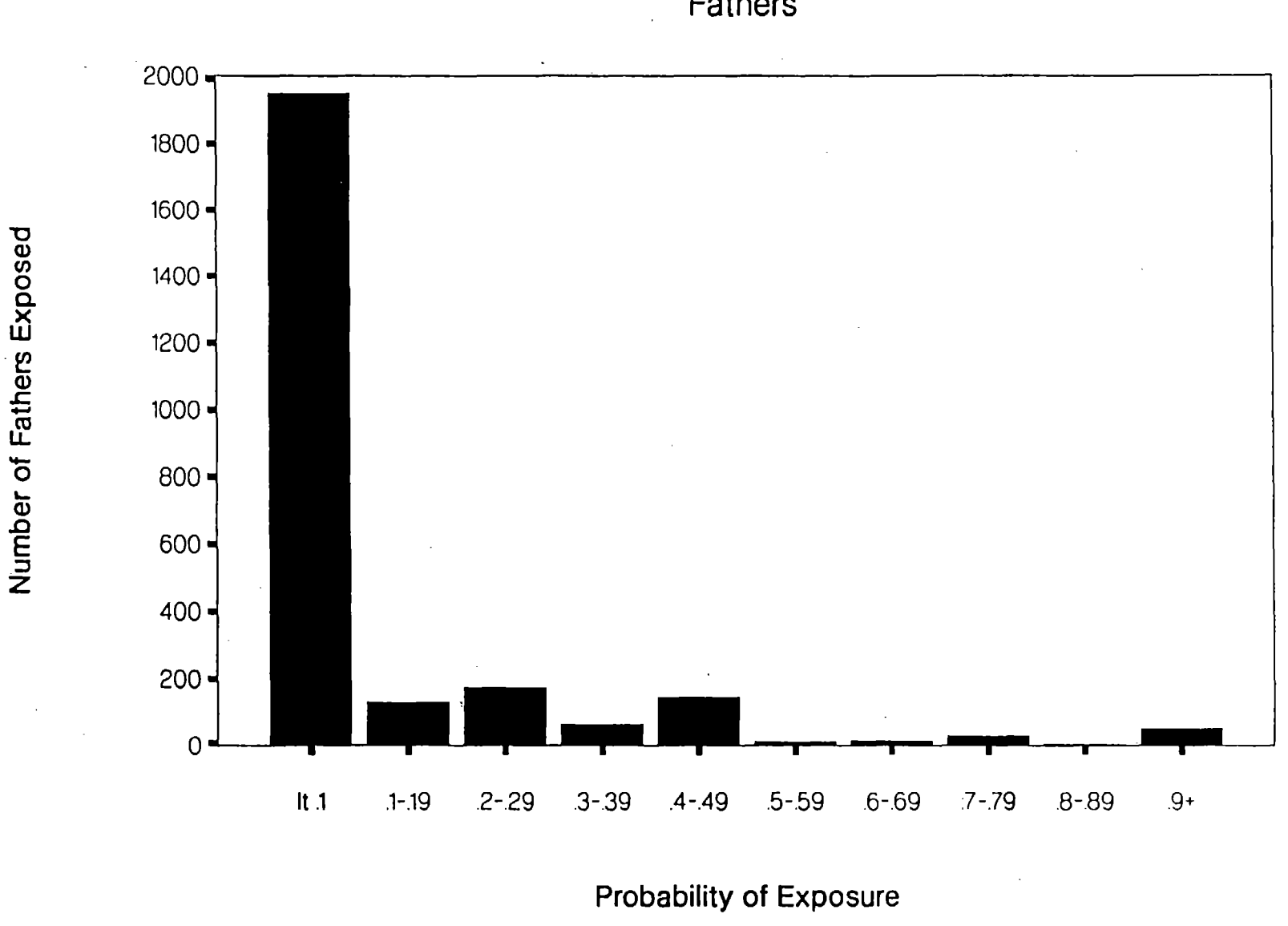

Figure 11

Distribution of Exposure Probabilities
Soap

Mothers

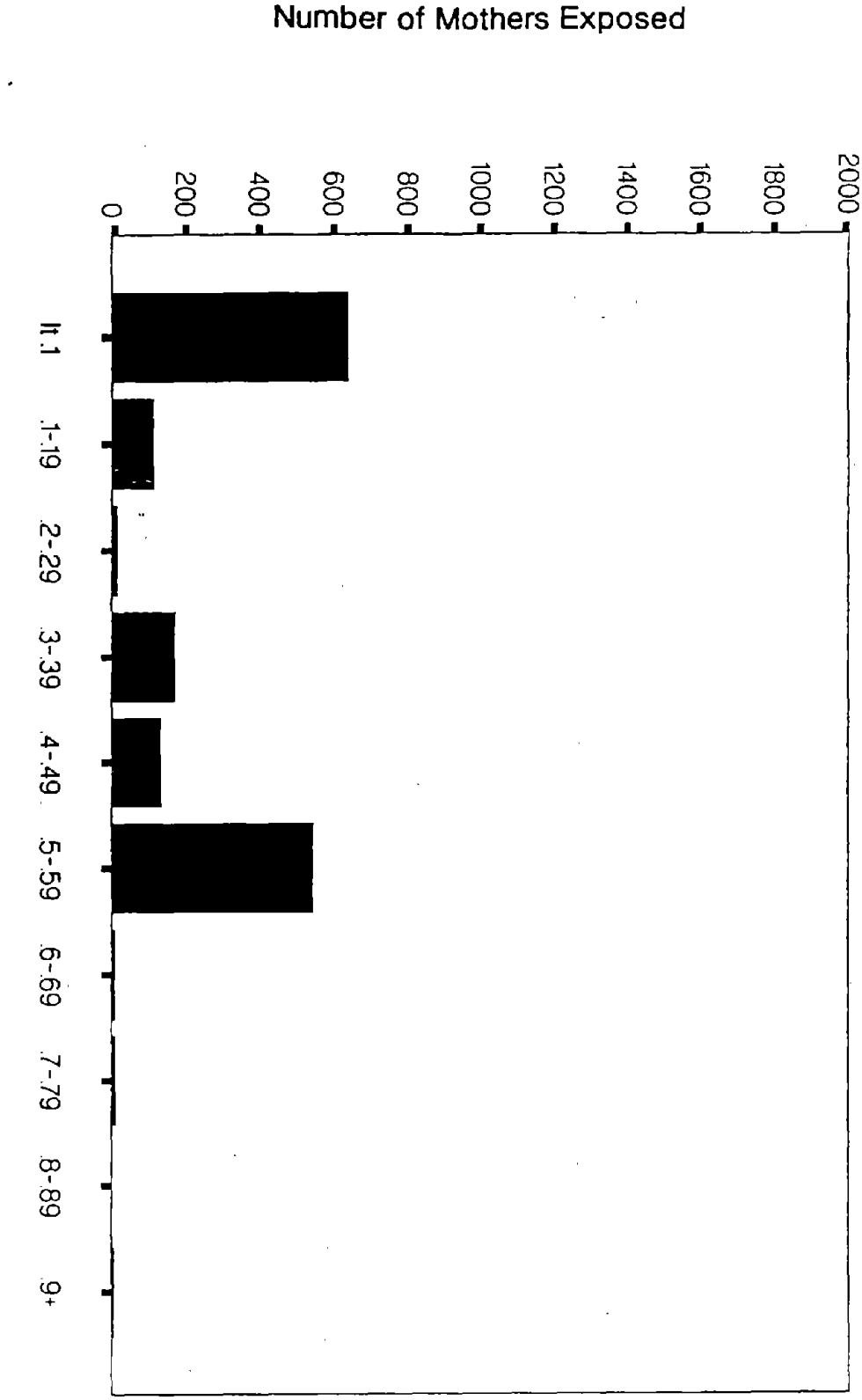

Figure 12

Distribution of Exposure Probabilities Paper

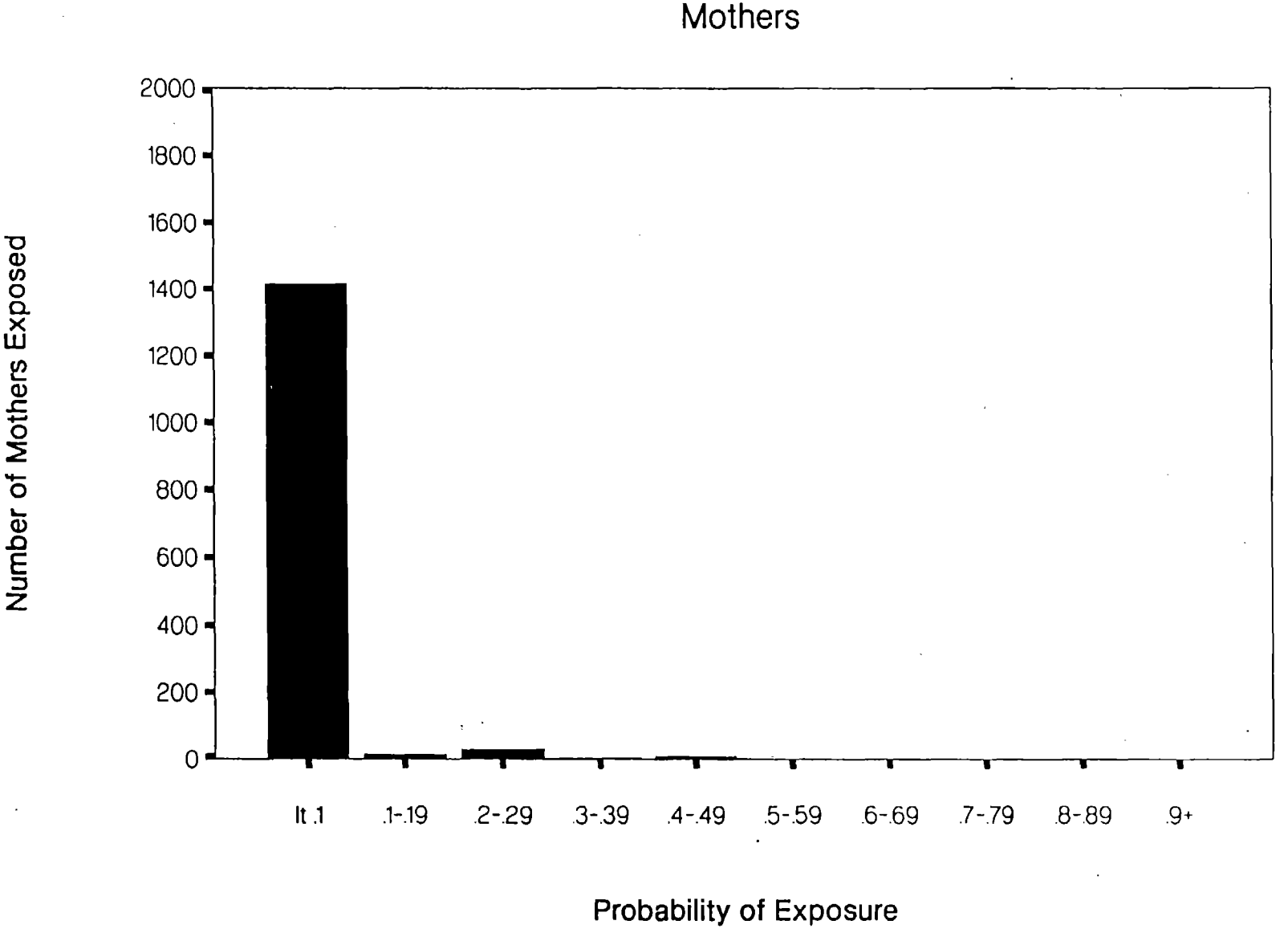

Figure 13

Mean and Median Sample Sizes of Occupations according to exposure probability

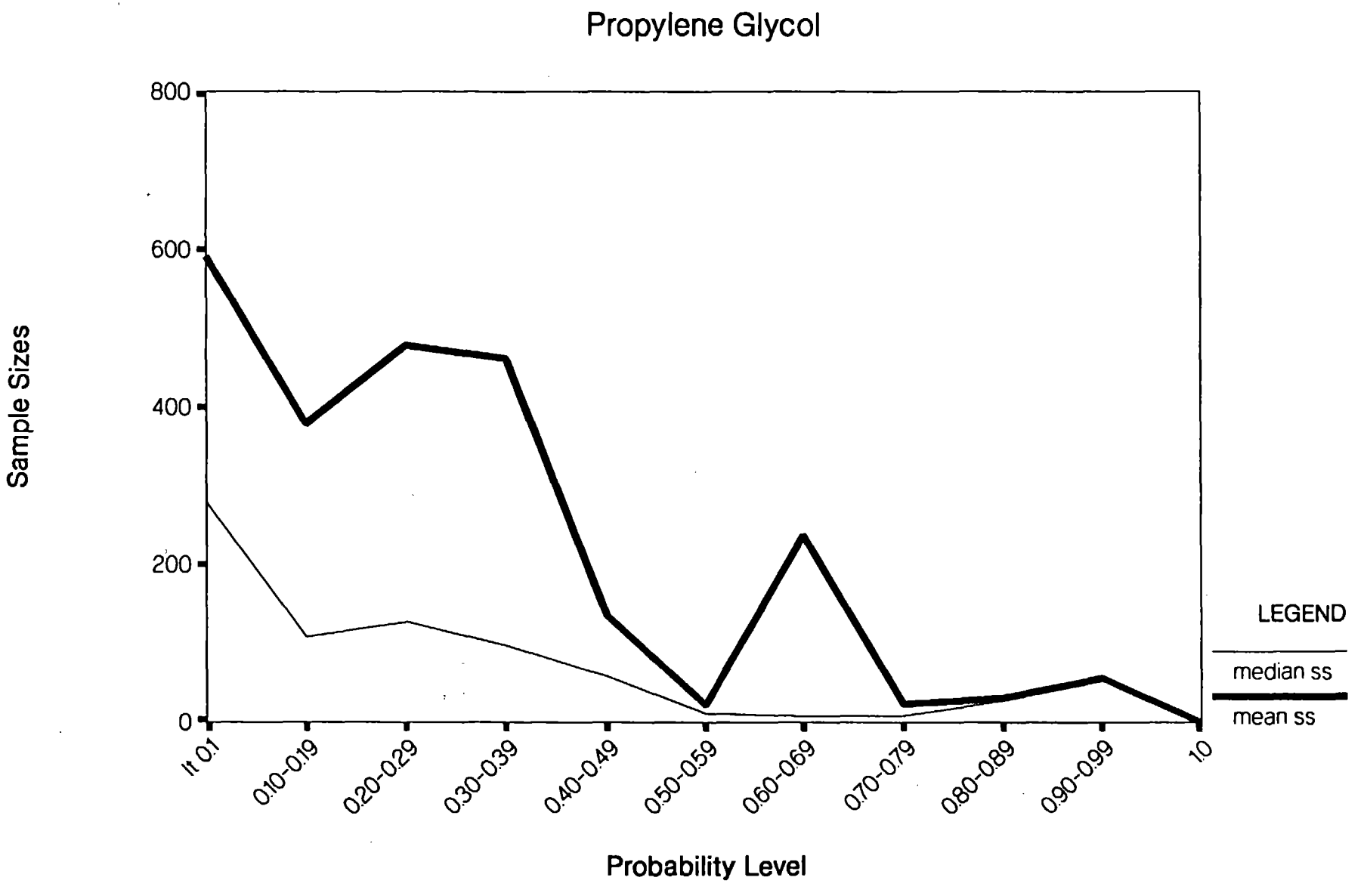

Figure 14

Mean and Median Sample Sizes of Occupations, according to exposure probability

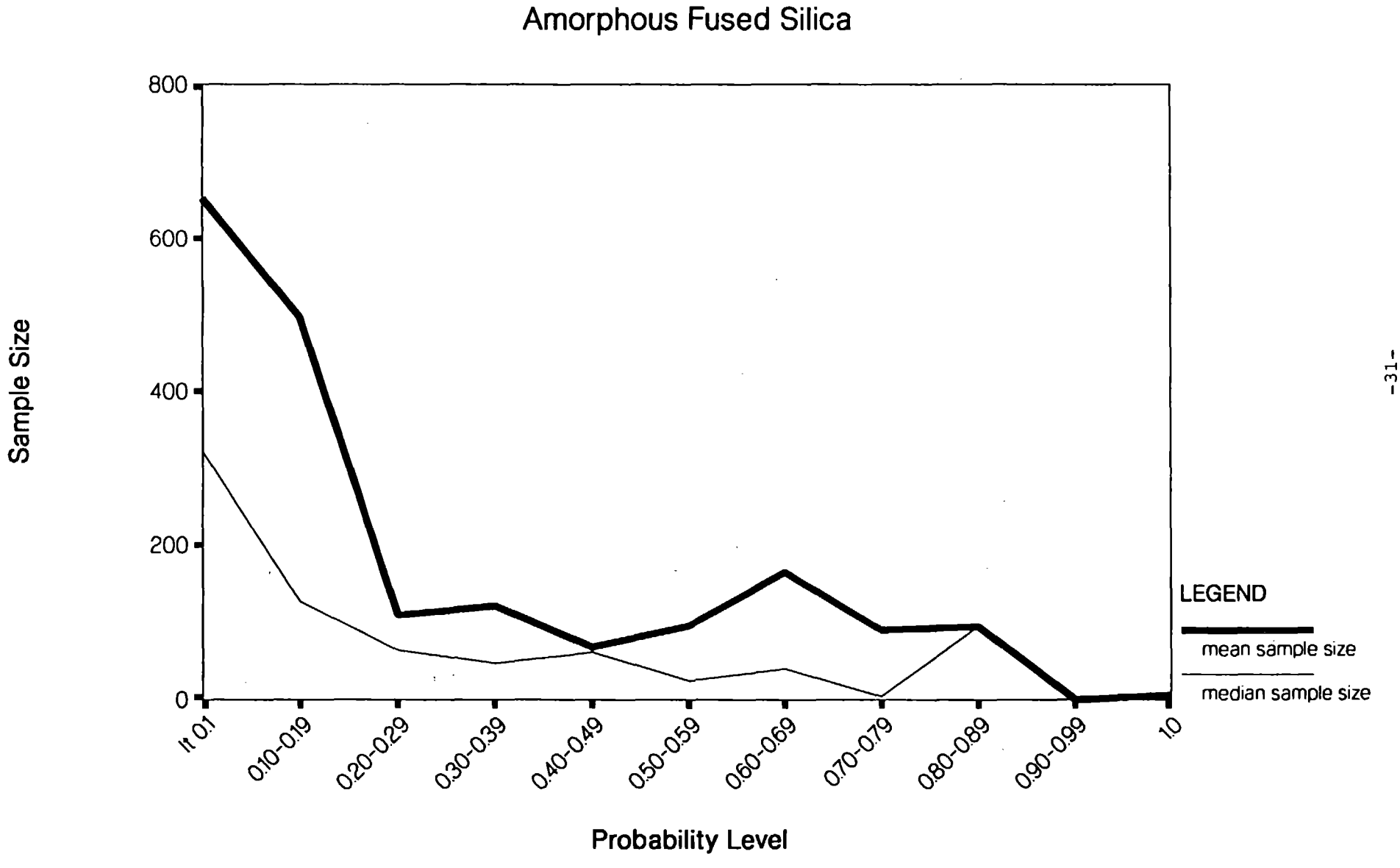

Figure 15

Mean and Median Sample Sizes of Occupations, according to exposure probability

Dichlorodifluoromethane

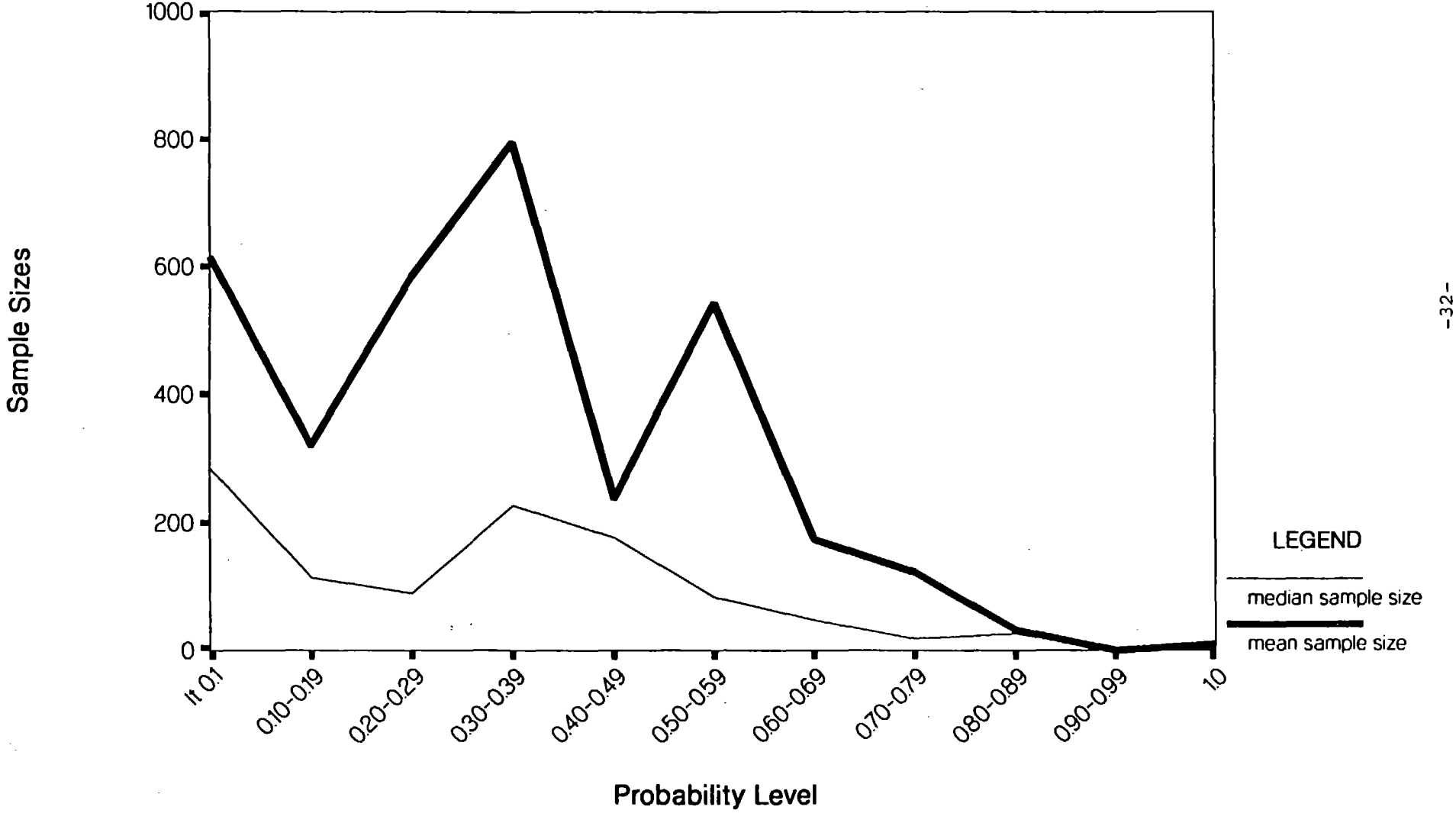

Table 1

Associations between Maternal Occupational Exposures and Specific Birth Defects

	BDS screen results				
Literature	Exposure (n)	Defect (n)	No. exposed with defect	Relative risk	p value
Mercury and CNS malformations[1,2]	Mercury (16)	Brain anomalies (67)	1	10.7	p <.01
	Mercury sulfide (14)	Brain anomalies (67)	1	18.7	p <.001
Organic solvents and GU system[3]	Benzene (625)	Anomalies of kidney (100)	13	2.7	p <.001
		Anomalies of ureter (102)	14	2.8	p <.001
Organic solvents and CV defects[4]	Xylene (1184)	Anomalies of aortic valve (65)	13	2.2	p <.01
		Conotruncal defects (351)	46	1.4	p <.05

[1]Koos BJ and Longo LD. Mercury toxicity in the pregnant woman, fetus, and newborn infant. Am J Obstet Gynecol 1976;126:390-409.

[2]Chang LW et al. Prenatal and neonatal toxicology and pathology of heavy metals. Adv Pharmacol Chemother 1980;17:195-231.

[3]McDonald JC, Lavoie J, Cote R, McDonald AD. Chemical exposures at work in early pregnancy and congenital defects: a case-referent study. Br J Ind Med 1987;44:527-33.

[4]Tikkanen J, Heinonen OP. Cardiovascular malformations and organic solvent exposure during pregnancy in Finland. Am J Ind Med 1988;14:1-8.

Table 2

Associations between Paternal Occupational Exposures and Specific Birth Defects

Literature	BDS screen results: Exposure (n)	Defect (n)	No. exposed with defect	Relative risk	p value
Mercury and CNS malformations[1,2]	Mercury (94)	Anencephaly (55)	2	6.2	p <.01
		Hydrocephaly/ Ventriculomegaly (230)	7	3.6	p <.001
Organic solvents and CNS malformations[3]	Xylene (2563)	Spina bifida (164)	47	1.5	p <.05
	Benzene (688)	Anencephaly and Spina bifida (624)	47	1.5	p <.05

[1]Koos BJ and Longo LD. Mercury toxicity in the pregnant woman, fetus, and newborn infant. Am J Obstet Gynecol 1976;126:390-409.

[2]Chang LW et al. Prenatal and neonatal toxicology and pathology of heavy metals. Adv Pharmacol Chemother 1980;17:195-231.

[3]Olson J. Risk of exposure to teratogens amongst laboratory staff and painters. Dan Med Bull 1983;30:24-8.

Table 3

Kidney Malformations and Maternal Benzene Exposure

Benzene exposure	Kidney malformation No. (%)	Controls No. (%)
Yes	18 (34)	612 (16)
No	25 (66)	3136 (84)
Odds Ratio (95% CI)	2.7 (1.4, 5.1)	
Adjusted* Odds Ratio (95% CI)	3.2 (1.5, 6.8)	

*Adjusted for maternal age, maternal education, parity, religion, calendar time, maternal smoking, paternal smoking, geographic center, baby's sex.

Table 4

Rates of Agreement* of Exposure Status Between Experts
According to Probability Level
Benzene

JEM-assigned probability level	No. Jobs	Both experts agree		One expert agrees		Neither expert agrees	
		No.	(%)	No.	(%)	No.	(%)
<.1	44	30	(57)	12	(27)	2	(5)
.1-.19	11	7	(64)	4	(36)	0	--
.2-.29	3	2	(67)	1	(33)	0	--
.3-.39	3	2	(67)	1	(33)	0	--
.4-.49	0	--	--	--	--	--	--
.5-.59	3	2	(67)	1	(33)	--	--
.6-.69	1	1	(100)	0	--	0	--
.7-.79	0	--	--	--	--	--	--
.8-.89	1	1	(100)	--	--	--	--
.9-.99	1	1	(100)	--	--	--	--
1.0	0	--	--	--	--	--	--
TOTAL	67	46	(69)	19	(28)	2	(3)

*Experts defined exposure only as dichotomous ("yes/no") variable.

Table 5

Rates of Agreement* of Exposure Status Between Experts
According to Probability Level
Xylene

JEM-assigned probability level	No. Jobs	Both experts agree		One expert agrees		Neither expert agrees	
		No.	(%)	No.	(%)	No.	(%)
<.1	141	83	(59)	54	(38)	4	(3)
.1-.19	32	17	(53)	12	(38)	3	(9)
.2-.29	17	9	(53)	8	(47)	0	--
.3-.39	7	4	(57)	1	(14)	2	(29)
.4-.49	9	7	(78)	1	(11)	1	(11)
.5-.59	7	5	(71)	1	(14)	1	(14)
.6-.69	2	1	(50)	1	(50)	0	--
.7-.79	4	4	(100)	0	--	0	--
.8-.89	2	2	(100)	0	--	0	--
.9-.99	1	1	(100)	0	--	0	--
1.0	5	2	(40)	0	--	3	(60)
TOTAL	227	135	(59)	78	(34)	14	(6)

*Experts defined exposure only as dichotomous ("yes/no") variable.

Table 6

Geographic Distribution of Exposure Probabilities
Propylene Glycol (Mothers)

	Boston		Philadelphia		Toronto		Iowa		TOTAL	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<.1	333	(47)	402	(51)	380	(64)	61	(39)	1176	(52)
.1-.19	40	(6)	37	(5)	32	(5)	14	(9)	123	(5)
.2-.29	207	(29)	224	(28)	117	(20)	48	(31)	596	(27)
.3-.39	61	(9)	38	(5)	18	(3)	13	(8)	130	(6)
.4-.49	1	(0.1)	--	--	--	--	--	--	1	--
.5-.59	--	--	1	(0.1)	--	--	--	--	1	--
.6-.69	32	(4)	41	(5)	11	(2)	5	(3)	89	(4)
.7-.79	37	(5)	44	(6)	30	(5)	14	(9)	125	(6)
.8-.89	--	--	2	(0.2)	4	(0.6)	1	(0.6)	7	(0.3)
.9-.99	--	--	--	--	--	--	--	--	--	--
1.0	--	--	--	--	--	--	--	--	--	--
TOTAL	711		789		592		156		2248	

Table 7

Geographic Distribution of Exposure Probabilities
Propylene Glycol (Fathers)

	Boston		Philadelphia		Toronto		Iowa		TOTAL	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<.1	572	(74)	721	(71)	489	(73)	101	(65)	1883	(72)
.1-.19	127	(16)	185	(18)	102	(15)	28	(18)	442	(17)
.2-.29	37	(5)	68	(7)	45	(7)	19	(12)	169	(6)
.3-.39	16	(2)	13	(1)	12	(2)	3	(2)	44	(2)
.4-.49	3	(0.3)	5	(0.5)	2	(0.3)	1	(0.6)	11	(0.4)
.5-.59	1	(0.1)	3	(0.3)	3	(0.4)	1	(0.6)	8	(0.3)
.6-.69	8	(1)	9	(0.8)	6	(0.9)	1	(0.6)	24	(0.9)
.7-.79	9	(1)	6	(0.6)	1	(0.2)	0	--	16	(0.6)
.8-.89	1	(0.1)	4	(0.4)	5	(0.8)	1	(0.6)	11	(0.4)
.9-.99	0	--	1	(0.1)	1	(0.2)	0	--	2	(0.1)
1.0	0	--	0	--	0	--	0	--	0	--
TOTAL	774		1015		666		155		2610	

Table 8

Geographic Distribution of Exposure Probabilities
Silica (Mothers)

	Boston		Philadelphia		Toronto		Iowa		TOTAL	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<.1	408	(78)	446	(76)	257	(72)	81	(76)	1192	(76)
.1-.19	56	(11)	69	(12)	49	(14)	16	(15)	190	(12)
.2-.29	5	(0.1)	5	(0.8)	3	(0.8)	--	--	13	(0.8)
.3-.39	9	(2)	11	(2)	3	(0.8)	2	(2)	25	(2)
.4-.49	1	(0.2)	4	(0.7)	3	(0.8)	--	--	8	(0.5)
.5-.59	1	(0.2)	--	--	--	--	--	--	1	--
.6-.69	4	(0.8)	5	(0.8)	3	(0.8)	2	(2)	14	(0.9)
.7-.79	32	(6)	39	(7)	29	(8)	5	(5)	105	(7)
.8-.89	--	--	--	--	1	(0.3)	1	(0.9)	2	(0.1)
.9-.99	--	--	--	--	--	--	--	--	0	--
1.0	8	(2)	10	(2)	9	(3)	--	--	27	(2)
TOTAL	524		589		357		107		1577	

Table 9

Geographic Distribution of Exposure Probabilities
Silica (Fathers)

	Boston		Philadelphia		Toronto		Iowa		TOTAL	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<.1	512	(59)	641	(74)	454	(60)	79	(54)	1686	(59)
.1-.19	142	(16)	200	(23)	119	(16)	29	(20)	490	(17)
.2-.29	17	(2)	16	(2)	12	(2)	2	(1)	47	(2)
.3-.39	46	(5)	64	(7)	48	(6)	7	(5)	165	(6)
.4-.49	6	(0.7)	10	(1)	6	(0.8)	1	(0.6)	23	(0.8)
.5-.59	4	(0.5)	3	(0.3)	4	(0.5)	0	--	11	(0.3)
.6-.69	53	(6)	68	(8)	28	(0.4)	11	(8)	160	(6)
.7-.79	75	(9)	92	(11)	68	(9)	14	(10)	249	(9)
.8-.89	0	--	0	--	1	(0.1)	0	--	1	--
.9-.99	0	--	0	--	0	--	0	--	0	--
1.0	12	(1)	13	(1)	13	(2)	3	(2)	41	(1)
TOTAL	867		1107		753		146		2873	

Table 10

Geographic Distribution of Exposure Probabilities
Dichlorodifluoromethane (Fathers)

	Boston		Philadelphia		Toronto		Iowa		TOTAL	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<.1	414	(46)	491	(42)	403	(50)	68	(39)	1376	(45)
.1-.19	176	(20)	248	(21)	138	(17)	34	(20)	596	(20)
.2-.29	96	(11)	137	(12)	73	(9)	26	(15)	332	(11)
.3-.39	40	(4)	58	(5)	34	(4)	12	(7)	144	(5)
.4-.49	29	(3)	49	(4)	40	(5)	11	(6)	129	(4)
.5-.59	29	(3)	41	(4)	22	(3)	1	(0.6)	93	(3)
.6-.69	11	(1)	14	(1)	3	(0.4)	2	(1)	30	(1)
.7-.79	78	(9)	95	(8)	71	(9)	16	(9)	260	(9)
.8-.89	1	(0.1)	4	(0.3)	7	(0.9)	3	(2)	15	(0.5)
.9-.99	0	--	0	--	0	--	0	--	0	--
1.0	20	(2)	21	(2)	13	(2)	0	--	54	(2)
TOTAL	894		1158		804		173		3029	

Table 11

Geographic Distribution of Exposure Probabilities
Dichlorodifluoromethane (Mothers)

	Boston		Philadelphia		Toronto		Iowa		TOTAL	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<.1	140	(22)	171	(24)	125	(26)	32	(23)	468	(23)
.1-.19	43	(7)	35	(5)	28	(6)	8	(6)	114	(6)
.2-.29	255	(39)	248	(34)	124	(26)	50	(36)	677	(34)
.3-.39	78	(12)	98	(14)	52	(11)	21	(15)	249	(12)
.4-.49	1	(0.2)	5	(0.7)	2	(0.4)	--	--	8	(0.4)
.5-.59	77	(12)	104	(14)	103	(21)	15	(11)	299	(15)
.6-.69	9	(1)	12	(2)	4	(1)	2	(1)	27	(1)
.7-.79	36	(6)	41	(6)	30	(6)	7	(5)	114	(6)
.8-.89	1	(0.2)	2	(0.3)	5	(1)	2	(1)	10	(0.5)
.9-.99	--	--	--	--	--	--	--	--	--	--
1.0	10	(2)	6	(1)	13	(3)	--	--	29	(1)
TOTAL	650		722		486		137		1995	

Acknowledgment

We gratefully acknowledge the substantial contributions of our expert consultants Howard Frumkin, Michael Ellenbecker, and Rose Goldman. We also wish to thank Roy Fleming, Karl Sieber, and Joyce Salg at NIOSH for their advice and cooperation.

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