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A CASE-CONTROL STUDY OF MALIGNANT MELANOMA AMONG LAWRENCE LIVERMORE NATIONAL LABORATORY EMPLOYEES:

A CRITICAL EVALUATION

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July 1, 1987

Lawrence Livermore National Laboratory

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A Case-Control Study of Malignant Melanoma Among Lawrence Livermore National Laboratory Employees: A Critical Evaluation

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Executive Summary

Introduction

Background of Austin/Reynolds Study.

The intent of Report #3 of Austin and Reynolds, "A Case-Control Study of Malignant Melanoma Among Lawrence Livermore National Laboratory Employees", was to identify occupational factors that were associated with the occurrence of malignant melanoma at LLNL. Austin and Reynolds used a matched case-control study design, with approximately four controls matched to each of 31 cases, involving a total of 141 study subjects. Eight risk factors emerged from their study as potential occupational risk factors for melanoma. Of these eight factors, Austin and Reynolds expressed confidence that five ("working around radioactive materials", "presence at site 300", "working around volatile photographic chemicals", "presence at the Pacific nuclear test site", and "chemist job duties") were genuine occupational risk factors associated with malignant melanoma at LLNL.

Purpose of Study.

This is a report of our reanalysis of the data of the Austin and Reynolds study. We were asked by LLNL to confirm Austin and Reynolds's numerical results and to address specific questions about the choice of controls, statistical significance of the results, possible sources of bias, and approaches to modeling the data other than those used by Austin and Reynolds. Finally, we were asked to recommend further action based on our results.

Our study can be divided into four parts: 1) a validation of Austin and Reynolds's analytical results, 2) an extension of their analysis, 3) an examination of possible bias and other factors that may distort their results, and 4) recommendations for further work.

We treated this study as a hypothesis generating study, designed to reveal candidates for possible occupational risk factors among employees of LLNL. Also, it is obvious that any analysis of potential risk factors that investigates risk within the LLNL population alone cannot hope to throw much light on the question of whether or not there is more melanoma at LLNL than we should expect. Furthermore, there are simply too few cases in this study, and too many potential risk factors to screen, to be able to claim with much certainty that a particular factor can be strongly implicated as a melanoma risk factor.

On the other hand, the data set is admirably designed to narrow the search for a presumed occupational risk factor. Many of the occupational questions asked of the subjects did not pertain as much to specific exposures as to general experiences. This is certainly the case for factors such as "worked at site 300", but it is also true of such specific-sounding exposures as "worked around radioactive materials". For those occupational exposure questions that gave rise to the coding for the variables describing inhaled, skin, and miscellaneous exposures, the relevant question asked on the questionnaire was "Did you ever work around [substance]?". When these coded variables are seen as answers to this question, it is clear that they actually serve to group LLNL employees into exposure groups whose members may have several exposures in common.

Validation of Austin/Reynolds Study

First Stage of Validation: Check Accuracy of Original Data.

The first stage of validation was to check the data tapes against the original questionnaires for accuracy of data transcription. We selected a sample of questions from the original Austin / Reynolds questionnaire, including most of the information used in the final analysis, and recoded the answers for all the cases in the study and a 20% random sample of the controls. The recoded answers were then compared to the codes on the original data tapes. No errors were found in the parts of the data used in their final analysis. As a result of this validation procedure, we feel confident that the data analyzed reflect the information collected during the personal interviews and recorded on the questionnaires.

Second Validation Stage: Examine Control Selection.

The next stage of validation was to determine to what extent the controls chosen for the study might differ from the population of non-diseased individuals at LLNL, and, further, to evaluate the impact that such a deviation might have on inferences drawn from an analysis of these data. We had extensive information on the distribution of job classification codes and radiation badge readings on the LLNL employee population. This allowed us to determine job classification codes whose bearers among the LLNL employee population tended to receive higher than normal radiation doses. We could then check whether the actual controls used for the Austin / Reynolds study might contain a smaller proportion of subjects who might be expected to work around radioactive materials than the LLNL population at large. Although we

tried several different ways of classifying job classification codes using the badge data, as well as looking at general categories such as "scientists and engineers", there was no credible evidence that the controls were anything other than representative of the LLNL population from which they were chosen. In the process, we used data on radiation-badge-measured radiation exposure among the LLNL employee population to group job classification codes into those that are "radiation-related" and those that are not. It turned out that melanoma cases were significantly more likely to have worked at jobs that were deemed "radiation-related" by this criterion.

Third Validation Stage: Confirm Statistical Calculations.

As the third step of validation, we recalculated the conditional logistic regression models reported by Austin and Reynolds in their Tables 34, 35, 37, 38, and 39, as well as additional models designed to explore possible confounding between pairs of occupational factors. There were no discrepancies between the original odds ratio estimates and our recalculated odds ratios; however, because of the way Austin and Reynolds handled missing data, they seem to have attributed more importance to the occupational factor "1969 building" than it deserves. We then calculated regression diagnostics for each of the models, as recommended by Storer and Crowley (1981). This kind of diagnostic is designed to identify matched sets in the data that have an undue influence on parameter estimates. Generally, we found no undue influence on the estimated odds ratios.

Fourth Validation Stage: Examination of Additional Models.

For the effect of an occupational factor to be correctly estimated, the

effects of all other risk factors that are correlated with that occupational factor must be taken into account. Generally, this means that either all risk factors correlated with the given occupational factor must be included in any regression model used to estimate the adjusted effect of that occupational factor, or the data must be stratified on all of the risk factors and the effect of the occupational factor estimated using a method that takes the stratification into account. Therefore, we cannot be certain of properly estimating an odds ratio for an occupational factor if we are unsure of other risk factors. In the case of melanoma, a number of studies have identified factors associated with melanoma in other populations. Although many of the risk factors are similar across studies, some risk factors are unique to individual studies. To estimate reliably the effect of occupational factors on melanoma occurrence, we would need to include all potential risk factors in every model used to estimate occupational factor effects. However, there are too few matched sets in this study to do this. An alternative is to estimate the effect of occupational factors in a collection of models that include different sets of variables (obtained from the literature on melanoma) that represent plausible guesses of important risk factor combinations. If the occupational factor effects estimated from these different models do not vary much from each other, it is likely that confounding has been adequately dealt with in the estimation of occupational factor effects in these data. Alternatively, if effect estimates differ substantially from one model to another, we would be less certain of what a reliable estimate of the occupational effect should be. Using this approach, we carried out an extensive analysis of the eight occupational factors identified in the Austin/Reynolds study. We found that three occupational factors withstood

rigorous testing, and hence we consider them to be reliable risk factors associated with relatively stable effect estimates. These factors were: "working around radioactive materials". "present at site 300", and "working around photographic chemicals".

Extension of the Austin/Reynolds Study

Analysis of Additional Radiation Data.

To further examine the A/R study, we extended the original analysis in two directions. Since the variable "worked around radioactive materials" remained such an important factor, we used additional data supplied by LLNL on ionizing radiation exposure to further evaluate this exposure as a risk factor for melanoma. In a previous study, Austin and Reynolds had reported a lack of association between ionizing radiation and melanoma. Their dose measure was the logarithm of the total cumulative gamma radiation dose measured by badges, accumulated up to the time of their study. Because of the apparently strong and reliable association between melanoma and the factor "working around radioactive materials", we re-examined the association between ionizing radiation and melanoma using data from the LLNL personnel records on individual badge readings. We found no association between melanoma case status and cumulative ionizing radiation dose measured at the time of case diagnosis. In addition to cumulative ionizing radiation dose, we also examined the relation between portions of the overall dose and melanoma status in two ways: early doses (in case ionizing radiation serves as an initiator

for melanoma), and doses immediately preceeding diagnosis (in case ionizing radiation serves as a promoter for melanoma). We found no significant association between ionizing radiation exposures and melanoma in either instance, although the confidence limits for some of the odds ratio were quite large. On the basis of the badge data, then, it is unlikely that ionizing radiation is an important risk factor for melanoma. This result, however, does not necessarily indicate that the odds ratios estimated for the factor "working around radioactive materials" are in error. There may be other unrecorded exposures common to persons who work around radioactive materials. It is also possible that badge records do not record the relevant exposures, either because the relevant exposures occurred before record-keeping commenced, or because badges do not record them accurately.

Examination of the Time Factor.

The occupational factors identified by Austin and Reynolds represent exposures that may have changed their nature over time. For example, suppose that employees who work around radioactive materials are exposed to a substance which is an unknown risk factor for melanoma, and to which other LLNL employees are not exposed. If the relative frequency of exposure to that specific substance changes over time, then the risk of melanoma among those employees would depend upon the time when they had worked around these radioactive materials. Identifying and describing such temporal variation could prove helpful in isolating previously unidentified risk factors for melanoma. Our analysis also shows that the occupational factors: "presence at site 300", "working around radioactive materials", and "working in a building constructed in 1969" have greater risks in earlier reference years than in

later ones. The odds ratio for "working in a building constructed in 1969" increases rapidly in early reference years, then declines nearly as rapidly. A time dependence for this risk factor was observed by Austin and Reynolds, and is consistent with the hypothesis of a short term exposure to an unknown risk factor. This factor could have been present for only a short time after the building was opened and produced illness soon after exposure. This type of general pattern is consistent with a hypothetical risk factor that could have been associated in early years with the three occupational risk factors cited above. As time passes, either exposure to this hypothetical risk factor becomes less prevalent, or the association between it and the above three occupational factors becomes less strong.

Examination of bias.

Bias can be defined as a systematic error which results in estimated odds ratios which misrepresent the values of the true odds ratios. Selection bias deals with potential errors in case or control selection. In general, we did not find strong evidence for selection bias in the A/R study. Recall bias (i.e., errors caused by either cases or controls selectively remembering or forgetting exposures which might lead to melanoma) is difficult to detect and quantify. Some indirect evidence, however, suggests that recall bias is not an important factor in the A/R study. The close similarity of the non-occupational odds ratios estimated by the A/R study to those reported in the literature provides evidence for lack of recall bias and lack of selection bias, at least for the non-occupational factors of the study. Although similar data for occupational factors are not available in the literature, our extensive investigation of the potential confounding of the occupational odds

ratios suggests that the estimated odds ratios for "radioactive materials", "site 300", and "photographic chemicals" are probably reasonably good measures of the true effects. Because of the large number of statistical tests performed on the data, the probability of falsely declaring a factor (or factors) significant is quite high. The possibility of making this type of error cannot be ignored; and since the statistical nature of this error does not allow one to conclude that a specific factor or factors have been erroneously claimed to be important, we must conduct further studies to validate those factors found to be significant in hypothesis-generating studies. However, the practice of performing a large number of significance tests in an exploratory study is not unusual , and is scientifically appropriate as long as the results are taken as hypothesis generating (i. e., to be confirmed by future hypothesis testing studies). And, finally, although of less importance in this study, we may have missed finding some additional risk factors of melanoma because of the small number of cases in the study.

Recommendations for Further Work

As a general statement, we conclude that, after rigorous analytical validation and testing of the Austin/Reynolds data, three occupational factors remain strongly associated with malignant melanoma at LLNL in this particular data set: "working around radioactive materials", "presence at site 300", and "working around volatile photographic chemicals". However, since these results were obtained in an hypothesis-generating study, they cannot be

considered as viable risk factors for malignant melanoma without further investigation. Therefore, we recommend that LLNL continue to investigate the possible occupational etiology of melanoma using another case-control study at the Laboratory. We suggest that the cases be subdivided into four groups: 1) living cases who contracted melanoma subsequent to leaving LLNL, 2) A/R study cases, 3) cases identified subsequent to A/R study, but not through the LLNL screening program, and 4) cases identified through the LLNL screening program. Controls should be carefully chosen as discussed in our chapter on recommendations. Also, attention should be paid to potential sources of bias, as outlined in the bias chapter of this report. In addition, a more detailed history of sun exposure in youth is needed. To further improve the study, an industrial hygienist should be involved in planning the questionnaire for this future study. The occupational factors that we have identified in this report as most reliable should be used as a starting point to help identify possible chemical exposures, or other exposures that may be uniquely associated with those chemical exposures. It would also be profitable to look for exposures that were specific to persons who worked around radioactive materials, or worked at site 300, or worked around photographic chemicals in the 1960's and early 1970's, (i.e., exposures which are not now used, or are now more generally distributed at LLNL). This new case-control study would try to re-evaluate those exposures identified in the original A/R study, and to further screen other exposures identified by the industrial hygienist as common to the risk groups identified in the A/R study.

I. Introduction

In 1981, members of the Resource for Cancer Epidemiology of the California Department of Health released a study that reported that the rate of malignant melanoma among employees of Lawrence Livermore National Laboratories (LLNL) was three to four times the expected rate for that population. On the strength of this first report, the same investigators undertook to determine conditions of employment at LLNL that were associated with melanoma. The rarity of the disease (32 cases had been reported among LLNL employees between 1969 and 1980) dictated that the study of melanoma among the employees of LLNL be a matched case-control design. Each of the 32 cases was associated with four controls who matched the case on sex and race, were within five years of the case's age, and were employed by LLNL sometime in the calendar year in which the case was diagnosed. One case and thirteen controls did not participate, leaving a total of 141 subjects, including 31 cases.

The sources of data for the study were a mailed, self-administered questionnaire and an extensive personal interview. The investigators collected information on lifestyle factors, such as outdoor recreational activities, and constitutional and family history factors, such as skin color and family history of skin cancer, that had been implicated in previous studies as possible risk factors for melanoma. In addition, the participating subjects reported on a number of occupational factors in the LLNL work environment that the investigators felt were unusual (P. Reynolds, personal communication). Chapter II of this report goes into more detail about the

structure and coding of the personal interview questionnaire.

Austin and Reynolds used two methods to screen the occupational variables for potential risk factors. First, they used estimated crude odds ratios to screen both the occupational and non-occupational variables for factors that seemed to be associated with melanoma case status. This was only a preliminary screen, however, since crude odds ratios are subject to confounding. "Confounding" refers to the distortion of the effect estimate for a factor that occurs when that factor is correlated with other risk factors for the disease being investigated. Confounding can cause the effect estimate for a factor to be large even if the factor is not a true risk factor, or confounding can mask the effect of a true risk factor. The effect of confounding on the estimate of the odds ratio for a potential risk factor can be reduced or eliminated by controlling for known risk factors. This can be done using regression methods, or by stratifying on such known risk factors and using an estimation method that takes the stratification into account. To control for confounding in the LLNL data set, Austin and Reynolds estimated the adjusted odds ratios for occupational factors using conditional logistic regression models that included terms for non-occupational factors and other occupational factors.

Through their analysis of crude odds ratios, Austin and Reynolds identified eight potentially important occupational variables, all based on answers to questions during the personal interview: namely, "worked around radioactive materials", "worked around volatile photographic chemicals", "worked at site 300, a non-nuclear test site", "chemist duties", "scientist duties", "worked around fumes of high explosives", "visited a Pacific test site during an atmospheric nuclear test", and "ever worked in a building

constructed in 1969". After controlling for confounding by constitutional and other occupational factors, five of these factors remained, namely: "worked around radioactive materials", "worked at site 300", "worked around volatile photographic chemicals", "visited the Pacific test site", and "chemist duties". The authors claimed causal status for these factors, and recommended that LLNL initiate a further case-control study using cases that had been diagnosed since their study, and that LLNL should set up a melanoma screening program for their employees.

In late 1984, the Melanoma Task Force of LLNL approached our group at UNC with a request to reanalyze the Austin / Reynolds case-control data. LLNL had specific questions: "Were the numerical results reported by Austin and Reynolds reproducible?", "Were the controls a representative sample of the undiseased laboratory population?", "Were there likely to be sources of bias that would invalidate the conclusions of Austin and Reynolds's analysis of these data?", "Were the asymptotic P-values valid?", "Did the large number of significance tests carried out in the course of this study present a problem?" Finally, LLNL wanted to know, "Are there other methods for modeling the data?"

We added our own concerns to those initially framed by LLNL. First of all, we wanted to check the data management aspects of the case-control study to assure ourselves that the data accurately represented the responses of the subjects as recorded on the questionnaires. Secondly, we were concerned that confounding may not have been adequately controlled in the original study. The non-occupational factors used to control confounding had all been determined through a preliminary screen of the same data. There is a danger that some important confounders will be missed if only factors that are initially statistically significant are used in the final analysis. We wanted

to explore another approach to the control of confounding that would not rely upon the crude associations in the data at hand for determining which non-occupational factors were likely to be confounders. Third, we wanted to explore in greater detail than had Austin and Reynolds in their original study the possibility that ionizing radiation exposure was a risk factor for melanoma. Fourth, we wanted to know if the excess risk apparently associated with the occupational factors listed above had been constant over time, or if some of the risk factors might not have been more important at one time than another.

Each of the chapters of this study reflect our response to either one of LLNL's concerns or our own about the Austin/Reynolds analysis of the case-control data set. Chapter II reports the result of checking the validity of the data. In Chapter III, we address the concern that the controls might not be a representative sample from the LLNL employee population, thereby resulting in possible selection bias in the estimates of the odds ratios for occupational factors. In Chapter IV, we recalculate certain key conditional logistic regression models from Austin and Reynolds's report, using regression diagnostics to evaluate the stability of the effect estimates. Chapter V discusses an innovative general approach to assessing the importance of confounding on effect estimates in studies such as this, and presents the results of applying this new technique to these data. Since one of the occupational groups that seems to be at increased risk of melanoma in these data is the set of employees who have reported working around radioactive materials, we were interested in determining if the relevant risk factor for these subjects was ionizing radiation exposure. We report in Chapter VI on an analysis of the association between ionizing radiation exposure, as measured

by radiation badges, and melanoma case status. In Chapter VII, we analyze the apparent temporal heterogeneity of some occupational risk factors identified by Austin and Reynolds. Observational studies such as this are plagued by the possibility of various types of bias. In Chapter VIII, we evaluate the hypothesis that an occupational factor at LLNL acts to elevate the number of benign nevi. In Chapter IX, we discuss different types of bias that normally afflict observational studies in epidemiology, and how they might influence the results of the Austin/Reynolds study. Finally, in Chapter X, we summarize the conclusions about the Austin/Reynolds analysis of these case-control data, and we present our recommendations for future work.

Although each chapter contains the rationale for its own analytical approach, it is appropriate here to outline our general approach to the analytical problems presented by these data.

An analysis of factors within the employee population can give us only limited information about the risk for melanoma of working at LLNL versus not working at LLNL. Finding strong candidates for risk factors would be further evidence for an increased risk of melanoma among LLNL employees as a whole. However, if we do not find a strong risk factor, we cannot take this as evidence against the presence of such a risk factor; we may simply have not asked the right question, or the risk factor may be an exposure to which nearly all LLNL employees are exposed.

Our task, then, is to sift through a list of potential occupational risk factors and identify those most likely to be actual risk factors. In practice, this means estimating an odds ratio (or whatever other effect estimate we choose to use) for each potential occupational risk factor, and then using statistical methods to evaluate the magnitude of that odds ratio

relative to 1.0. To do this, of course, it is important that we have estimates for odds ratios that are as unbiased as possible. In particular, we want to avoid confounding. For this reason, we avoid standard precision-based variable selection methods, such as step-wise regression. Precision-based variable selection methods may produce well-fitting models in a data set, but the parameter estimates produced by these methods are likely to be biased estimates of the true effects of the associated risk factors (Kleinbaum, Kupper, and Morgenstern, 1982). Instead of precision-based methods, we use validity-based regression strategies to estimate an odds ratio for each of the occupational factors we wish to screen, while controlling for a multitude of different sets of non-occupational risk factors, and perhaps for other occupational factors. We will generally have to use models with several terms in them to get these estimates, and the standard errors of these estimates may be somewhat larger than in the less complex models obtained via precision-based methods. However, the parameter estimates obtained from our models can be interpreted as reasonably valid effect estimates.

At the end of this activity, we will have carried out a large number of statistical tests. The null hypothesis of each test is that there is no effect for the potential risk factor being tested, i.e., that the odds ratio for that factor is 1.0. Even if the null hypothesis is true in each instance, if we use a conventional Type I error rate of 0.05, roughly 1 in 20 of these tests will be expected to be statistically significant. Therefore, even if there were no true occupational risk factor for melanoma, there is an excellent chance that these procedures would erroneously identify some occupational factors as melanoma risk factors. On the other hand, if there is, in fact, an occupational risk factor for melanoma, this screening

procedure focuses the search on a smaller list of factors which then has a good chance of containing the true risk factors.

A potential problem with this strategy is that the P-values for each test may not be strictly correct. Typically, the P-values from conditional logistic regression are approximations based on the behavior of the estimates in large samples. The Livermore melanoma case-control data probably do not constitute a large sample, at least for some of the estimates, and the true P-values for some of the tests may differ from those we have reported. If we were primarily interested in hypothesis testing (i.e., in confirmatory statistics), this would be a serious problem, and we would need to explore ways (if they exist) to get more accurate estimates of P-values. However, since we see this as primarily a hypothesis generating study, this is not a major problem at this time.

Finally, we have resisted the temptation to identify occupational factors with specific exposures from the case-control study. Instead, we have thought of each occupational factor as dividing the LLNL employee population into groups of employees who share a common (but probably unknown) exposure status for the surrogate of that exposure defining the group. It is likely that the members of such groups share other exposures as well. Although this distinction is clear for some of the occupational factors identified by Austin and Reynolds (such as "worked at site 300", or "visited a Pacific test site during an atmospheric nuclear test"), exposures such as that to radioactive materials and volatile photographic chemicals are defined by the answer to the question "Did you ever work around [substance]?". It is quite possible that subjects were not even asked about their exposure to the "true" risk factor for melanoma, if it exists. However, if we have sufficient information about

enough different occupational factors, the chances are good that some of the occupational factors we have measured will be correlated with the unknown, true risk factors (if they exist). The estimated adjusted odds ratios for such surrogate occupational factors would be greater than 1.0. This possiblity must always be kept in mind when interpreting the final results of this or any similar study.

Reference

Kleinbaum, D. G., Kupper, L. L., and Morgenstern, H. 1982. Epidemiologic Research. Lifetime Learning Publications, Belmont, CA.

II. Data Verification

Introduction

As part of this statistical re-evaluation of the Austin/ Reynolds case-control study, it is important to determine how faithfully the data recorded on the final data tapes reflected the information gathered on questionnaires and during interviews with subjects. The following review of the process that produced the final data will help to clarify the procedures we used to look for errors in the data.

The study data resulted from the coding of two questionnaires: a self-administered questionnaire mailed to each subject, followed by a questionnaire completed during a personal interview conducted by a trained interviewer. The self-administered questionnaire elicited information about residence history, family health history, and general job history. The interview questionnaire elicited information about the subjects' educational background, job history, chemical and other substances worked around on the job, history of off-site activities (i.e., visits to nuclear and non-nuclear test sites), history of wearing protective clothing on the job, and a number of questions eliciting information about non-occupational matters such as recreational activities, diet, chemical exposures not associated with employment, family medical history, personal health history, and residence history.

The conversion of the information from the questionnaires to data suitable for analysis by conventional statistical methods can be divided into

three steps. First, the questions of the questionnaire were translated into a series of other questions whose answers could be determined from answers given on the questionnaire and which were easily coded as numbers, (such as measurements, dates, or one of a fixed set of alternatives). Along with those questions, a set of acceptable answers was defined, and procedures established for what to do when the subject's answer to a question fell outside the set of acceptable answers to that question. These questions and their associated sets of acceptable answers were collected together as a coding manual. Each question in the coding manual was associated with a unique data field on each record in the final data set.

Next, a coder translated the information on the questionnaires into codes, using the coding manual. There was often no simple one-to-one correspondence between questions on the questionnaire and questions listed in the coding manual; most questionnaire questions required several coding manual questions to capture the desired information. Therefore, the translation process required more than a simple mechanical translation of codes, and was by far the slowest part of the conversion of the information on the questionnaires into data for analysis.

Finally, the results of the translation were entered into a computer using standard key-data-entry procedures.

The three steps have very different potentials for contributing error to the final data set. Although the first step, the generation of a coding manual from the questionnaire, has great potential for corrupting the information in the questionnaire (primarily through selective omission of information), it is easy to check this step without recourse to any data other than a blank questionnaire and the coding manual. The manual does a good job of

capturing the questionnaire information. Errors made during the coding step would be difficult to catch, since generally only one coding pass was made through a questionnaire. Standard key-data-entry protocols call for data to be entered twice by different operators, virtually assuring that this third stage of the process proceeded without error. Taking all this into consideration, it was most important to check the coding stage of the process, and of less importance to confirm only that the codes had been keyed correctly.

Methods

To simplify and speed up the process of data verification, only a portion of the questionnaire was recoded. We examined the selected portion for all of the cases and a 20% simple random sample (22 subjects) of the controls. The selected portions of the questionnaire were:

1) All of the non-occupational questions.
2) All of the off-site visit questions.
3) A subset of the fields for the substances worked around on the job: the name of the substance, the job during which the subject worked around the substance, and whether or not the subject actually came into contact with the substance.

This portion of the questionnaire includes five of the eight Austin/Reynolds occupational factors and all of the non-occupational factors deemed to be important by them.

It was more difficult to recode some parts of the questionnaire than it was others; hence, different error checking strategies were required for different parts of the questionnaire. Non-occupational questions generally required specific answers (such as yes/no, dates, and numbers), so the coding manual generally required only a simple transcription of an answer from the questionnaire. Therefore, workers with no previous coding experience could simultaneously recode and verify this entire section of the questionnaire. The workers were aided in this task by a computer program which prompted the worker with a screen containing a request for information for each data field in turn, the place in the questionnaire to find the information, and the possible codes for that information. The worker entered the code for the answer he or she found in the questionnaire, and the program compared that answer with the answer found in the corresponding field of the data tape. If the two answers did not agree, the computer would signal a discrepancy, and the verifier would be given a chance to correct any mistyping or misreading. The verifiers were instructed not to "fish" for an answer that matched the data tape in this case, and, if in doubt regarding the correct interpretation of an answer on the questionnaire, to refer the problem to their supervisor. When the answer matched the corresponding data field, or a discrepancy was confirmed, the section of the coding manual for the next data field would be displayed. The program kept track of the subject ID, question number, and both responses for each mis-match. Later, a second verifier confirmed each putative mismatch by checking the appropriate questionnaire.

Occupational questions were more open-ended, so coding decisions in this part of the questionnaire were more difficult. Therefore, a professional coder recoded the occupational questions using the coding manual written for the original case-control study. Our non-professional verifiers used a modified version of the computer program described above to compare the newly recoded answers to the data on the data tapes for the off-site visit information. The recoded data were compared directly with a list of the relevant section of the data file for the questions about what substances the subjects had worked around. As with the non-occupational questions, all discrepancies were confirmed with the original questionnaires.

Results and Discussion

There were no errors in the fields encoding the occupational and non-occupational factors from the final Austin/ Reynolds models in any of the 53 questionnaires examined. There were a total of 107 errors found in all in the non-occupational portion of the questionnaire (out of 53 subjects and 350 data fields in this portion of the questionnaire). We can summarize the error rate for this portion of the questionnaire by the average probability that a particular data field for a particular subject would contain a mistake. This probability is approximately 0.0058 for the non-occupational questions. There were 85 errors in the data for the off-site visit portion of the questionnaire. Since there were 103 data fields in this portion of the questionnaire, the average probability that a given data field for a particular

subject contained an error is 0.0156. Both of these error rates are quite small.

The occupational exposure data need to be summarized differently, since the number of substances worked around differs from person to person. Furthermore, each subject held several jobs at LLNL, and each was asked about the substances he or she had worked around for each job separately. For each substance on each job, there is one job-substance record in the data set. The subjects chosen for verification had a total of 721 job-substance records. Recoding revealed an additional six job-substance records, distributed between two controls. This yields an increase in the number of job-substance records of 0.83%. However, this is misleading. The two controls were missing a total of six job-substance records. However, the only information used in any analysis of association between substances worked around and melanoma was whether the subject had <u>ever</u> worked around the substances in <u>any</u> of the jobs he or she had held at LLNL. Although these two controls were missing six job-exposure records, one of the controls, missing two job-substance records, had worked around the same substances on other jobs; and, the other control, missing four job-substance records, had worked around one of the substances on other jobs. For this control, two of the other three missing job-substance records were for the same substance. Thus, as far as the analysis of association between working around various substances and melanoma is concerned, one control was incorrectly coded as having never worked around two substances.

Eight exposures, distributed among two subjects, were originally scored "NO" for the question, "Did you ever have direct skin contact /inhale/direct contact with this substance?". On reexamination, we found that these subjects

responded "I don't know". This is an error rate of 1.1% per previously reported exposure for this sort of error. Since this data field was not used in the analysis of associations with melanoma, these miscoded fields had no effect on occupational associations.

Since we checked every case in the study, it is possible to specify exactly the error probabilities for the cases in each of these blocks of questions. The error probability for the non-occupational data fields was 0.0064 per field. The error probability for the occupational, off-site visits fields for the cases was 0.021. Among the errors found for substances worked around on the job, the eight miscoded values were all among two cases (in data fields that went unused in the final analysis), and were the only errors found among the cases in this block of questions.

A number of the "coding errors" reported here were due to the difficulty of forcing free-form answers to open-ended questions into a small set of answer codes. The relatively higher probability of apparent errors among the occupational off-site visit questions was due mainly to difficulties in deciding how to code information about the duration and frequency of off-site visits. These and other ambiguous portions of the questionnaire were generally not used in the final analysis.

In conclusion, it seems that the data on the data tapes reflect the data gathered during the interviews accurately enough that coding errors were not an important source of error in analyses of the relationships between occupational and non-occupational factors and melanoma.

III. Selection of Controls

Introduction

A study based on a case-control design will lead to incorrect inferences about the association between disease and exposure if the controls differ substantially from the population which they were chosen to represent. The bias in an effect estimate due to this kind of deviation is referred to as selection bias. One of our tasks in reviewing the Austin/Reynolds report was to determine to what extent the controls chosen for the study might differ from the population of non-diseased individuals at Lawrence Livermore National Laboratories (LLNL), and, further, to try to evaluate the impact that this deviation might have on the inferences drawn from an analysis of these data. Ideally, to accomplish this, we would like to have compared the actual controls' responses on the questionnaire to the responses given by all the potential controls for any particular case. To the extent that these two sets of responses differed, the controls would not have represented the LLNL employee population.

Although it was impossible to confirm that the controls represented the employee population with respect to all relevant characteristics, we were able to determine whether jobs that involve a higher likelihood of radiation exposure were underrepresented among the controls for this study, relative to the employee population. If they were, then the elevated odds ratio for the variable "worked around radioactive materials" would be at least partially due

to selection bias.

Methods

Stratified Sampling.

Controls were matched to their cases on age (within five years), sex, and race, and had to have worked at LLNL sometime in the calendar year in which the case was diagnosed. The controls for a particular case should comprise a simple random sample from the subpopulation of LLNL employees who satisfied the matching criteria for that case. In what follows, we will refer to the subpopulation of non-diseased individuals matched to a particular case as the potential controls for that case. For example, if a case was female, white, 36 years old, and diagnosed on 10 July 1972, the potential controls would be all LLNL employees who worked at LLNL during any part of 1972 and were female, white, and between 31 and 41 years old in 1972. The controls selected from this population and used in the Austin/Reynolds study will be referred to as the actual controls.

Job Categories and Radiation Badge Readings.

The Austin/Reynolds data tapes include two variables that reflect a job category for each individual. One variable, JCLASS, is a three-digit code taken from personnel records, and reflects a classification of the tasks to which the person was assigned. A second variable, PACC, is a four-digit code that indicates the project to which the person's time and expenses were

billed. The most recent version of each code is part of the records of every present and former LLNL employee. So that the information we used about job classification would be comparable between actual and potential controls, we requested and received from LLNL both the current job classification code and the current payroll account code for each case, each control, and each LLNL employee who was eligible to be chosen as a control for a case in the case/control study.

In order to be able to determine objectively the likelihood that an employee with a particular job classification or payroll account code would have worked around radioactive materials, we also requested and received from LLNL the total of all the radiation badge readings for the ten years preceeding the reference date for each person in each set of potential controls. We have taken the position that the distribution of badge readings among LLNL employees with a particular job classification or payroll account code is a good indicator of the likelihood that a case or control with that code worked around radioactive materials, regardless of the subject's personal badge reading.

Grouping.

The general strategy was to produce a dichotomous variable such that individuals who receive the code "1" would be deemed more likely to have worked around radioactive materials than individuals who received the code "0", using evidence from their job classifications or payroll account codes. Although this variable would have to be based on our information about the distribution of badge readings among the bearers for each specific job classification code or payroll account code, without additional information

there is no single reclassification that is guaranteed to produce a grouping that efficiently predicts whether or not a person would have worked around radioactive materials. Therefore, we used several different groupings. To make these different groupings, we first calculated the average badge reading, the proportion of badge readings greater than 200 mrem, and the proportion of badge readings greater than 1 rem among the potential controls for each job classification and each payroll account code. Then we created six dichotomous variables, three for each of JCLASS and PACC: JC02, JC10, JCAVG, PA02, PA10, PAAVG. If at least 40% of all the potential controls in a particular job classification (over all sets of potential controls) have badge readings of at least 200 mrem, the value of JC02 for a subject with that job classification would be "1", and would be zero otherwise. PA02 reflects a similar coding for payroll account codes. For a subject to receive a code of "1" for JC10, at least 20% of all the potential controls with the same job classification code must have had badge readings of at least 1 rem. Again, PA10 reflects the same coding for payroll account code. Finally, JCAVG and PAAVG are "1" for a subject if the average badge reading among potential controls with the same job classification (for JCAVG) or payroll account code (for PAAVG) was at least 200 mrem.

We also grouped JCLASS and PACC into "scientists and engineers" and "all others", with "scientists and engineers" receiving the code "1". Anyone with a payroll account code greater than 9700 or a job classification code between 200 and 300 was classified as a scientist or engineer for purposes of this grouping. The variable derived from JCLASS that resulted from this grouping we called JCENSCI, and that derived from PACC we called PAENSCI.

Testing.

We want to know if there are fewer "1"'s, for any of the groupings of JCLASS or PACC, among the actual controls than we would expect from the proportion of "1"'s among the potential controls. The proportion of "1"'s changes from one set of potential controls to another, so we would like to do a test that takes this variation into account. A simple way to do this is to calculate the difference between n_s, the observed number of "1"'s among the actual controls for the sth matched set (s = 1, 2, ..., 31), and $N_s p_s$, the expected number of "1"'s among the actual controls for the sth matched set, where N_s is the number of actual controls for the sth matched set and p_s is the proportion of "1"'s among the potential controls for that matched set. If the actual controls are a simple random sample from the potential controls for the sth matched set, n_s will have a binomial distribution, with mean $N_s p_s$ and variance $N_s p_s(1 - p_s)$. Thus, a "goodness of fit" test comparing observed versus expected numbers of "1"'s can be based on the statistic

$$\chi^2 = \sum_{s=1}^{31} x_s \quad ,$$

where

$$x_s = (n_s - N_s p_s)^2 / N_s p_s(1 - p_s) \ .$$

Here,

- s indexes matched sets, and ranges from 1 to 31;
- n_s is the number of actual controls in job categories that were likely to involve radiation exposure for case s;
- p_s is the proportion of the potential controls in job categories that were likely to involve radiation exposure for case s;
- N_s = number of actual controls matched to case s;

χ^2 should be approximately chi-squared with 31 degrees of freedom under H_0: for every s (s = 1, 2, ... ,31), the N_s actual controls are representative of the population of potential controls for the sth case.

Controlling for Selection Bias

It would not be sufficient just to determine whether the actual controls represented the potential controls with respect to "radiation-related" job classification or payroll account code categories. In order for a possible conclusion that the actual controls are "unrepresentative" with respect to certain job categories and that such unrepresentativeness is important, it must be shown that this unrepresentativeness materially changes the magnitude of the effects observed for the variable "worked around radioactive materials".

The estimate of the true effect of "worked around radioactive materials" could be biased if any set of job categories associated with working around radioactive materials was under- or overrepresented among the actual controls relative to the potential controls. However, if we knew in advance of any such group of over- or underrepresented jobs, we could estimate the effect of working around radioactive materials separately among subjects who worked in underrepresented jobs and among subjects who worked in overrepresented jobs, and pool the estimates to obtain a valid estimate of the effect of working around radioactive materials (assuming the true effect of working around radioactive materials is the same among workers in both groups of jobs). Equivalently, we could control for over- or underrepresented jobs by modeling, using a dichotomous variable that takes the value "1" if the subject worked in one of the overrepresented jobs and "0" if the subject worked in one of the underrepresented jobs (Miettinen and Cook, 1981).

Specifically, we used conditional logistic regression models to estimate the odds ratio for self-reported exposure to radiation in a model that contained confounder variables, a dichotomous exposure variable that takes the

value "1" if the subject reported working around radioactive materials in the ten years prior to the reference date and takes the value "0" otherwise, and one of the dichotomous variables derived from JCLASS or PACC. The odds ratio for working around radioactive materials from these models was compared with the odds ratio for this same exposure variable in a model that differed only in that it did not contain the dichotomous variable derived from JCLASS or PACC. If the estimates of the odds ratio for working around radioactive materials changed materially, depending on whether or not one of the dichotomous "job" variables was included in the model, we might conclude that sampling had biased the estimates of the effect of working around radioactive materials.

To help ensure that any decision about selection bias based on the conditional logistic regression modelling was not affected by whether or not other factors were controlled for, we chose a small collection of sets (called confounder sets) of potential confounder variables, and repeated each regression model with each confounder set. The sets of confounder variables were chosen from among a large collection of such sets, whose constitution is described in Chapter V of this report. Chapter V also describes how each confounder set is associated with an estimate of the effect of working around radioactive materials. For this analysis of selection bias, we chose the confounder sets associated with the minimum, first quartile, median, third quartile, and maximum values of the distribution of estimates of the effect of working around radioactive materials, as well as the non-occupational variables used by Austin and Reynolds in Table 39 of their report. The confounder sets are listed in Table 2.

Results and Discussion

Table 1 lists the results of the goodness of fit tests for the eight recoded job classification and payroll account code variables, along with the expected and observed proportion of "1" codes for each variable. There is no evidence here for significant underrepresentation of radiation-related jobs or of scientific or engineering related jobs among the actual controls, relative to the potential controls.

Table 2 reports the odds ratios for "working around radioactive materials" as estimated in a number of different models. The columns of Table 2 correspond to families of models that have in common a set of confounders, and differ among themselves only in the variable used to indicate job classification (JC02, JC10, JCAVG, PA02, PA10, PAAVG). The first row corresponds to models in which there is no job classification variable. If selection bias of the type we have been considering was present and was detrimental, then the odds ratio values in rows two through seven would have been substantially lower than the values in corresponding columns in row one. Generally this is not the case, although the estimates for the row that corresponds to JCAVG are smaller than the corresponding estimates for the first row in the first four columns.

JCAVG and Melanoma Risk: a digression.

The odds ratios for JCAVG (JCAVG is "1" for a subject if the average radiation-badge measured dose among holders of that subject's job classification code is greater than 200 mrem) reported in the last row of

Table 2 are suprisingly large, too large to be accounted for by the slight difference between cases and controls in the frequency of radiation-related jobs as measured by JCAVG. These are all statistically significantly different from 1.0 with P = 0.05 or better. These large odd ratios prompted further modeling of the effects of radiation-related jobs to determine if JCAVG was a surrogate for some of the other occupational melanoma risk factors discussed in Chapter VI of this report. The general procedure followed was to test the statistical significance of JCAVG in a model that contained the variables of a confounder set and other occupational factors, chosen from the set "worked around radioactive materials", "worked around volatile photographic chemicals", and "worked at site 300", and then to test the significance of the same occupational factors in a model that contained the same confounder set and JCAVG. For better control of the size of the tests, which we set at 0.05, we used likelihood ratio tests to test the significance of the regression coefficients. We used the sets of confounders already described for the variable "worked around radioactive materials".

Briefly, the results were as follows: "worked at site 300" is statistically significant in four of six models that contain confounder set variables and that occupational variable. JCAVG and the other occupational variables are statistically significant in all models that contain just the confounder set variables and the one occupational variable. JCAVG is always significant in models that contains only confounder set variables and JCAVG, as well as in models that contain confounder set variables, JCAVG, plus one or any pair of the other occupational variables. JCAVG is also statistically significant in five of the six models with confounder set variables, JCAVG, plus all three occupational variables. From these results, it seems that

JCAVG definitely contains information about risk of melanoma over and above that carried by the other three major occupational variables.

If, in models that contained confounder sets, JCAVG, and different combinations of the other occupational variables, the other occupational variables were never statistically significant, then there might be grounds for claiming that all the information they carried about melanoma risk was summarized by JCAVG. This seems to be partially, but not entirely, true. When we tested the other occupational variables singly in such models, "worked at site 300" was significant in none, "worked around volatile photographic chemicals" was significant in three, and "worked around radioactive materials" was significant in five. JCAVG seems to contain all the information about melanoma risk that "worked around photographic chemicals" contains, and some (but not all) of the information that the other two variables contain.

Conclusion

Taken together, these observations fail to provide sufficient evidence that the large odds ratio for working around radioactive materials is due to an error or bias in sampling the controls. In addition, a new occupational variable that measures propensity for having worked around radioactive materials is strongly associated with case status. This new variable is based upon job classification codes and radiation badge readings among the LLNL population at large, and so is presumably not subject to recall bias. It is our conclusion that, if the estimate of the effect of working around

radioactive materials is incorrectly large, it is not because of an improper choice of controls.

Reference

Miettinen, O. S., and E. F. Cook. 1981. Confounding: essence and detection. American Journal of Epidemiology 114: 593 - 603.

Table 1

Results of goodness of fit tests for the reclassified job classification code and payroll account code variables. The P-value is the probability of observing a χ^2 value with 31 df at least as large as that actually observed if H_0 is true. H_0 is rejected if the P-value is less than some predetermined value, typically 0.05 or 0.01. See text for variable definitions.

Variable	Proportion of "1" among Controls: Potential	Actual	χ^2 (31 df)	P-value
JC02	0.109	0.109	24.41	0.75
JC10	0.102	0.100	17.96	0.97
JCAVG	0.555	0.482	34.97	0.28
PA02	0.174	0.118	20.30	0.93
PA10	0.122	0.127	24.42	0.79
PAAVG	0.589	0.636	35.66	0.26
JCENSCI	0.330	0.345	32.49	0.39
PAENSCI	0.701	0.664	35.66	0.26

Table 2

Estimates of the odds ratio for working around radioactive materials in models that include different confounder sets. Each model included the variables in one of the six confounder sets, one of the job classification variables (JC02, JC10, JCAVG, PA02, PA10, PAAVG), or no job classification variable (indicated by "-") and a dichotomous variable indicating whether or not the subject claimed to have worked around radioactive materials in the ten years previous to the reference date. The odds ratio for a particular model is reported in the row corresponding to the job classification variable and the column corresponding to the confounder set. In addition, odds ratios for JCAVG, corrected for self-reported radioactive materials exposure and confounder set variables, are listed in the second part of the table. See Chapter V of this report for a discussion of the confounder sets and a key to the variables.

Odds Ratios For Self-Reported
Radioactive Materials Exposure

	A/R	MIN	Q1	MED	Q3	MAX
-	5.44	2.96	6.39	5.41	28.0	46.4
JC02	5.73	3.85	6.84	8.78	32.7	46.2
JC10	5.81	2.95	6.53	5.85	28.0	47.4
JCAVG	4.11	2.00	4.29	4.45	29.7	1897.0
PA02	5.12	3.74	6.86	6.12	31.7	45.37
PA10	6.47	4.41	8.39	7.94	36.13	53.56
PAAVG	5.80	3.04	7.70	6.69	50.58	60.11

Odds Ratios for JCAVG

JCAVG	10.78	13.39	8.04	6.45	10.51	907.4

See Chapter V, Table 4 for confounder set definitions.
The confounder sets are:

A/R: 110010110000000000000000
MIN: 102001100000110000100000
Q1: 110011010000010000001000
MED: 200000001111001000100000
Q3: 210011010000000000001000
MAX: 210021010000010000000100

IV. Recalculation of the Austin / Reynolds Conditional Logistic Regression Models

Introduction

Before we entered into extensive calculations and tests to evaluate the Austin / Reynolds findings, we duplicated the core of the computations from the original report. We had four objectives in doing so: to assure ourselves that our data set agreed with the one Austin and Reynolds used, to check the original calculations for accuracy, to evaluate the reasonableness of the logistic models and identify possible influential observations, and to carry out a preliminary analysis of confounding between pairs of occupational variables. To meet these objectives, we recalculated the conditional logistic regression models summarized by Austin and Reynolds in their Tables 34 through 39. This allowed us both to check that we were interpreting the data set correctly, and to confirm the original calculations. The program we used for this reanalysis (and much of the rest of the analysis described in this report) is PECAN, written originally in FORTRAN by Jay Lubin, and modified by Barry Storer to include regression diagnostics. The regression diagostic procedures allowed us to look for matched sets that were particularly influential, in the sense that estimates based on the data minus the particular matched set deemed influential would differ substantially from estimates based on all the data. Finally, we fit models that included the confounders identified by Austin and Reynolds and pairs of occupational

factors as a preliminary analysis of confounding among occupational factors.

Methods

This section of the analysis was based entirely on the data tape labeled "analytic tape", which apparently contained the data in the form in which Austin and Reynolds finally used them. The only special consideration in handling the data at this stage involved deciding how to treat missing data, since no record used to fit a model can have missing values for any variable. There were two choices: for each model, select that one particular data subset for which there was the most data available for fitting that model, or select a data subset that would permit all of a set of related models to be fit with that subset. The former strategy allows the most precise possible estimates; but, if one is interested in the variation of the estimates of a particular parameter among models that differ by the presence or absence of different confounders, one must worry about variation induced by using different subsets of the data to fit different models whose estimates are to be compared. As far as we can tell, Austin and Reynolds allowed the constitution of the data sets to vary from model to model, as missing data required; and so, when trying to match their estimates, we did the same.

Conditional logistic regression models were estimated with the program PECAN. PECAN was written in FORTRAN by Jay Lubin, and was modified by Barry Storer to include regression diagnostics of the sort described in Storer and Crowley (1985). One of us (R. W. Setzer) further modified PECAN to run in an

MS-DOS (Trademark of Microsoft Corp.) environment on IBM PC's (Trademark of International Business Machines Corp) and compatible computers. PECAN uses a modified Newton-Raphson method to get maximum-likelihood estimates for the regression coefficients in conditional logistic regression models.

Storer-Crowley regression diagnostics indicate the effect on a parameter estimate of eliminating one or a set of observations (in our case, a matched set). Such diagnostics are typically expressed as the difference between the parameter estimated using all but one matched set and the parameter estimated using all the matched sets, possibly standardized by the estimated standard error of the parameter (estimated using all the data). The statistic thus created is typically plotted against some aspect of the subset of subjects missing from the data set used to calculate the diagnostic, usually the index number of the subject or matched set. An influential matched set will be associated with a diagnostic that is substantially greater, in absolute magnitude, than diagnostics for other matched sets.

We recalculated the odds ratio estimates from Tables 34 - 39 in the Austin and Reynolds report, and plotted and examined regression diagnostics for each variable in each model. We used both index plots (in which the diagnostics are plotted versus a number that identifies the eliminated matched set) and histograms to help identify diagnostics with outlying values.

To check for confounding among occupational factors, we calculated odds ratios for each of seven occupational factors ("scientist job classification", "worked around radioactive materials", "worked around volatile photographic chemicals", "worked around fumes of high explosives", "present at a Pacific test site during an atomospheric nuclear test", "worked at site 300", and "chemist duties") in conditional logistic regression models that included the

occupational factor whose effect was being estimated, another occupational factor, and the constitutional factors used by Austin and Reynolds in their Table 39 ("six or more moles", "previous diagnosis of basal or squamous cell carcinoma", "parental skin cancer", "subjects burns without tanning with prior sun exposure", and "advanced degree").

Results

We duplicated Austin and Reynold's numerical results exactly (to within reasonable roundoff error) for each of the odds ratio estimates in their Tables 34 - 39. This indicated both that we were interpreting the data tapes correctly, and that both they and we were correctly estimating the coefficients in a conditional logistic regresion model.

However, we encountered a likely misinterpretation by Austin and Reynolds that was apparently due to the way that they handled missing data. When Austin and Reynolds fit their models to the data for the series of models represented by Tables 34 - 39, they apparently eliminated, for each model, those records that were missing values for any variable used in that model. Thus, each model was fit using a slightly different data set from other models. When they assessed the degree of confounding between factors by measuring the variation of odds ratio estimates between models, they were actually measuring both the effects of confounding and this effect of using slightly different data sets.

The statement on page 31 of their report ("Although the risk associated

with 1969 buildings is not itself a significant risk factor with these covariables [the covariables used to produce Table 39], it appears to interactively influence the risks associated with moles and education.") is, in fact, the result of just such a combination of effects. In their Table 39, the odds ratios for "six or more moles" and "advanced degree" in a model that excluded "1969 building" are 6.5 and 4.4, respectively. In a model that included "1969 building", but otherwise contained the same variables, those odds ratios are 50.9 and 9.9, substantially larger. However, fourteen records, two of them cases, of the total 141 have missing values for "1969 building". When a case has missing values, the entire matched set must be eliminated from the data set. The result of this is that the data set for the model that included the 1969 building variable contained only 120 records, instead of all 141. When this reduced data set is used for both models, including and excluding "1969 building", quite a different picture emerges. In the reduced data set, the odds ratios for "six or more moles" and "advanced degree", estimated in models that do not include "1969 building", are 47.5 and 9.0, respectively. Since these values are not substantially different from the values estimated when "1969 building" is in the model, there does not seem to be any evidence for confounding effects of "1969 building" on these two variables.

A similar problem invalidates Austin and Reynolds's claim, based on the stepwise addition of variables to a conditional logistic regression model of melanoma risk, that "1969 building" is an important explanatory variable. On page 31 of their report, they say, "Working in a 1969 building, however, appears to contribute a great deal of information." This statement refers to their Figure 2, in which the increase of the log-likelihood, expressed as a

per cent of the original log-likelihood, is reported for each new model as each of the leading occupational and non-occupational factors were added to the model. This "% explained log-likelihood" (to be used roughly like R^2 in ordinary least squares regression) jumps from 41.2% to 59.8% as "1969 building" is added to the model. We repeated the stepwise process, making sure to use the same data set for each model. When we did this, the "% explained log-likelihood" changed only from 57.3% to 59.1% when "1969 building" was added to the model. The difference between our result and Austin and Reynolds's is due to the large number of records that need to be eliminated to estimate models that include "1969 building". Thus there do not appear to be strong grounds for claiming that "1969 building" is an important explanatory factor with regard to melanoma case status.

The regression diagnostics did not indicate any problem of overly influential observations. As an example of these plots, Figure 1 gives a diagnostic plot for "worked around radioactive materials" in a model that included the constitutional covariables used by Austin and Reynolds.

Table 1 gives the estimates for the odds ratio for the relationship between each of the occupational variables (except for "1969 building") and melanoma case status, adjusted for the covariables "six or more moles", "previous history of basal cell carcinoma", "at least one parent had skin cancer", "burns without tanning", "advanced degree", and each of the other occupational variables in the list. The variable "1969 building" was excluded to increase the sample size. If there was substantial confounding between a pair of occupational factors, the odds ratio estimate for at least one of the factors would be substantially reduced towards one in a model that contains the other. This table does not reveal much, if any, confounding among the

occupational factors we considered, although there is a suggestion that odds ratio estimate for "scientist" might be reduced in the presence of "volatile photographic chemicals", and that "fumes of high explosives" is reduced in the presence of any of the other occupational factors.

Summary of Conclusions

Overall, the computations in the Austin/Reynolds report were carried out correctly. Those authors do not seem to have been sufficiently aware of the problems that missing data can cause, and it seems likely that part of their argument for the importance of "1969 building" disappears when missing data are handled properly. None of the parameter estimates seems to be excessively influenced by any one matched set. To that extent, conditional logistic regression models are appropriate to these data. There is not much confounding between pairs of the occupational factors we considered here, when the constitutional factors identified as risk factors in this data set are taken into account.

References

Storer, B. E., and Crowley, J. 1985. A diagnostic for Cox regression and general conditional likelihoods. JASA 80: 139 - 147.

Table 1
Odds Ratios for Occupational Factors, Adjusted for other Occupational Factors and Constitutional Factors

Each entry is the odds ratio for the occupational factor listed in the first column, adjusted for the occupational factor associated with the column in which the entry appears and the constitutional factors: "six or greater moles", "previous diagnosis of basal cell carcinoma", "parental skin cancer", "burning or burning with tanning when exposed to the sun after a prior exposure", and "advanced degree". Numbers above the columns refer to the numbered occupational factors in the first column. Numbers on the diagonal, underlined for emphasis, are odds ratios for the "row" occupational factor, unadjusted for any other occupational factor.

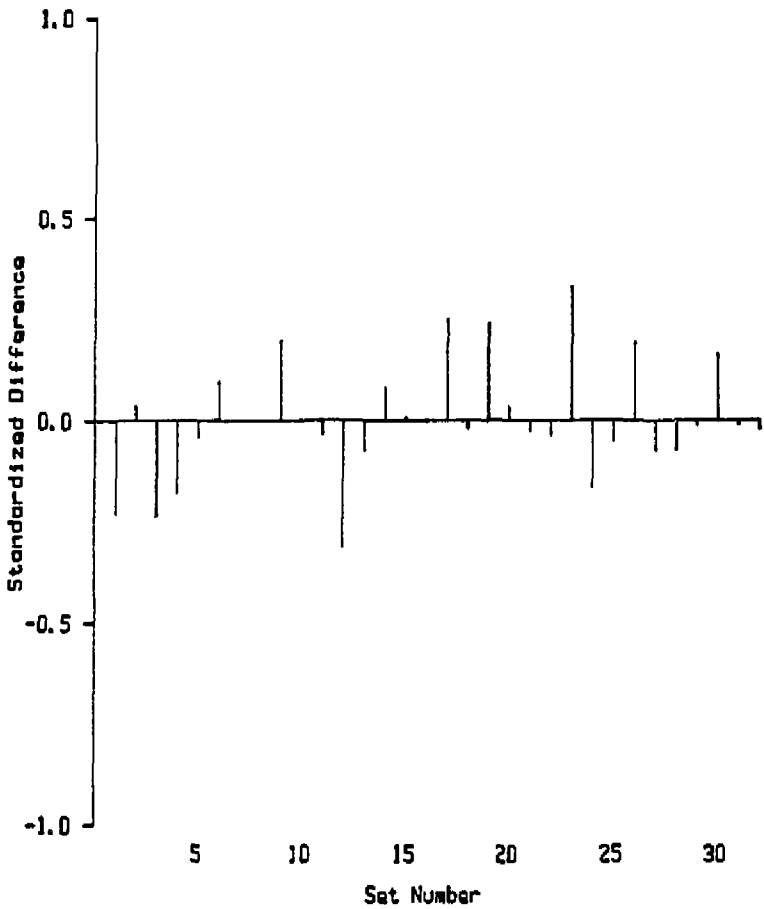
	Occupational Factor						
	1	2	3	4	5	6	7
1. Scientist	2.4	2.6	1.4	1.9	2.2	2.2	2.2
2. Worked Around Rad. Materials	3.6	3.3	2.6	2.8	4.3	2.6	3.6
3. Worked Around Vol. Phot. Chems.	7.1	6.6	7.8	6.5	8.6	7.2	7.8
4. Worked Around HE Fumes	3.8	3.4	2.6	4.5	3.3	3.2	3.4
5. Pac. Test Site During Atm. Test	7.2	14.4	8.0	5.7	9.2	10.7	8.7
6. Worked at Site 300	2.9	2.5	3.0	2.7	3.2	3.1	2.8
7. Chemist Duties	11.1	24.8	16.8	9.6	12.5	7.8	13.1

Figure 1

The Change in the Regression Coefficient for
Radioactive Materials
Resulting from Deleting Each Matched Set
Plotted Versus Matched Set Number

Storer-Crowley diagnostics for the coefficient for "worked around radioactive materials", adjusted for "six or more moles", "previous diagnosis of basal cell carcinoma", "parental skin cancer", "burning without tanning with prior sun exposure", and "advanced degree". The coefficient estimated using all the data, minus the coefficient estimated using all but the matched set identified on the horizontal axis, divided by the estimated standard error of the coefficient (estimated using all the data), is plotted as a solid vertical bar based, on the horizontal axis, on the identification number for the matched set that was eliminated.

Figure 1
The Change in the Regression Coefficient for
Radioactive Materials
Resulting from Deleting Each Matched Set
Plotted Versus Matched Set Number



V. An Examination of the Confounding Effects of Non-Occupational Variables on the Association Between Occupational Factors and Malignant Melanoma

Introduction

A goal of the Austin/Reynolds analysis of their case-control data was to identify factors, associated specifically with employment at LLNL, that enhanced employees' risk of contracting malignant melanoma. In their analysis, Austin and Reynolds first estimated crude odds ratios for all possible risk factors, both occupational and non-occupational, in order to select factors that were associated with disease incidence. Since correlations among these factors may cause the estimates of the occupational factor odds ratios to be biased, odds ratios must be adjusted for other factors. Thus, once Austin and Reynolds identified a number of strong occupational and non-occupational risk factors, they fit models that included more than one of the factors at a time.

Although this approach controls for confounding among variables that are strongly associated with melanoma, the possibility remains that proper control of confounding was not achieved. Some important constitutional factors may not have been statistically significantly associated with the disease in this data set and hence may have been ignored, or the association may not have been estimated correctly due to correlations among non-occupational and occupational factors.

Ideally, to estimate unbiasedly the effect of a variable on risk, that

variable and all other risk factors must be included in a model and their effects estimated jointly. In this ideal situation, much would already be understood about the disease of interest, and the point would be to examine the effects of a few new factors hypothesized to be risks.

There are several hypotheses resulting from epidemiologic studies about the etiology of melanoma, and the risk factors for this disease are still only imperfectly understood. Exposures which seem to be risk factors in some studies are not so in others. For example, in two studies (Williams, 1976, Williams and Horn, 1977), beer and wine consumption was associated with an increase in the risk of melanoma. However, this has not been reported in other studies; in fact, in one study, beer and wine consumption was associated with a decrease in the risk of melanoma (Elashoff et al, 1982). Such contradictory findings occur for several other purported risk factors for melanoma. Since the "true" non-occupational risk factors have not yet been identified, one would have to include quite a few potentially confounding variables in any model to estimate with reasonable accuracy an occupational effect. This would lead to fitting models with so many variables that the estimated coefficients and their standard errors would be totally unreliable.

An innovative and reasonable approach to assess confounding would be to examine the distribution of an occupational effect estimate (e.g., an odds ratio) that arises when different sets of non-occupational factors are included in the model (such sets of non-occupational factors will be called "confounder sets"). Although we cannot say which estimate, if any, is the closest to the true parameter value, we can determine the range of such estimates that a data set can produce. If we restrict the confounder sets to sets of factors that have been shown to be associated with melanoma in

previous studies, the shape of the distribution of the resulting estimates for various occupational factors tells us something about the degree to which mis-specification of confounders would change the estimates of occupational effects. Any occupational factor would be suspect whose estimated effect varied wildly depending on what set of non-occupational variables is included in the model; conversely, an occupational factor would deserve close attention when its estimated effect was stable and significant over a wide variety of models involving different sets of non-occupational factors.

Methods

We prepared several lists of non-occupational factors that have been shown in other studies to be associated with malignant melanoma, and that could be extracted as variables from the Livermore data set. The confounder sets are combinations of variables from these different lists. For the sake of brevity, we only used a subset of the set of all possible combinations of non-occupational factors. Some subsets of non-occupational factors always appear together in confounder sets. These comprise non-occupational factors that were jointly identified as melanoma risk factors in the same study. One factor, a measure of the number of moles that a subject has, appears in some form in every model, since it is well-established as a strong risk factor for melanoma.

The following sets of operations were carried out for the occupational factors identified by Austin and Reynolds:

1) For each confounder set, estimate the separate effect of each occupational factor in a regression model that includes that occupational factor (and no others) and all the variables in the confounder set. Thus, for each occupational factor, there are as many occupational factor odds ratio effect estimates as there are confounder sets. We used conditional logistic regression methods to estimate odds ratios for the association between various occupational factors and case status while controlling for other potential confounders (i.e., confounder sets)

2) For each pair of occupational factors and each confounder set, estimate the simultaneous effects of both occupational factors in a model that contains both occupational factors and all the variables in the confounder set. This allows for associations between pairs of occupational factors to be taken into account.

3) Combine the estimates from steps 1) and 2), and describe their distribution.

The first list of potentially confounding variables comprised the non-occupational variables selected from the data by Austin and Reynolds. These variables (as listed in Table 39 of the Austin/Reynolds report) are "greater than six moles", "a previous diagnosis of skin cancer", "parental skin cancer", "sunburn with thirty minutes of exposure", and "possession of an advanced degree". These and all other non-occupational variables used in this study are defined precisely in Table 1.

The second list comprised the variables found by Holman to be important in his case-control study of 511 individuals. Holman's variables are: "the number of raised nevi (moles) on the arms", "acute reaction to sunlight",

"chronic reaction to sunlight", and "age at arrival in Australia" (Holman found that people who emigrated to Australia at an early age were at increased risk for melanoma. We substituted "age at arrival in California", since Californians generally seem to be at increased risk for melanoma).

The third list comprised the variables which Elashoff included in at least one of his final models. These factors included "eye color", "hair color", "greater than 4 moles", "exposure to chemicals", "alcohol consumption" and "skin reflectance".

The variables in the Austin/Reynolds, Elashoff et al., and Holman studies are compared to those variables which we used in this analysis in Table 3. While we tried to use the variables as originally defined, this was not always possible because of the different information which the three groups of investigators collected. Of the variables compared in Table 3, the biggest difference is among the definitions of "moles". While Elashoff et al. and Austin/Reynolds asked the respondent to estimate the number of moles as big as or bigger than a #2 pencil eraser over their entire body, Holman counted the number of raised nevi on the subjects' arms. In addition, the definition of eye color varies between Elashoff et al's study and this analysis. Austin and Reynolds coded shades 5 and 6 as blue, while Elashoff coded these shades as brown.

Elashoff et al. and Holman identified several variables, which we could not duplicate in the Austin/Reynolds data set. We could not construct a variable "age at arrival in California" (Holman's variable was age at arrival in Australia) because, for 37 subjects, the residence history did not extend beyond 10 years before the reference date. We used two variables to measure exposure to solar radiation during youth. The first was a dichotomous

variable which indicated whether the respondent was born in California. The second was a variable which reflected the average number of times per year a subject was sunburned before the age of 21, "BURN<21". We were unable to use "skin reflectance" (measurements of solar reflectance from a reflectance spectrophotometer) because there were 10 missing values for this variable. We did not include variables indicating exposure to chemicals here because it is an occupational variable.

In addition to the constitutional factors described in Table 2, we used the variables "X-Ray" and "Physical Exam" as defined in Table 1. The variable "X-Ray" was included as another way of measuring exposure to ionizing radiation. The variable "physical exam" was used to determine whether the difference between the cases and controls was merely due to the number of physician visits. (Hiatt and Fireman also evaluated the number of physician visits among LLNL employees who belonged to the Kaiser Health Plan.)

Each confounder set is briefly described by a 15 digit number, the model descriptor, in which each position in the number corresponds to a particular factor. The digit occupying a position in the model descriptor indicates whether or not the corresponding variable is present in the indicated set. A few variables were used in a few different forms, and each form is indicated by a different digit. For example, in models in which "BURN<21" was used as a continuous variable, its position (namely, 3) holds a "1"; in models in which that variable is used as a dichotomous variable, the third position holds a "2". A "0" in any position indicates that the corresponding variable is missing from that confounder set. The "Position" column of Table 1 associates each variable with its corresponding position in a model descriptor, and the "Code" column matches each possible form of a variable with its identifying

digit. The model descriptors for the 84 confounder sets we used and an example of interpreting the model descriptors are given in Table 4.

Any record in the data set that was missing a value for any variable in any of the models to be estimated was excluded from the data set used for all analyses. When this record was for a case, the entire matched set was excluded. Thus, none of the variation among different models is due to the exclusion of records with missing data. However, the variable "BUILDING-1969" (see Table 2) had missing values for a large number of subjects. This resulted in numerical instability in a number of the estimates. In particular, none of the models that included the occupational variable "PTSATM" (present at the Pacific Test Site during an Atmospheric Nuclear Test) could be estimated due to these missing values. Since "BUILDING-1969" seemed to be unimportant (see Figure 1), the analysis was completely re-done excluding this variable, and readmitting into the data set all records that had been excluded solely because of this variable.

Results and Discussion

The point of this analysis was to determine to what extent the effect estimates for the occupational factors depend on the choice of non-occupational and occupational covariates. We are concerned about the possibility that an occupational factor may have a large estimated effect because an important confounder was not considered. An occupational factor whose effect estimate does not change appreciably, no matter what other

covariates are included in the model, is deemed to be more reliable than a factor whose estimate varies considerably with the choice of covariates in the model.

We have used four characteristics of the distributions of effect estimates (i.e., estimated odds ratios) for each occupational factor to rank the reliability of the occupational factors. The most important statistic is the inter-quartile range, the absolute distance between the first and third quartile of the distribution of the estimated odds ratios. This statistic reflects the range of the majority of the estimates, and so gives the primary measure of the stability of the estimates.

Next in importance is the fraction of the estimates that would have been considered significantly different from one based on using a one-sided test with a Type I error rate of 0.05. This is a measure of the influence that different confounder sets have on the statistical reliability of the occupational effect estimates. That occupational factor whose estimated odds ratio is significantly greater than one no matter what other variables are in the model is to be given more credence than a factor whose statistical significance varies considerably depending on what other variables are in the model. We gave the other two characteristics of the distributions equal weight in our overall evaluation: the total range of the estimates, and the median of the distribution of estimates.

In Figure 1, each narrow bar represents the range of the estimated odds ratios for an occupational factor. The ends of the shorter box mark the first and third quartiles of the distribution of odds ratios, and the short vertical solid line intersecting each box indicates the median of the distribution of odds ratios for each factor. The dashed vertical line indicates an odds ratio

of one. The shaded portion of each narrow bar indicates the proportion of models in which the odds ratio was significantly greater than one, using a one-sided test and a Type I error rate of 5 per cent.

The purported occupational risk factors seem to fall into two groups based on the fraction of statistically significant estimated odds ratios, but the other important characteristics of these distributions seem to lie on a continuum. To rank the occupational factors in order of reliability, we constructed a composite index by first ranking the factors on each of the four characteristics listed above, and then constructing the composite as a weighted average of these four ranks. The weights reflect the relative importance of each characteristic to the overall index. The rank of each occupational risk factor for each characteristic separately, the weights, the weighted average or composite index for each occupational factor, and the overall rankings based on the composite indices, are listed in Table 5.

The weighted average ranks seem to partition the eight occupational variables into three distinct groups. Group 1 comprises "worked around radioactive materials", "presence at site 300", and "inhalation exposure to photographic chemicals". Group 2 comprises the single factor, "scientist". Group 3 comprises "chemist duties", "presence in a building constructed in 1969", "presence at a Pacific atmospheric nuclear test", and "worked around high explosive fumes". Group 1 then comprises the factors that this analysis deems most reliable while Group 3 contains those factors which are least reliable. The variable "scientist" falls somewhere in between.

Generally, when the odds ratio estimate for an occupational factor changes considerably, depending on whether or not some other variable is in the model used to estimate that odds ratio, then that other variable should be

included in any model used to estimate that odds ratio. We used the distribution of effect estimates associated with the collection of confounder sets to identify occupational and non-occupational factors that seem to have a large effect on the occupational factor odds ratio estimates. We grouped the estimates for a particular occupational factor effect into groups defined by the form of one of the variables in the confounder sets. For example, to determine whether DEGREE has a substantial influence on the effect estimate for RADIOACTIVE MATERIALS, the effect estimates for RADIOACTIVE MATERIALS were grouped into three groups: those estimated using confounder sets that did not include DEGREE at all (that is, position 2 is coded "0" in their model descriptors), those estimated using the definition of DEGREE associated with code 1 (i.e. "1" if the subject holds a Master's degree, Ph.D. or M.D., and "0" otherwise), and those estimated using the definition of DEGREE associated with code 2 (i.e., "1" if the subject holds some kind of doctorate, and "0" otherwise). Then, as if this were an analysis of variance problem, we calculated the ratio of the among group sum of squares to the within group sum of squares with the response variable being the natural logarithm of the odds ratio (because the distribution of the odds ratio is generally quite skewed), standardized by the estimated standard error of the logarithm of the odds ratio. Large values of this ratio indicate variables that have a large influence on the estimate of the occupational factor effect, and small values indicate a negligible influence. Only the joint influence on occupational factor effect estimates of variables that were either all in or all not in any confounder set could be determined, for example, BURN/TAN II and BORN IN CALIFORNIA. Figure 2 reports the result of this analysis. Here, each variable or group of variables is represented by a ray in a star burst

pattern. The length of the solid line along each ray is proportional to the magnitude of the ratio of the among- to within- group sum of squares of the occupational factor effect estimates when the variable corresponding to the ray is used to group the estimates. Long solid rays indicate influential variables. The central star in Figure 2 indicates the relationship between rays and variables in the other diagrams. Each of the surrounding stars shows the results for one of the occupational factors. Note that one should beware of making inferences from Figure 2 back to the parent population. Figure 2 only says that some factor(s) is associated with relatively large variation of an odds ratio estimate in this data set. It may well be that some genuine confounders would not be identified by this procedure, through accidents of sampling.

A few patterns are apparent in this figure. A group of factors composed of "Degree" (represented by the ray labeled 2), "Burn<21" (ray 3), "Parental Skin Cancer" (ray 4), "Burn/Tan II" & "Born in California" (ray 5), and "Skin Cancer" (ray 6) strongly effect the estimates for "Pacific Test Site" and "Scientist", and less strongly effect the estimates for "Photographic Chemicals", "High Explosives", "1969 Building", and possibly, "Site 300". The three factors identified as most stable by this analysis turn out to affect each other, namely, "Radioactive Materials" (ray 10), "Photographic Chemicals" (ray 11), and "Site 300" (ray 13). This suggests that effects for these three factors should be estimated jointly, to control for mutual confounding.

We jointly estimated the odds ratios for these three occupational factors, using 16 different confounder sets: the Austin/Reynolds confounder set, and the confounder set associated with the minimum, first quartile, median, third quartile, and maximum estimate of the odds ratio for each of the

three occupational factors. The geometric means of these estimated adjusted odds ratios are: for "worked around radioactive materials", 5.49; for "worked around volatile photographic chemicals", 13.46; and for "worked at site 300", 2.95.

Conclusions

Of the eight occupational factors identified in the Austin/Reynolds study as possible occupational risk factors, the three factors "Radioactive Materials", "Photographic Chemicals", and "Site 300" are least likely to have been incorrectly identified as occupational risks because of confounding by suspected constitutional risk factors. Effects for these three factors should be estimated jointly.

References

Elashoff, R. M., Hunter, T. D., Mohilef E. 1982. Final report on the epidemiology of melanoma. NICHD Contract, HD-8-2803.

Williams, R. R. 1976. Breast and thyroid cancer and malignant melanoma promoted by alcohol-induced pituitary secretion of prolactin, T.S.H. and M.S.H. Lancet 1: 996-999.

Williams, R. R. and Horn, J. W. 1977. Association of cancer cites with tobacco and alcohol consuption and socio-economic status of patients: interview study from the Third National Cancer Survey. JNCI 58: 525-547.

Table 1

The Coding of the Non-Occupational Variables

Abbreviation	Position in Model Descriptor (see Table 4)	Code	Description
	All	0	Variable is absent from the model.
MOLES	1		Number of moles larger than a pencil eraser -
		1	Two states: < 5.5, > 5.5
		2	Three states: < 2.5, between 2.5 and 5.5, > 5.5, coded as a categorical variable
		3	Square root transformed
DEGREE	2	1	Subject possesses a Master's degree or some kind of doctorate. Two states: no, yes.
		2	Subject possesses some kind of doctorate. Two states: no, yes.
BURN <21	3		Average number of times per year the subject was sunburned before the age of 21.
		1	Used continuously.
		2	Two-states: < 3.5, >3.5.
	4		always zero
PARENTAL SKIN CANCER	5		Subjects parent(s) have been diagnosed as having skin cancer.
		1	Two states: Neither parent diagnosed, at least one parent diagnosed.
		2	Three states: Neither parent, one parent, two parents diagnosed, coded as a categorical variable with three levels.

BURN/TAN I (No Previous Exposure)	6	1	Response to half-hour noontime exposure if not already tanned. Two states: Usually tan with little or no burning, usually burn with little or no tanning.
BURN/TAN II (With Previous Exposure)	7	1	Response to half-hour noontime exposure after a few days of sun exposure. Two states: Usually tan with little or no burning, usually burn with little or no tanning.
SKIN CANCER	8	1	Subject ever told a doctor to have basal or squamous cell carcinoma of the skin. Two states: no, yes (1 is yes).
HAIR COLOR	9	1	Hair color. Hair was blonde, red, or auburn both at age 6 and at age 20.
FRECKLES - SAME	10	1	Subject has freckles that stay with or without sun exposure. Two states: no, yes.
EYE COLOR	11	1	Blue eyes. Two states: no, yes.
WINE/BEER	12	1	Number of 4 oz. glasses of wine plus the number of bottles of beer the subject drinks per week. Continuous.
BORN IN CALIFORNIA	13	1	Born in California. Two states: no, yes.

X-RAY	14	1	Ever had fluoroscopy, major diagnostic x-ray, or been treated for any of a number of ailments with x-ray. Two states: no, yes.
PHYSICAL EXAM	15	1	Number of physical examinations at LLNL plus the number of physician's visits during a two-year period. Continuous.

Table 2

The Coding of the Occupational Variables

Abbreviation	Position in Model Descriptor	Code	Description
BUILDING - 1969	17	1	Ever worked in a building constructed in 1969 within 10 years of the reference date. Two states: No, yes.
RADIOACTIVE MATERIALS	18	1	Ever worked around radioactive substances within 10 years of the reference date. Two states: No, yes.
PHOTOGRAPHIC CHEMICALS	19	1	Ever worked around volatile photographic chemicals within 10 years prior to the reference date. Two states: No, yes.
HIGH EXPLOSIVES	20	1	Ever worked around fumes from high explosives within 10 years prior to the reference date. Two states: No, yes.
SITE 300	21	1	Ever worked at site 300 (a non-nuclear test site). Two states: No, yes.
PACIFIC TEST SITE	22	1	Ever present at an atmospheric atomic testing at the Pacific Test Site. Two states: No, yes.
SCIENTIST	23	1	Personnel file code classifies the individual as a scientist. Two states: No, yes.
CHEMIST DUTIES	24	1	Individual actually carried out laboratory chemist duties. Two states: No, yes.

Table 3

Comparisons of Definitions of Variables Used in This Analysis, with Those Used by Austin and Reynolds, Elashoff et al., and Holman.

Variable Name	Definitions Used by Other Investigators	Definitions Used in This Analysis
Moles	Austin and Reynolds	
	Asked subject to estimate moles on body larger than a pencil eraser: a dichotomous variable, 0 = fewer than 6 moles 1 = 6 or more moles	Number of moles larger than a pencil eraser: 1) a dichotomous variable: 0 = < 5.5, 1 = > 5.5
	Elashoff et al.	2) a categorical variable: < 2.5, between 2.5 and 5.5, > 5.5
	Asked subject to estimate moles on body larger than a pencil eraser: a dichotomous variable, 0 = fewer than 4 moles 1 = more than 4 moles	3) a continous variable: square root transformed
	Holman	
	Counted number of raised nevi on the arm; a categorical variable; categories: 0, 1-4, 5-9, ≥ 10	
	(May have used moles in a continuous form, but not clear)	
SKIN CANCER	Austin and Reynolds	
	The subject was told by a physician that he or she had basal or squamous cell carcinoma, a dichotomous variable: 0 = no, 1 = yes	Same

PARENTAL SKIN CANCER	Austin and Reynolds		
	Parents have a history of skin cancer, a dichotomous variable 0 = no, 1 = at least one parent diagnosed.	1) same 2) a categorical variable: neither parent, one parent, two parents.	
BURN/TAN I	Holman		
	Acute reaction to the sunlight after exposure for the first time in summer for one hour: 1) tan without sunburn, 2) mild burn, then tan, 3) painful burn followed by peeling, 4) severe sunburn with blisters.	Response to half-hour noontime exposure if not already tanned. A dichotomous variable: 0 = usually tan with little or no burning. 1 = usually burn with little or no tanning.	
BURN/TAN II	Holman		
	Chronic reaction to the sun 1) tan without sunburn, 2) mild burn, then tan, 3) painful burn followed by peeling, 4) severe sunburn with blisters.	Response to half-hour noontime exposure after a few days of sun exposure. A dichotomous variable: 0 = usually tan with little or no burning. 1 = usually burn with little or no tanning.	
ADVANCED DEGREE	Austin/Reynolds		
	Yes or No?	1) Subject possesses a master's degree or some kind of doctorate. Dichotomous variable: 1 = Yes, 0 = No. 2) Subject possesses a doctorate. Dichotomous variable: 1 = Yes, 0 = No.	

EYE COLOR	Austin/Reynods	
	A dichotomous variable: 1 = Blue, 0 = Not Blue. Measured by interviewer who compares subject's eye color with colors on a chart: 1-4 = Brown 5-12 = Blue	A dichotomous variable: 1 = Blue, 0 = Not Blue 1 = have a value for "blue" eye chart 0 = have no value for blue eye chart
HAIR COLOR	Austin/Reynolds	
	A dichotomous variable: 1 = light hair, 0 = does not have light hair. If the respondent answered "yes" to the following questions: 1) did you have light colored hair at age six? 2) Is your natural hair color light now? (at the time of the interview)	

Table 4

Model Descriptors for the Confounder Sets

Each 15-digit string corresponds to one confounder set: each position corresponds to a different variable, as described in Table 1. If a position in a model descriptor is non-zero, the corresponding variable is used in the model. The value of the digit for a variable identifies the form of the variable for that model. For an example of how to interpret a model descriptor, consider the confounder set 320021010000011: MOLES, form 3 (square root transformed) ; DEGREE, form 2 (doctorate holders versus non-doctorate holders) ; PARENTAL SKIN CANCER, form 2(three states: no parent, one parent, both parents diagnosed, coded as a categorical variable, with two indicator variables) ; BURN/TAN I ; SKIN CANCER ; X-RAY ; PHYSICAL EXAM (the last four variables were used in only one form).

In other chapters in this report, there are an additional nine positions to the right of each 15-digit model descriptor, making a total of 24 positions. In these long model descriptors, position 16 is always zero, and positions 17 through 24 correspond to occupational variables, as indicated in Table 2, column 2.

320021010000011	320021010000010	320021010000001	320021010000000
320011010000011	320011010000010	320011010000001	320011010000000
310021010000011	310021010000010	310021010000001	310021010000000
310011010000011	310011010000010	310011010000001	310011010000000
302001100000111	302001100000110	302001100000101	302001100000100
301001100000111	301001100000110	301001100000101	301001100000100
300000001111011	300000001111010	300000001111001	300000001111000
220021010000011	220021010000010	220021010000001	220021010000000
220011010000011	220011010000010	220011010000001	220011010000000
210021010000011	210021010000010	210021010000001	210021010000000
210011010000011	210011010000010	210011010000001	210011010000000
202001100000111	202001100000110	202001100000101	202001100000100
201001100000111	201001100000110	201001100000101	201001100000100
200000001111011	200000001111010	200000001111001	200000001111000
120021010000011	120021010000010	120021010000001	120021010000000
120011010000011	120011010000010	120011010000001	120011010000000
110021010000011	110021010000010	110021010000001	110021010000000
110011010000011	110011010000010	110011010000001	110011010000000
102001100000111	102001100000110	102001100000101	102001100000100
101001100000111	101001100000110	101001100000101	101001100000100
100000001111011	100000001111010	100000001111001	100000001111000

Table 5
Ra ting the Characteristics of the Distributions
of the
Log Odds Ratios

Occupational Factor	Range	Interquartile Range	P Value	Median	Weighted Average Rank	Overall Rank
	Distribution Characteristics					
Weights	1/7	3/7	2/7	1/7		
Radioactive Materials	1	2	1	4	1.9	1
Site300	2	1	3	5	2.3	2
Photographic Chemicals	5	3	2	1	2.7	3
Scientist	3	4	4	6	4.1	4
Chemist Duties	6	6	6	2	5.7	5
1969 Building	7	5	7	7	6.1	6.5
Pacific Test Site	6	8	5	3	6.1	6.5
High Explosives	4	7	8	8	7.0	8

Figure 1

Ranges of Odds Ratios
for Occupational Factors

Each line summarizes the distribution of the estimates of the odds ratios for the corresponding occupational factor. The long horizontal bar indicates the range of the log odds ratio estimates. The proportion of the bar filled in with hash marking is the proportion of the regression coeeficients that were nominally significantly different from one in a one-sided test with a type I error less than 0.05. The short solid vertical line in each figure marks the median of the log odds ratios, and the ends of the shorter box mark the first and third quartiles of the distribution of the log odds ratios.

Each line summarizes approximately 588 odds ratio estimates. The odds ratio for each occupational variable was estimated using each of the 84 confounder sets listed in Table 4. These odds ratios were combined with estimates from models using each of the 84 confounder sets, and each of the other occupational variables, one at a time, with the exception that "1969 Building" was not included in any model used to estimate effects for the other occupational variables, due to the small sample size required to accomodate missing values for this variable, and the further exception that all of the models that included "1969 Building" and "Pacific Test Site" were numerically unstable, so that it was impossible to get odds ratio estimates from them. Thus, for each occupational variable, there are a total of 84 estimates using only confounder set variables in addition to the given occupational variable, and 84 x 6 = 504 estimates using confounder set variables, the given occupational variable, and one other occupational variable. Occasionally, one of the 588 models was numerically unstable, so a few of the summaries are based on slightly fewer than 588 estimates.

Figure 1

DISTRIBUTIONS OF ESTIMATED ODDS RATIOS

FOR OCCUPATIONAL FACTORS

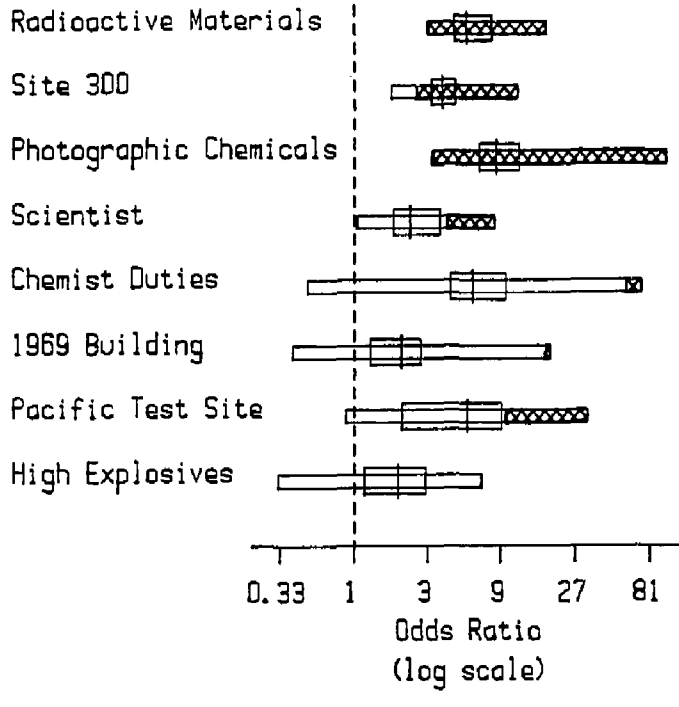


Figure 2

Confounding of Occupational
Factors by Confounder Set Factors

For each confounder set factor, the standardized regression coefficients (Z-scores) for the labelled occupational factor were divided into groups, corresponding to the codes for the non-occupational factors in Table 1 and the codes for the occupational factors in Table 2. For example, the standardized regression coefficients for the occupational factor "Scientist" were divided into three groups, depending on whether the variable "Degree" was absent from the model (code 0), whether a Master's Degree was sufficient to classify a subject as holding an advanced degree (code 1), or whether a Doctorate was required to classify a subject as having an advanced degree (code 2).

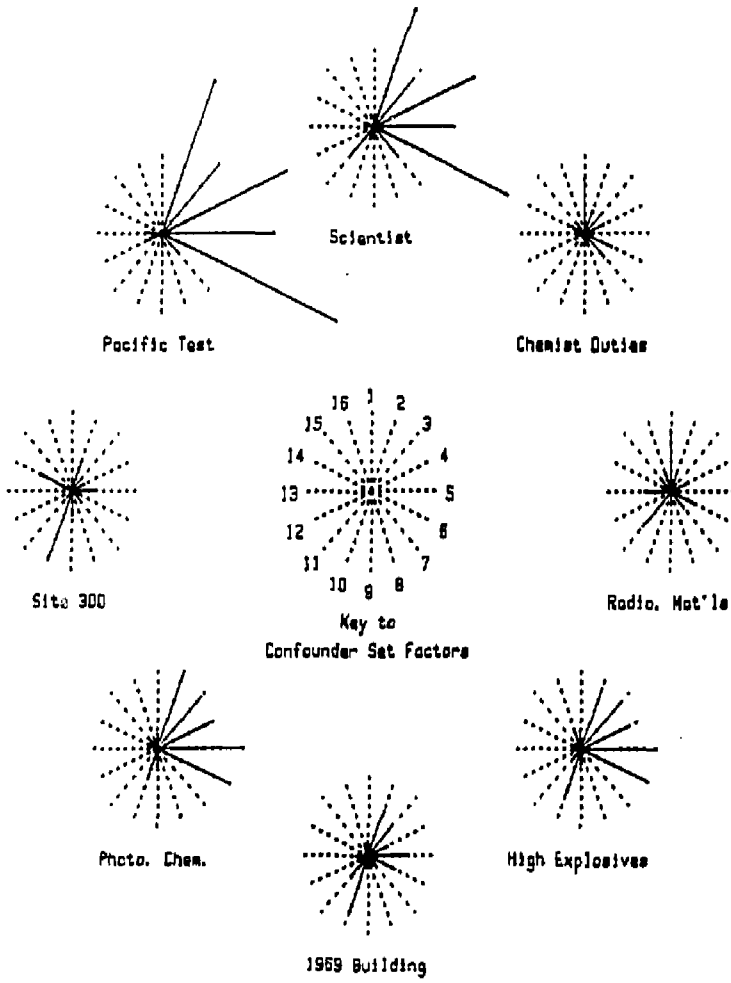
The length of each solid ray is proportional to the square root of the F-statistic from a test of the homogeneity of the Z-scores among the groups.

Confounder Set Factors
See Tables 1 and 2 for definitions.

1 Moles
2 Degree
3 Burn < 21
4 Parental Skin Cancer
5 Burn/Tan II & Born in Ca.
6 Skin Cancer
7 Burn/Tan I, Hair Color, Freckles-same, Eye Color, Wine/Beer
8 X-ray
9 Physical Exam
10 Radioactive Materials
11 Photographic Chemicals
12 High Explosives
13 Site 300
14 Pacific Test site
15 Scientist
16 Chemist Duties

Figure 2

CONFOUNDING OF OCCUPATIONAL FACTORS BY CONFOUNDER SET FACTORS



VI. Ionizing Radiation and Melanoma at LLNL

Introduction

The fact that melanoma cases were more likely to have reported working around radioactive materials than were controls raises the possibility that some exposure, received by employees who work around radioactive materials, might have caused the disease in these workers; that is, "working around radioactive materials" could be a surrogate for the exposure that actually caused the disease. One reasonable candidate for such an exposure is ionizing radiation.

In an earlier report on malignant melanoma at LLNL, Austin et al. (1981) found no association between cumulative exposure to ionizing radiation and melanoma. Their measure of ionizing radiation exposure was the logarithm of the total cumulative gamma radiation dose, current as of the time of the study, 1981. Since the reference dates ranged from 1969 to 1980, and the information for the case-control study was gathered in 1981, their measures of ionizing radiation exposure included radiation received after the reference date (i.e., the date melanoma was diagnosed in the case) for most subjects with ionizing radiation exposure. Substantial ionizing radiation doses could have been acquired between the reference date and the interview date, and such acquisition could complicate making an accurate assessment of a possible relationship between ionizing radiation exposure and melanoma.

Even if doses received after the reference date were excluded, a simple

cumulative ionizing radiation exposure measure may not be the best index to use when looking for an association between ionizing radiation dose and melanoma. First of all, it may be that the intensity of the exposure as well as the total dose is necessary to fully account for the efficacy with which exposure to ionizing radiation produces melanoma. That is it may be that the same total cumulative dose of ionizing radiation may be more effective as a cause of melanoma if it is received over a short time. Since the only detailed ionizing radiation exposure information available for each employee comes from radiation badge readings, and the shortest interval between radiation badge readings is one month, we cannot directly assess the impact of this sort of intensity-related exposure effect.

Furthermore, it may be that only a portion of a person's total exposure to ionizing radiation is relevant to predicting case status. This depends upon the manner in which ionizing radiation might operate to cause melanoma. There are essentially two situations to consider. In the first situation, exposure to ionizing radiation might initiate a physiological process that would ultimately lead to the development of melanoma, as long as certain other exposures or physiological events occurred following the initial exposure to ionizing radiation. Thus, the exposure that ultimately led to the disease would be followed by a latency period, during which further ionizing radiation exposure would be irrelevant to the ultimate development of disease. In this instance, the measure of ionizing radiation exposure most strongly associated with case status would be the cumulative ionizing radiation exposure a subject received up to a time before diagnosis; this time would be equal to the length of the latency period. Alternatively, ionizing radiation exposure could be the final step in the chain of events that leads to melanoma. That is, ionizing

radiation could serve as a promoter for melanoma. Under this scenario, the measure of exposure that would be most strongly associated with case status would be the amount of ionizing radiation exposure just prior to disease onset.

Employees who are likely to be exposed to ionizing radiation routinely wear radiation badges and LLNL keeps a permanent record of the dose recorded for each interval as a part of its personnel records. We used LLNL's detailed records of employee ionizing radiation exposure, as measured by radiation badges, to evaluate the possibility that "working around radioactive materials" is a surrogate for ionizing radiation exposure in the original analysis of these data. Using the detailed exposure data, we created four variables that measured different portions of the total ionizing radiation dose accumulated while employed at LLNL: up to 15, eight, and five years before the reference date, and up to the reference date itself. We created four more variables that measured total ionizing radiation dose received within the time periods of one, two, five, and 15 years prior to the reference date. We estimated effects for these eight cumulative ionizing radiation exposure measures, while controlling for non-occupational factors and the factor "worked around radioactive materials" in conditional logistic regression models.

Methods

Employees at LLNL who work around radioactive materials routinely wear radiation badges to monitor exposure to ionizing radiation. The badges are read at regular intervals whose lengths depend upon the expected exposure of the employee. There is a permanent record of all the badge readings, as well as an updated record of each employee's cumulative exposure while employed at LLNL. LLNL linked their detailed ionizing radiation exposure records with the Austin/Reynolds case-control data set, and gave us a complete record of all badge readings for each of the 36 subjects in the LLNL melanoma case-control study who had a total lifetime exposure of at least 200 mrem. The data set we received contains the dates covered by each badge reading, the laboratory at which the exposure occurred, the radiation type, the organ monitored (whole body or skin), and the dose accumulated over the interval associated with each badge reading. For each such employee, we calculated the total accumulated ionizing radiation dose, in rems, at the time of the reference date, five years prior to the reference date, eight years prior to the reference date, and 15 years prior to the reference date. We also calculated the accumulated ionizing radiation doses, in rems, received between the reference date and one year prior to the reference date, two years prior to the reference date, five years prior to the reference date, and 15 years prior to the reference date. We included all exposures received while the subject was employed at LLNL, no matter where the exposure was received, what the organ was, or what the type of radiation was. Anyone who had a lifetime dose of less than 200 mrem was considered to have received a dose of zero rem for each of these exposure

measures. Thus, one measure of radiation exposure we used was a continuous measure that had the value "zero" if a person had less than 200 mrem total lifetime exposure, and reflected badge readings for persons who had greater than 200 mrem lifetime exposure. A dichotomous variable which took the value "1" when the associated continuous variable was non-zero, and which took the value "0" when the associated continuous variable was zero, was also created for each of the eight continuous variables. Odds ratios for these dichotomous exposure variables would not be adversely influenced by the few large exposure values found when treating the exposure measures continuously.

Odds ratios for each of the sixteen ionizing radiation exposure variables were estimated jointly with the odds ratio for "working around radioactive materials" in conditional logistic regression models. If "working around radioactive materials" is indeed a surrogate for exposure to ionizing radiation, and ionizing radiation is the only melanoma risk factor correlated with working around radioactive materials that we have not controlled for, then we would expect estimates of the odds ratio for working around radioactive materials to be around one, and estimates of the odds ratio for exposure to ionizing radiation to be significantly greater than one. Even if there are other, uncontrolled-for risk factors for melanoma correlated with working around radioactive materials, as long as exposure to ionizing radiation is a risk factor for melanoma, odds ratio estimates for the ionizing radiation exposure variables ought to be greater than one, although the magnitude and statistical significance of the estimates would depend upon the portion of the risk attributed to working around radioactive materials that is due to exposure to ionizing radiation.

To assess the possible effect of confounding by non-occupational and some

other occupational factors, the confounder sets associated with the minimum, first quartile, median, third quartile, and maximum effect estimates for the variable "worked around radioactive materials" (see Chapter V of this report), as well as the set of non-occupational variables identified by Austin and Reynolds in their analysis of the case-control data, were included in models used to estimate the effects of the sixteen badge exposure variables. These were the same confounder sets used in Chapter IV, and are listed in Table 2 of that chapter.

Results and Discussion

Nine cases and 27 controls had each accumulated more than 200 mrem of ionizing radiation exposure while employed at LLNL. The median dose accumulated by the reference date was 1.24 rem for the cases with greater than 200 mrem, and 0.620 rem for controls with greater than 200 mrem. None of the odds ratio estimates for any of the sixteen ionizing radiation dose measurements was statistically different from 1.0 using a type I error of 0.05; in contrast, the odds ratio for "working around radioactive materials" was greater than 2.6 in all models, and was significantly different from 1.0 for all but one confounder set. All of the odds ratios for exposure to ionizing radiation accumulated up to specified times before the reference date were close to 1.0. However, the odds ratios for recent exposures, especially the odds ratios for exposures accumulated in the year before the reference date and for exposures accumulated in the two years before the reference date,

cover a much wider range, even though none of them is statistically significantly different from 1.0. The estimated standard errors for the odds ratios for (continuous) cumulative ionizing radiation exposures between two years before the reference date and the reference date, and between one year before the reference date and the reference date are very large, due, no doubt, to the small number of subjects with non-zero values for these variables (14 subjects received greater than 200 mrem in the year immediately preceeding the reference date, and 17 subjects received greater than 200 mrem in the 2 years before the reference date). The minimum, median, and maximum of the six estimates for the odds ratio for each of the 16 ionizing radiation exposure variables (the odds ratio for each exposure variable was estimated with each of six sets of potential confounder variables) are listed in Table 1.

The models used to estimate the odds ratios for the ionizing radiation exposure variables were specifically chosen to test the hypothesis that having "worked around radioactive materials" is a surrogate for exposure to ionizing radiation. If exposure to ionizing radiation were indeed an important cause of melanoma, and "worked around radioactive materials" were a surrogate for exposure to ionizing radiation, then estimates of the odds ratios for at least some of the ionizing radiation exposure variables would have been significantly greater than 1.0; and, in those models in which there was a significant odds ratio for the ionizing radiation exposure variable, the odds ratio for working around radioactive materials would have been reduced towards 1.0. Instead, the ionizing radiation exposure odds ratios were around 1.0 for all but the continuously coded exposures in the year before the reference date and two years before the reference date, and working around radioactive

materials remained a substantial risk factor in all models. Thus it seems unlikely that the underlying reason for the apparent elevated risk of contracting melanoma among persons who work around radioactive materials is exposure to ionizing radiation.

It is important to remember that eliminating ionizing radiation as a risk factor for melanoma does not automatically imply that the large odds ratio for working around radioactive materials is invalid. Several possible explanations may account for the association in this data set between melanoma and having worked around radioactive materials: 1) People who work around radioactive materials may be exposed to some other substance that is a risk factor for melanoma, i.e., "working around radioactive materials" may be a surrogate variable for some other as yet unknown risk factor for melanoma (the risk associated with the variable JCAVG described in Chapter IV tends to support this hypothesis); 2) Ionizing radiation may be a risk factor for melanoma, but badge readings do a poor job of measuring the relevant exposure; 3) There may be recall bias; that is, cases and controls may not be equally likely to remember that they had ever worked around radioactive materials; 4) Finally, the association in this data set may be due to chance, being simply the result of screening a large number of variables for an association with melanoma. It is impossible in this data set to determine which of these explanations is the most plausible.

Reference

Austin, D. F., Reynolds, P. J., Synder, M. A., Biggs, M. W., Stubbs, H. A. 1981. Malignant melanoma among employees of Lawrence Livermore National Laboratory. Lancet 2: 712 - 715.

Table 1.

Odds Ratios for Ionizing Radiation Exposure
as Measured by Radiation Badges.

Odds ratios were estimated in conditional logistic regression models that contained the variables in each of six confounder sets, a variable that was "1" for subjects who indicated that they had worked around radioactive materials and was "0" otherwise, and either a continuous measure of radiation exposure measured in rems (odds ratios in columns labeled "Continuous"), or an indicator that was "1" if the continuous exposure variable was non-zero and was "0" otherwise (odds ratios in columns labeled "Dichotomous"). The median odds ratio for each set of six estimates (one for each confounder set) is presented under the heading "Median OR", and the minimum and maximum odds ratios are presented under the heading "Range of ORs".

None of the odds ratio estimates is significantly different from "1" for a Type I error of 0.05.

Odds ratios for ionizing radiation exposure accumulated between the first recorded exposure and Lag years before the reference date.

	Continuous		Dichotomous	
Lag	Median OR	Range of ORs	Median OR	Range of ORs
0	1.2	1.0 - 2.2	0.2	0.2 - 0.5
5	1.2	1.0 - 2.4	0.2	0.2 - 0.5
8	1.1	0.9 - 1.9	0.2	0.1 - 0.5
15	0.9	0.8 - 1.0	0.1	0.02 - 0.3

Odds ratios for ionizing radiation exposure accumulated between Lag years before the reference date and the reference date.

	Continuous		Dichotomous	
Lag	Median OR	Range of ORs	Median OR	Range of ORs
1	3.2	0.5 - 177.5	2.3	1.5 - 16.8
2	2.3	1.3 - 905.9	0.7	0.3 - 1.1
5	1.6	1.2 - 23.6	0.5	0.3 - 1.1
15	1.3	1.2 - 2.7	0.4	0.2 - 0.6

VII. The Role of Time

Introduction

The occupational factors identified in the Austin/Reynolds study pertain to exposures that may well have changed their natures over time. For example, suppose that subjects who work around radioactive materials are exposed to a variety of materials to which other LLNL employees are not exposed, and that one of these exposures is a risk factor for melanoma. If the relative frequency of exposure to the melanoma risk factors among subjects who work around radioactive materials changes over time, then the risk of contracting melanoma among employees who had worked around radioactive materials would depend upon when they had worked around radioactive materials. Identifying and describing such temporal variation could prove helpful in identifying previously unidentified occupational risk factors for melanoma. In this section of our report we describe our search for such temporal variation of occupational effects.

Five temporal factors could have a bearing on the interpretation of the Austin/Reynolds case-control data: (1) The dates of diagnosis for the cases ranged over a period of 12 years. (2) The ages of the cases in this study range from 25 to 56 years old. (3) The cases represent different birth cohorts, from approximately 1914 to approximately 1955. (4) The subjects interviewed for this study were hired at different times, between approximately 1945 and 1980. (5) The subjects had worked at LLNL for different

lengths of time (from only a few months to over 32 years) when they were interviewed about occupational exposures.

Not only might the actual effect of a measured occupational factor change over time, but also the estimate of an occupational effect might be different for different times (even if the actual effect did not change). Different lengths of time elapsed between occupational exposures and the interview since all the subjects were interviewed in a relatively short time in 1981, the reference years range from 1969 to 1980, and subjects were asked to remember occupational exposures they received between ten years before the reference date and the reference date. Subjects from early reference years had to remember exposures from further in the past than subjects from more recent reference years, and so may well have been more subject to recall bias.

We used two complementary approaches to identify occupational factor effects that might have changed over time. First, we cut the time variable at a convenient value to make a dichotomous, categorical variable, and then used conditional logistic regression methods to test the significance of the interaction between the categorized time variable and each of the occupational factors. A significant interaction effect would indicate that the main effects had changed over time. However, the lack of a significant interaction might only indicate that the cutpoint for the categorized time variable was chosen at the "wrong" place, so we also attempted to estimate effects for the occupational variables for each value of the time variable, and examined a plot of these main effects estimates against the time variables. Although there is as yet no reliable way to use these plots for statistical inference, they roughly describe the relationships present in the data, and can be used for hypothesis generation.

Methods

Strategy of Analysis.

Each of the Austin/Reynolds occupational factors was examined separately for time interactions. Separately, for each of the time variables (date of diagnosis, age, year of birth, duration of employment, year hired at LLNL), models consisting of confounder set variables, the occupational variable under consideration, and a variable that was the cross-product of the occupational variable and the time variable under consideration, were fit to the data using conditional logistic regression methods. Main effects for variables on which the subjects were matched (date of diagnosis, age, year of birth) cannot be estimated, so there was no main effect term in these models; in contrast, for the variables relating to duration of LLNL employment and the year hired by LLNL, a main effect term was also included. To allow for the uncertainty about confounding discussed in Chapter Five, five confounder sets spanning the range of estimates of the odds ratios of the occupational factor were selected, as well as the Austin/Reynolds confounder set. Each of the models outlined in this paragraph was fit using variables from each of the confounder sets in turn, resulting in determinations of the occupational factor main effect, the interaction effect, as well as the main effect estimates for duration of employment and year hired.

An odds ratio estimate was considered to be significantly different from one if the corresponding regression coefficient divided by its estimated standard error lay outside the interval (-1.96, 1.96).

Time Variable Coding.

The time related variables and their coding were:

REFERENCE YEAR - the year in which the case was diagnosed. Each control must have been employed at LLNL in the calendar year in which the matching case was diagnosed.

IREFYR - 1 if the reference year was 1975 or earlier.
0 if the reference year was later than 1975.

IBRTHYR - 1 if the case was born in or before 1930.
0 if the case was born after 1930.

IAGE - 1 if the case was 44 years old or older in the reference year.
0 if the case was younger than 44 years old in the reference year.

YEAR HIRED - the year the subject was first hired by LLNL.

IHIRE - 1 if the subject was first hired by LLNL in or before 1962.
0 if the subject was first hired by LLNL after 1962.

WORKTIME - the time interval, in years, between the date the subject was first hired at LLNL and the reference date, regardless of any intervening interruption.

Missing Values.

For each occupational variable, a data set was constructed that excluded any control which was missing data for any variable required to estimate any of the models for the analysis of the relationship of that variable and the time variables. In addition, when a case was missing a response for one of the necessary variables, the case and its matched controls were excluded from the analysis.

The Change in Effects of Occupational Variables with Time.

We wanted a more descriptive assessment of the relationship between the values of the occupational variable effects and the different time variables, so we arranged the subjects into groups that had similar values of the time variable and estimated odds ratios for each of the occupational variables within each group. Since each group included only a few of the subjects in the study, it was impossible to control for confounding by all of the known and suspected confounders. However, number of moles is a particularly strong risk factor in these data, so it was important to control the effect estimates for number of moles. The subjects in each time group were stratified on number of moles (coded as "0" if the subject had fewer than six moles larger than a pencil eraser, and "1" if the subject had six or more such moles), and Mantel-Haenzel odds ratio estimates used to estimate effects for the occupational factor for each group. Note that, in general, the original matching in the data was not maintained in the grouping by time variable. When the time variable was one of the matching variables, matched sets were combined, and when the time variables were not matched, matched sets were split up.

To produce a smoother picture of the relationship between occupational factor effects and time, the range of each time variable was divided into overlapping intervals. Each interval defined a group of subjects for which the occupational variable effects were estimated. The variable "Reference Year", which ranges from 1969 to 1980 was divided into ten three-year intervals: 1969 - 1971, 1970 - 1972, etc. The variable "Year Hired" was divided into five approximately nine-year intervals: 1945 - 1958, 1953 - 1962, 1959 - 1966, 1963 - 1973, 1974 - 1980. The variable "Worktime" was divided into the intervals: 0 - 8, 4 - 12, 9 - 17, 13 - 20, and 18 - 32 years. The intervals for these last two variables were chosen to insure, as much as possible, equal numbers of subjects in each interval, while keeping the intervals close to the same length. The odds ratio estimated for each time interval for each occupational variable was plotted against the mean value of the time variable among the subjects used to estimate the effect.

Results and Discussion

Tables 1 through 7 give the results of the tests for time interactions for seven of the eight Austin/Reynolds occupational factors. The eighth factor, "chemist duties", is not shown. Five matched sets contain individuals with this exposure, and, in these sets, only one case was not an active chemist. When the sets are divided into two groups by reference date, one or the other group must either contain no matched sets with exposed individuals, or all the sets with exposed individuals must have an exposed case. When the

latter situation occurs, there is no local maximum for the likelihood, so attempts to find one end in numerical failure. Estimating an effect for the interaction between a dichotomized reference year variable and an occupational factor is logically equivalent to estimating a separate effect for the occupational factor in each of the two time domains defined by the dichotomized reference year variable. Therefore, subjects with the exposure "chemist duties" were not necessarily at any greater risk in one time period than in another.

We looked for three characteristics of the interaction effects estimates from the regression models to indicate that occupational effects were heterogenious in time: statistical significance of the interaction term, the magnitude of the effect estimate for the time interaction term, and consistency of any pattern among the estimates using different confounder sets. Due to the small sample sizes, none of the evidence for the patterns described below is very strong. Nevertheless, if the results are taken in the spirit of an exploratory investigation, the patterns that this analysis reveals may be useful in helping to find hitherto unidentified occupational risk factors for melanoma.

The salient features of the analysis of the interaction effects between occupational factors and time variables are briefly described. Neither the date a person was hired (IHIRE) nor the duration of employment (WORKTIME) seems to have a significant effect on a person's risk for melanoma. None of the occupational variables seems to have a significant interaction with age or date of birth. Presence at site 300, working around radioactive materials, and having worked in a building constructed in 1969 are greater risks in matched sets from reference years before 1975 than after 1975. However,

presence at site 300, classification as a scientist, and having worked in a building constructed in 1969, all seem to present greater risks for people who were hired after 1962 than among people hired before 1962. They also represent greater risks among those who had worked a relatively shorter time.

The smoothed odds-ratios (Figures 1 - 3) lend insight into these conclusions. Figure 1 shows the relationship between "presence at site 300", "working around radioactive materials", "working in a building constructed in 1969" and "scientist" and "reference year". The first three of the occupational variables are clearly greater risks in earlier than later reference years, so the conclusions about the shape of the relationships between the first three of these occupational variables and reference year are supported by this figure. The observation of the relationship between the risk associated with working in a building constructed in 1969 and reference year is consistent with the suggestion of Austin and Reynolds in their analysis of the same data, that if the effect of working in these buildings is real, it was of short duration, produced illness soon after exposure, and was effective only in the few years after the buildings were occupied. The relationship between the effect for "scientist" and "reference year" seems to be relatively constant.

The analysis of the time interactions does not seem to have done justice to the relationships between these same four occupational variables and "year hired", however (Figure 2). The effect of "worked around radioactive materials" and, perhaps, "site 300", seems to have been highest among the earliest employees in the sample, then declined to a constant level among more recent employees, with perhaps a dip in the late '50's. The effect for "scientists" is higher in later than earlier employees, which is consistent

with the analysis of interaction effects, but, although it seems to be true that persons working in a building constructed in 1969 were at higher risk if they were hired after 1962, that risk seems to decline rapidly for more recently hired employees.

One might argue that the relationship between the effect of "radioactive materials" and "site 300" on the one hand, and "year hired" on the other, argue that there is an exposure or exposures, for which these occupational factors are proxies, that has a greater effect the longer a person is exposed. If this were the case, one would expect the odds ratio for these two exposures to increase among employees who had worked at LLNL for greater times. Figure 3 shows the effect of "worked around radioactive materials" and "site 300" plotted against the duration of employment at LLNL. The two curves have in common that they seem to be decreasing, or at least they are not increasing, as the time worked at LLNL increases. Thus, the pattern of risk for these two factors is not simply due to longer exposure to the persons hired in earlier years.

The suggestion that certain occupational factors are greater risks for subjects in early reference years than in later ones hints that some LLNL employees may have been exposed to a risk factor prior to or early in the study period, and that persons working around radioactive materials, persons who worked at site 300, and persons who had worked in buildings constructed in 1969, were more likely than others to have been exposed to this risk factor. The decline of the effect over time suggests either that the incidence of the exposure declined over time, <u>or</u> that the exposure became more wide-spread, and was no longer associated most strongly with the identified occupational factors.

It would be a mistake to come away from this analysis with the impression of strong evidence for temporal heterogeneity of occupational factor effects. We are unaware of any straightforward method for making confidence bands for these plots of odds ratios versus time, so any conclusions based on the plots of odds ratios versus time should be held as tentative. The occupational factor - time interactions, although often showing large effects, only occasionally achieved conventional statistical significance. Finally, we have not tried to take into account the correlations that occur among the different time variables, so that the results for the different time variables are not really independent. Nevertheless, the patterns that emerge seem to be interpretable, and involve two of the more reliable occupational variables (in the sense of Chapter V of this report), and at least suggest that some of the occupational exposures have changed their nature in time.

Caption For Tables 1 - 7:
Occupational Variables and Time.

Each table in this series follows the same format, and represents the results of an analysis of the relationship between one of the Austin/Reynolds occupational variables and the time variables defined in the text. The tabulated values are odds ratios for the main effects or interaction effects named in the first column of the table, estimated using conditional logistic regression methods. The same effects were estimated using different confounder sets, and the estimates are displayed under the column that corresponds to the confounder set used. Rows grouped together represent occupational factor main effects, time main effects, and time X occupational factor interactions that were estimated in the same model. Interaction effects are best interpreted as ratios of odds ratios. An effect for the interaction between an occupational factor and a dichotomous time variable is the ratio of the odds ratio for the occupational factor in the time domain associated with the value "1" of the time variable to the odds ratio for the occupational factor in the time domain associated with the value "0" of the time variable. For example, in Table 1, for the A/R confounder set, the term for the interaction between RadMti ("worked around radioactive materials") and IREFYR, is 8.10. According to the text, IREFYR is "1" if reference year is 1975 or earlier, and "0" otherwise, so the odds ratio for "worked around radioactive materials" among cases diagnosed in 1975 or earlier is 8.10 times the odds ratio for "worked around radioactive materials" among cases diagnosed after 1975. The main effect term then gives the odds ratio for the main effect in the time domain associated with the value "0" of the time variable: the odds ratio for "worked around radioactive materials" among cases diagnosed after 1975 is 2.62.

The confounder sets used were the Austin/Reynolds non-occupational factors and the confounder sets that gave rise to the minimum, first quartile, median, third quartile, and maximum estimate of the occupational factor effect in the analysis of confounding (Chapter 5). The confounder sets, described in the notation used in Chapter 5, and the abbreviations used for the occupational factors, follow.

"X" in the first column denotes the interaction between the time variable used in a particular model and the occupational factor.

* = $P < 0.05$, nominal significance uncorrected for multiple tests.

" - " indicates a model that could not be fit due to numerical instability.

Confounder Sets:

Every set of confounder sets includes the set of Austin/Reynolds non-occupational factors:

A/R: 110010110000000000000000

RadMtl - Worked Around Radioactive Materials

MIN: 102001100000110000100000
Q1: 110011010000010000001000
MED: 200000001111001000100000
Q3: 210011010000000000001000
MAX: 210021010000010000000100

SITE 300 - Site 300

MIN: 210011010000010001000000
Q1: 110021010000001001000000
MED: 301001100000100000010000
Q3: 220021010000001000010000
MAX: 201001100000111000100000

PHOTO - Photographic Chemicals

MIN: 200000001111000001000000
Q1: 320011010000010000000000
MED: 110011010000000000000100
Q3: 300000001111011000001000
MAX: 102001100000111000001000

SCI - Scientist

MIN: 310021010000001000100000
Q1: 220021010000011000000000
MED: 320011010000001001000000
Q3: 202001100000101000000100
MAX: 102001100000111001000000

69Bldg - 1969 Building

MIN: 202001100000111001000000
Q1: 210011010000010000000000
MED: 320011010000010000000010
Q3: 220021010000011000000001
MAX: 301001100000111000001000

PTSATM - Pacific Test Site

MIN: 202001100000110000010000
Q1: 202001100000111000001000
MED: 220011010000000000000000
Q3: 210021010000010000000001
MAX: 310021010000001000001000

HE - High Explosives

MIN: 102001100000100000100000
Q1: 102001100000100000000100
MED: 200000001111010000000010
Q3: 220011010000000000000000
MAX: 210021010000001000000000

Table 1

Time and the Relationship Between
Working Around Radioactive Materials and
Case Status

Odds Ratios & Interaction Effects

Model Variables \	Confounder Set: A/R	MIN	Q1	MED	Q3	MAX
RadMtl	5.49*	3.00	6.43*	5.44*	28.1*	46.4**
RadMtl	2.62	0.573	3.95	1.37	15.6	20.1
X IREFYR	8.10	17.2	2.98	22.0	2.80	6.93
RadMtl	4.39	1.91	5.29	3.94	42.6*	35.4*
X IBRTHYR	1.72	3.94	1.52	2.92	0.512	2.00
RadMtl	9.57*	2.93	7.90*	5.38*	52.63*	47.1*
X IAGE	0.403	1.06	0.679	1.03	0.351	0.967
RadMtl	5.40*	3.46	6.53*	5.36*	34.2*	56.5**
IHIRE	0.665	0.328	0.596	0.569	0.342	0.307
RadMtl	6.71*	3.80	8.61*	6.44*	35.9*	51.5*
IHIRE	0.893	0.365	0.831	0.730	0.366	0.164
X	0.562	0.788	0.534	0.586	0.835	3.61
RadMtl	5.53*	3.23	6.49*	5.49*	27.8*	46.1**
WORKTIME	0.992	0.957	0.984	0.994	0.979	0.963
RadMtl	10.28	8.49	8.82	11.3	29.1	32.7*
WORKTIME	1.01	0.986	0.995	1.01	0.981	0.945
X	0.943	0.905	0.972	0.930	0.994	1.06

Table 2

Time and the Relationship Between
Site 300
and Case Status

Odds Ratios & Interaction Effects

Model Variables \	Confounder Set: A/R	MIN	Q1	MED	Q3	MAX
SITE300	3.02	3.06	6.98*	3.85	7.28*	12.8*
SITE300	0.906	1.84	3.48	1.75	2.19	2.17
X IREFYR	24.4*	3.73	25.8	3.73	63.5*	17.8
SITE300	2.55	3.50	6.68	3.58	11.3	15.1
X IBRTHYR	1.40	0.750	1.11	1.15	0.521	0.733
SITE300	11.5	14.0	29.7*	5.86	44.8*	81.1*
X IAGE	0.140	0.0791	0.0852	0.480	0.0988	0.0849
SITE300	3.10	2.77	6.96*	4.10*	7.43*	12.7*
IHIRE	0.536	0.269	0.414	0.368	0.532	0.784
SITE300	7.04	31.6*	15.1*	9.11*	39.5*	48.3*
IHIRE	2.09	2.88	1.38	0.798	4.16	2.56
X	0.143	0.00559*	0.153	0.238	0.0488	0.111
SITE300	3.06	3.20	7.08*	3.85	7.36*	12.7*
WORKTIME	0.992	0.976	0.989	0.985	0.986	1.02
SITE300	9.76	149.3	29.7*	12.3	211*	53.2
WORKTIME	1.04	1.08	1.02	1.02	1.11	1.06
X	0.899	0.714	0.883	0.904	.758*	0.882

Table 3

Time and the Relationship Between
Working Around Photographic Chemicals
and Case Status

Odds Ratios & Interaction Effects

Model Variables \	Confounder Set: A/R	MIN	Q1	MED	Q3	MAX
PHOTO	7.63**	3.18	7.82*	10.6**	11.7**	102**
PHOTO	13.5**	3.73	12.5*	12.4*	12.9*	78.0*
X IREFYR	0.206	0.612	0.309	0.592	0.750	2.68
PHOTO	7.09*	7.54	4.74	9.14*	12.7*	40.4*
X IBRTHYR	1.19	0.187	3.44	1.46	0.843	59.1
PHOTO	9.25*	8.34	8.44	11.1*	14.2*	146*
X IAGE	0.707	0.190	0.884	0.907	0.701	0.541
PHOTO	7.40**	3.13	7.39*	10.8**	12.6**	190**
IHIRE	0.670	0.618	0.506	0.437	0.330	0.220
PHOTO	9.48*	4.48	9.67	13.6*	11.4*	98.4*
IHIRE	0.787	0.691	0.575	0.522	0.310	0.146
X	0.561	0.480	0.572	0.592	1.29	6.92
PHOTO	7.64**	3.18	7.82*	10.8**	12.3**	121**
WORKTIME	1.00	0.998	1.00	0.979	0.968	0.948
PHOTO	13.4	9.01	14.8	22.4*	14.6*	105.2*
WORKTIME	1.02	1.02	1.01	0.997	0.973	0.946
X	0.951	0.915	0.950	0.940	0.984	1.01

Table 4

Time and the Relationship Between
"Scientist" and
Case Status

Odds Ratios & Interaction Effects

Model Variables \	Confounder Set: A/R	MIN	Q1	MED	Q3	MAX
SCI	2.50	0.915	2.03	2.10	3.60*	8.16**
SCI	3.14	1.02	2.01	3.63	3.21	8.63
X IREFYR	0.585	0.808	1.02	0.364	1.24	0.901
SCI	2.01	0.751	1.74	2.82	4.12	16.4**
X IBRTHYR	1.56	1.48	1.45	0.554	0.706	0.179
SCI	2.75	1.53	2.42	4.92	7.29	45.0**
X IAGE	.856	0.419	0.748	0.260	0.286	0.0545
SCI	2.46	0.888	2.49	2.12	3.58	8.44**
IHIRE	0.569	0.330	0.359	0.466	0.480	0.310
SCI	4.78	1.99	4.38	4.87	7.26*	13.9**
IHIRE	1.12	0.722	0.640	1.04	0.960	0.489
X	0.254	0.172	0.269	0.151	0.185	0.243
SCI	2.49	0.915	2.06	2.13	3.59	7.85**
WORKTIME	1.00	0.986	0.996	1.02	0.992	0.974
SCI	26.8*	11.8	17.6	88.4*	42.8*	134**
WORKTIME	1.10	1.10	1.09	1.19	1.10	1.08
X	0.826*	0.787*	0.832	0.688*	0.805*	0.766*

Table 5

Time and the Relationship Between 1969 Building and Case Status.

Odds Ratios & Interaction Effects

Model Variables \ Confounder Set:	A/R	MIN	Q1	MED	Q4	MAX
69Bldg	1.06	0.411	1.40	1.96	2.44	17.9
69Bldg	0.118	0.057	0.031	0.008	0.024	8.73
X IREFYR	180*	18.9	1,600*	1,260,000	41,700	3.48
69Bldg	0.512	0.179	0.926	0.203	2.04	31.6
X IBRTHYR	4.96	3.31	2.23	237	1.43	0.351
69Bldg	0.785	0.375	3.29	2.54	10.0	30.8
X IAGE	1.70	1.13	0.255	0.665	0.110	0.475
69Bldg	1.03	0.374	1.28	1.77	2.23	12.2
IHIRE	0.781	0.532	0.544	0.465	0.688	0.146
69Bldg	1.43	0.531	2.53	2.52	4.51	113
IHIRE	0.962	1.36	1.02	0.885	1.35	0.152
X	0.277	0.0127	0.0786	0.0476	0.0423	0.00301
69Bldg	0.972	0.520	1.44	3.09	2.87	20.5
WORKTIME	1.05	1.13	1.06	1.18	1.09	1.05
69Bldg	1.28	1.54	3.93	3.72	8.70	15.4
WORKTIME	1.06	1.16	1.11	1.18	1.14	1.09
X	0.971	0.898	0.898	0.970	0.874	0.807

Table 6

Time and the Relationship Between
Presence at a Pacific Test Site and
Case Status

Odds Ratios & Interaction Effects

Model Variables \	Confounder Set: A/R	MIN	Q1	MED	Q3	MAX
PTSATM	8.99	0.889	1.94	5.40	8.47	38.6*
PTSATM	2.74	0.630	0.966	1.40	2.58	3.78
X IREFYR	5.32	1.62	3.02	7.23	4.01	23.5
PTSATM	8.42	2.73	6.38	4.60	11.8	28.7
X IBRTHYR	1.11	0.273	0.219	1.38	0.583	2.16
PTSATM	8.42	2.73	6.38	4.60	11.8	28.7
X IAGE	1.11	0.273	0.219	1.38	0.583	2.16
PTSATM	10.8	0.971	2.45	6.08	9.37	49.9*
IHIRE	0.469	0.435	0.370	0.539	0.347	0.277
PTSATM	-	-	-	-	-	-
IHIRE	-	-	-	-	-	-
X	-	-	-	-	-	-
PTSATM	9.92	0.947	2.24	5.33	9.55	58.4*
WORKTIME	0.983	0.980	0.974	1.00	0.974	0.936
PTSATM	331	8.55	1.40	524	469	47.6
WORKTIME	0.989	0.983	0.973	1.01	0.981	0.935
X	0.829	0.895	1.02	0.781	0.802	1.01

Table 7

Time and the Relationship Between
Working Around High Explosive Fumes
and Case Status

Odds Ratios & Interaction Effects

Model Variables \ Confounder Set:	A/R	MIN	Q1	MED	Q3	MAX
HE	3.85	0.325	1.16	1.90	3.22	8.40
HE	-	-	-	-	-	-
X IREFYR	-	-	-	-	-	-
HE	-	-	-	-	-	-
X IBRTHYR	-	-	-	-	-	-
HE	1.13	0.148	0.566	1.47	1.36	2.18
X IAGE	5.66	3.80	3.18	1.59	3.50	7.28
HE	3.54	0.247	0.978	1.84	3.03	7.99
IHIRE	0.716	0.399	0.578	0.684	0.671	0.404
HE	1.80	0.0752	0.732	1.42	1.31	3.73
IHIRE	0.487	0.267	0.541	0.634	0.450	0.323
X	9.47	14.8	2.74	2.07	8.44	8.76
HE	3.93	0.336	1.17	1.68	3.14	9.50
WORKTIME	0.991	0.983	0.984	1.03	1.01	0.971
HE	1.94	0.0920	1.05	0.946	1.98	6.26
WORKTIME	0.988	0.976	0.984	1.02	1.01	0.970
X	1.05	1.10	1.01	1.04	1.03	1.03

Figures 1 - 3:

The relationship between smoothed estimates of occupational factor effects and time (see Methods section of text for description).

Figure 2
The Effects of Four Occupational Factors
Among Employees Hired in Different Years

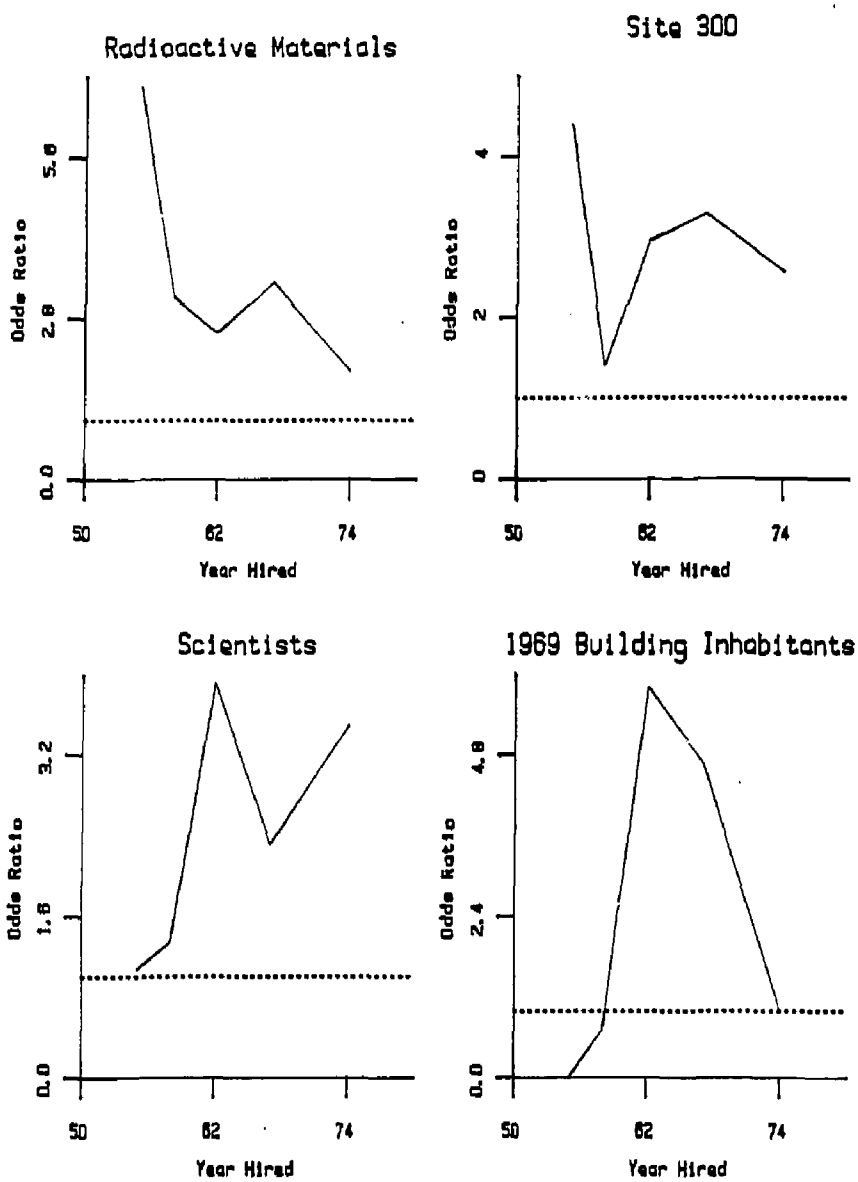


Figure 1
The Effects of Four Occupational Factors
in Different Reference Years

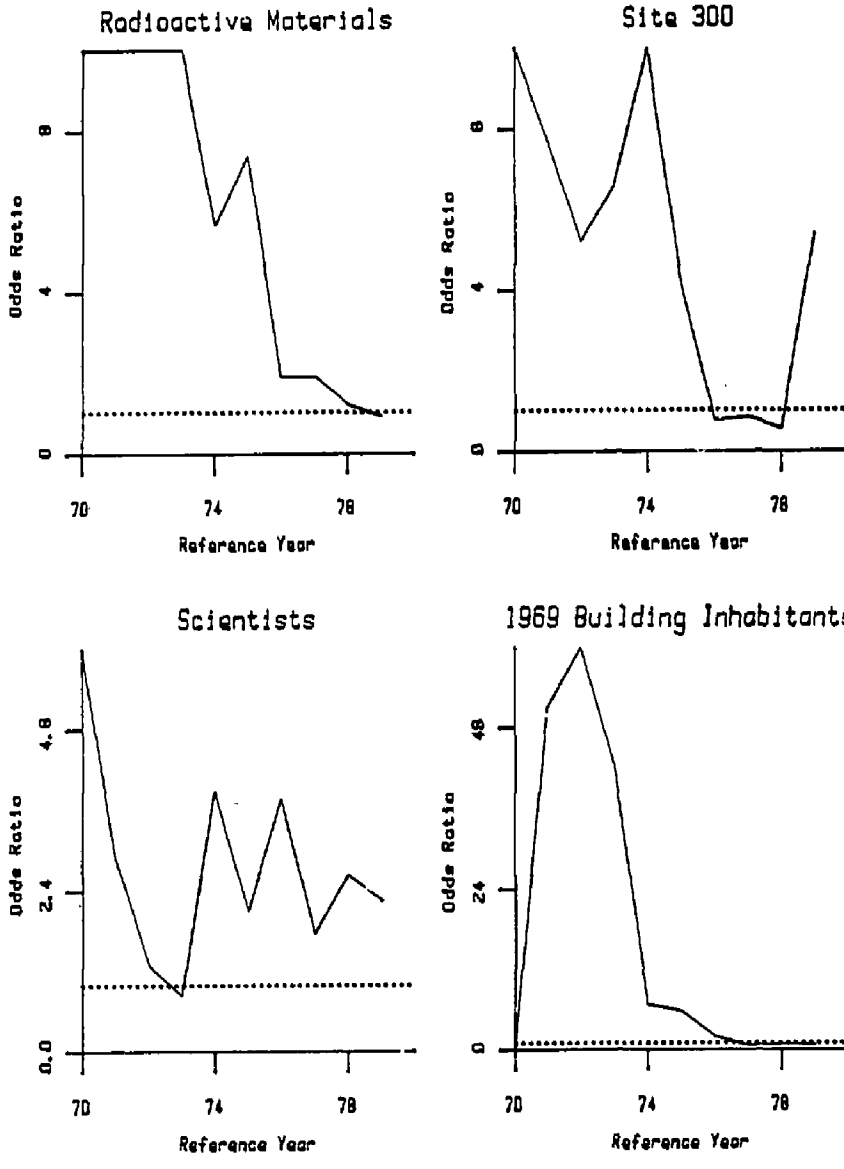
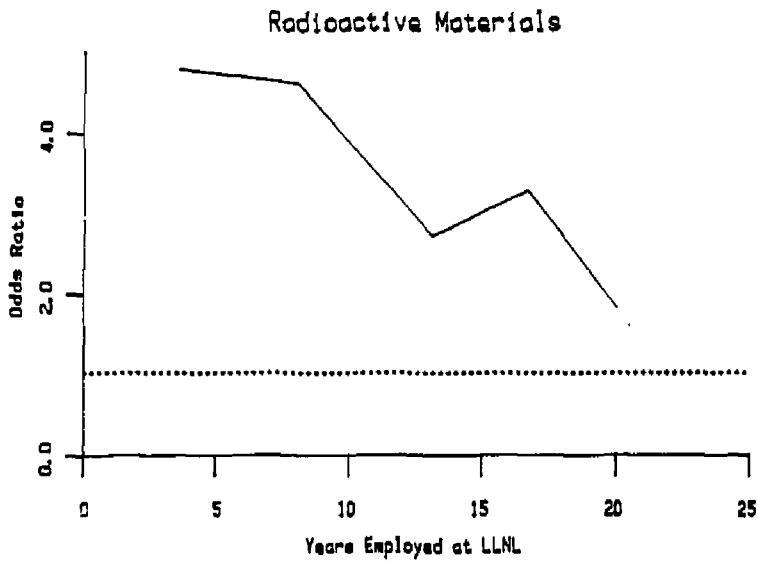
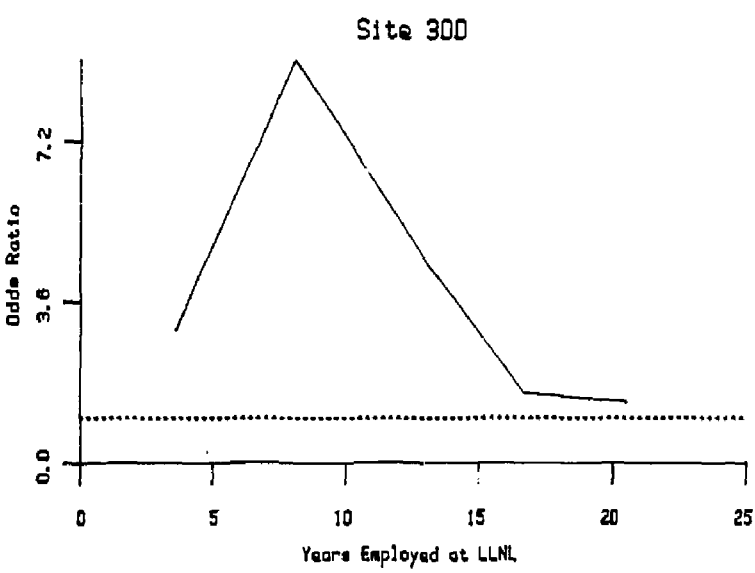


Figure 3
The Effects of Two Occupational Factors
Among Employees Employed for Different Times





VIII. Factors Associated with the Prevalence of Moles Among Control Study Subjects at Lawrence Livermore National Laboratory

Introduction

Holman and Armstrong (1984) have suggested that benign nevi may be precursors of cutaneous malignant melanoma (CMM). If this hypothesis is correct, then the elevated incidence rate of CMM at Lawrence Livermore National Laboratories (LLNL) may be due to the induction of benign nevi by some factor with which the workers come in contact. Furthermore, by including a measure of the number of moles in our models for melanoma case status, we might have obscured any relationship between melanoma case status and any such variable; that is, "number of moles" could be an intervening variable. The purpose of this analysis was to identify the determinants of having one or more large moles among individuals selected as controls for the A/R case-control study. Our first goal was to test the hypothesis that the occupational factors associated with the development of CMM at LLNL ("working around radioactive materials", "presence at site 300", "working around volatile photographic chemicals", "presence at the Pacific nuclear test site", "chemists' job duties") were the same as those associated with the prevalence of having one or more benign nevi. Our second goal was to screen the additional occupational variables observed by Austin and Reynolds for an association with the reported presence of large benign nevi.

Methods

The dependent variable, having one or more large benign nevi, was measured as a response to a question in the A/R questionnaire. Study subjects were shown a pencil eraser on a #2 pencil and were asked how many moles as large or larger than the pencil eraser they had on their bodies. We coded "the number of benign nevi (moles)" as "0" for those who reported no moles and as "1" for those who reported one or more moles. Armstrong et al (1986), in the only known analysis of the determinants of benign nevi, used a similar coding scheme.

When possible, we used the constitutional and solar exposure variables identified by Armstrong et al (1986) as potential confounding variables of the hypothesized association between the occupational factors and the reported presence of benign nevi. Our definition of the demographic variables, age in years and sex, was the same as those used by Armstrong and others. However, instead of the variable "Southern European Grandparents" which Armstrong and others used, we identified a group of study subjects who reported at least one grandparent coming from Italy, Puerto Rico, or Mexico. We replaced Armstrong's variable "age at arrival in Australia" with the variable "born in California". If the study subject was born in California, the variable was coded "1"; if the study subject was not born in California, the variable was coded "0". Most of our measurements of constitutional factors were similar to those used by Armstrong et al. They included tanning or burning in response to acute and chronic solar exposure, skin color reflectance of the upper inner arm, eye and hair color, a past history of melanoma, and a family history of

the disease. Unlike Armstrong and others, we had no measurement of the study subjects' body hair.

We had none of the measurements of solar exposure which Armstrong et al used in their Table 2; we therefore used the variables listed in the A/R report in Table 18 (except for the variable indicating the use of suntan lotion). These variables and their coding are described in Table 4.

Some of the occupational factors which we evaluated are listed in Tables 1-3. In addition, we examined 18 variables based on the radiation badge data. The radiation badge variables were both continuous and dichotomous and represented exposure to radiation at different periods during the study subjects' employment at LLNL. We also examined the job category variables and a dichotomous variable representing the time the study subject was hired. Finally, we included a dichotomous variable to indicate whether the study subject wore clothing designed to protect him or her from exposure to ionizing radiation. If a variable had missing values, these records were excluded from the part of the analysis which included that variable. Therefore, this comparison among variables is actually a comparison of slightly different data sets.

To model the association between the presence of moles and the occupational and constitutional factors, we used unconditional logistic regression. The exponentiated regression coefficients estimated prevalence odds ratios and were not estimates of prevalence rate ratios. We did not model the dependent variable as continuous because we did not believe that the measurement (a self-reported estimate of the number of moles) was adequately refined to do so.

We used a modeling strategy designed to test whether the non-occupational

variables that Armstrong et al. (1986) found were associated with the presence of moles, and to identify occupational factors associated with the presence of moles while controlling for confounding factors. First, the association between each non-occupational variable and moles was modeled alone. Next, to adjust for confounding, we estimated for each occupational factor the odds ratio for the association between that occupational factor and "moles" while adjusting for age and for each of the non-occupational variables one at a time. Although this strategy may not adequately control for confounding (e.g., as in the situation when two factors act jointly as confounders), the sample size is so small that fitted models involving several factors could produce unreliable results. From these models, we reported those prevalence odd ratios which were statistically significant or which had values of less than .4 or greater than 2.5. Although an odds ratio that is the largest of a set is more likely to overestimate the true parameter value (the smallest will be too small as well, Thomas et al (1985)), we reported such odds ratio estimates because they are of more interest to the investigator than are odds ratios near one. We reported odds ratios which were not statistically significant because of the relatively small sample size and its attendant low statistical power.

Results

Seventy-two individuals reported having no large moles and thirty-eight reported having one or more large moles. The prevalence odds ratios for the

potentially confounding variables (adjusted for the linear and quadratic effects of age) are shown in Table 4. Of the 13 variables for which Armstrong had a similar variable, eight were in the direction found by Armstrong, and 5 were not.

The crude odds ratios for the selected occupational variables (uncorrected for potential confounders), are shown in Table 5, along with the range of estimates of the odds ratio for the association between the occupational factor and "moles" that resulted when different potential confounders were included in the model. In this table, only the confidence intervals for the crude odds ratios for "hired before 1962" did not contain one. However, the confidence intervals for some of the estimated adjusted odds ratios for both "engineer" and "skin exposed to rare earth materials" also excluded one.

Discussion

The associations between "number of moles" and the non-occupational factors were weakly consistent with the results of Armstrong et al. That the consistency is not stronger is not surprising since Armstrong et al.'s odds ratios were not large, and also since this is a small data set. We have no reason to believe that the sample is dissimilar to that observed by Armstrong et al., and it is reasonable to adjust for the factors they reported as confounders.

Only five occupational variables ("physicist," "engineer", "hired before 1962", "skin exposed to rare earth metals", "radiation five years before the

reference date") were associated with a reported prevalence of one or more large benign nevi in an exploratory study of workers at LLNL. None of these are any of the occupational factors identified by Austin and Reynolds. We note in Chapter VII, Figure 2 of this report that there is a suggestion that "worked around radioactive materials" and "site 300" were greater melanoma risks among persons hired before 1962 than among those hired after 1962. It is possible that workers employed before 1962 were exposed to a substance which produced moles and melanoma. It is unlikely that the association between benign nevi and the time of hire stems from the greater age of individuals hired before 1962; this is because the prevalence odds ratio is approximately the same when the variable "time of hire" is adjusted for age.

The dependent variable in this analysis, the number of benign nevi, was crudely measured. Study subjects are, therefore, probably misclassified with respect to the variable benign nevi. If the misclassification rate is the same for the several levels of the exposure variables, then the misclassification has merely reduced the association between the "number of benign nevi" and the exposure variables. That is, the prevalence odds ratio estimates are possibly closer to one than they should be.

We conclude that this analysis does not indicate that there is presently a substance in the work environment at LLNL which is associated with the prevalence of benign nevi.

References

Holman CD, Armstrong BK. Pigmentary traits, ethnic origin, benign nevi, and family history of risk factors for cutaneous malignant melanoma: JNCI 1984; 72:257-266.

Armstrong BK, de Klerk NH, Holman CD. Etiology of common acquired melanocytic nevi: constitutional variables, sun exposure, and diet. JNCI 1986; 77:329-335.

Thomas DC, Siemiatycki J, Dewar R, Robins J, Goldberg M, Armstrong BK. The problem of multiple inference in studies designed to generate hypotheses. Am J Epid 1985; 122:1080-10

Table 1

Items on card handed to study subjects in A/R study to identify substances which LLNL workers inhaled.

A. Categories of substances that you may have inhaled*:

1. adhesive vapors
2. epoxy vapor
3. paints/primers (such as spray paints)
4. degreasing agents (e.g. perchloroethylene)
5. plasticizers
6. pyrolysis products (airborne results of burning)
7. volatile photographic chemicals
8. welding/soldering fumes (e.g. heliarc/silver solder)
9. toxic gases (e.g. flourine, vinyl chloride)
10. dielectric fluids (e.g. PCB's)
11. inert gases
12. metal vapors
13. polycyclic hydrocarbons (e.g. carbon black, oil shale, coal, or by-products)
14. urethane foam, urea formaldehyde foam
15. wood dusts
16. meal dusts
17. fumes from stored high explosives
18. high explosive residues
19. transite

* These variables were coded as dichotomous variables, 1 indicated exposure and 0 indicated no exposure.

Table 2

Items on card handed to study subjects in A/R study to identify substances which LLNL workers had skin contact.

B. Categories of substances with which you may have had skin contact*:

1. polyester resins (e.g. fiberglass kits)
2. adhesives (e.g. adiprene/MOCA)
3. epoxy systems
4. paints/primers (e.g. lead chromate)
5. degreasing agents (e.g. perchloroethylene)
6. plastic forming/shaping
7. pyrolysis products
8. photographic chemicals
9. dielectric fluids (e.g. PCB's)
10. polycyclic hydrocarbons (e.g. cargon black oil shale, coal or by-products)
11. metal plating/etching
12. urethane foam, urea formaldehyde foam
13. alkalai metals (e.g. sodium, lithium)
14. shielding material (e.g. boron, lead)
15. rare earth elements (e.g. neodymium, yttrium)
16. transite

* See footnote Table 2.

Table 3

Items on card handed to study subjects in A/R study to identify substances to which LLNL were exposed.

C. Miscellaneous*:

1. flash tubes
2. magnetic or electromagnetic fields
3. microwave sources (e.g. RF furnaces)
4. UV sources (e.g. mercury vapor lamp)
5. radioactive materials (e.g. uranium, plutonium)
6. accelerators (e.g. LINAC)
7. X-ray sources
8. lasers

* See footnote Table 2.

Table 4

Prevalence odds ratios for potentially confounding variables adjusted for age

Variable	Prevalence Odds Ratio (95% Confidence Interval)	Expected Direction of Odds Ratio, Based on Armstrong, et al.'s Results (1 means that no decision is possible)
Constitutional:		
Sex (1=male, 0=female)	0.99 (0.4, 2.4)	< 1
At least one Mediterranean grandparent (1=yes, 0=no)	1.53 (0.3, 7.3)	< 1
Born in California (1=yes, 0=no)	0.74 (0.3, 1.8)	> 1
Parent with skin cancer (1=yes, 0=no)	1.36 (0.4, 5.2)	> 1
Response to chronic solar exposure ("Usually burn with little or no tanning with prior sun exposure", 1=yes, 0=no)	1.13 (0.4, 3.1)	1
Response to acute sun exposure ("Usually burn with little or no tanning with no prior sun exposure", 1=yes, 0=no)	0.65 (0.3, 1.5)	1
Hair color (1=hair was blond, red or auburn both at ages 6 and 20, 0=hair was not blond etc.)	1.47 (0.6, 3.8)	1
Blue eyes (1=yes, 0=no)	.70 (0.3, 1.6)	1
Familial melanoma (1=an immediate blood relative has melanoma, 0= no blood relatives have melanoma)	2.21 (0.1, 37.7)	> 1

Table 4 (cont'd)

Prevalence odds ratios for potentially confounding variables adjusted for age

Variable	Prevalence Odds Ratio (95% Confidence Interval)	Expected Direction of Odds Ratio, Based on Armstrong, et al.'s Results (1 means that no decision is possible)
Upper inner arm reflectance readings using the amber filter (A continuous variable, the ratio of the odds of 50 percent reflectance to 40 percent reflectance.)	1.79 (0.5, 6.2)	> 1
Number of outdoor days as adult (1=>105, 0=<105)	0.79 (0.4, 1.8)	< 1
Solar Exposure:		
Outdoor days 3 years before the reference date (1=>100, 0=<100)	0.71 (0.3, 1.6)	1
Number of times per year burned as a youth:		
0 (reference level)	1.00	
1	1.24 (0.4, 4.0)	
2	0.54 (0.2, 1.8)	1
3+	0.78 (0.2, 2.4)	
Number of times per year burned as an adult		
0 (reference level)	1.00	
1	1.65 (0.6, 4.7)	
2	1.26 (0.4, 4.3)	1
3+	0.60 (0.1, 2.8)	

Table 4 (cont'd)

Prevalence odds ratios for potentially confounding variables adjusted for age

Variable	Prevalence Odds Ratio (95% Confidence Interval)	Expected Direction of Odds Ratio, Based on Armstrong, et al.'s Results (1 means that no decision is possible)
Number of times per year burned during the three years before the reference date:		
0	1.00	
1	0.87 (0.3, 2.2)	
2	0.46 (0.1, 1.9)	1
3+	1.46 (0.3, 7.3)	
Total number times burned as a youth: (1=>15,0=<15)	1.60 (0.7, 3.7)	> 1
Total number times blistered as a youth: (0=never, one, 1=more than once)	1.26 (0.6, 2.9)	> 1
Total number times burned as an adult (1=>10, 0=<10)	0.80 (0.4, 1.8)	> 1
Total number of times blistered as an adult (0=never, 1=more than one)	0.79 (0.3, 1.8)	> 1
Total number of times burned in the last three years (1=>1.5, 0=<1.5)	1.38 (0.6, 3.1)	> 1
Total number of times blistered in the last three years (0=never, once, 1=more than once)	0.86 (0.3, 2.6)	> 1

Table 5

Prevalence Odds Ratios for
Occupational Risk Factors

Variable	Prevalence Odds Ratio	95% CI	Range*
Physicist (1=yes, 0=no)	0.25	0, 2.1	.23, .51
Engineer (1=yes, 0=no)	2.88	1.0 , 8.5	1.29, 3.82
Hired before 1962 (1=yes, 0=no)	2.54	1.1 , 5.7	2.49, 6.36
Skin exposed to rare earth metals (1=yes, 0=no)	3.19	0.8 , 12.10	2.47, 5.58
Radiation from five years before the reference date. (The ratio of exposure to 1.5 rads of ionizing radiation to no exposure).	0.08	0 , 6.3	.17, .30

* The range of the estimated prevalence odds ratios observed among the models that included non-occupational confounders

IX. Sources of Bias and Other Types of Error in the Austin/Reynolds Case-Control Study

Selection Bias

We define bias as the misrepresentation of the true exposure-disease odds ratio caused by systematic error. In particular, selection bias can lead to a distortion of the odds ratio estimate resulting from an improper method of study subject selection (Kleinbaum et al., 1982). Because we cannot know how the total population of cases and potential controls would have answered the questionnaire, had they been interviewed, we can, for the most part, only speculate as to whether selection bias exists. (This is not to imply that quantifying bias is a more exhalted activity. The assumptions made to do so are usually both great and unsupported. Assigning numbers to conjectures gives one a false sense of "correctness" and is often less informative than a more qualitative discussion of the issues).

In general, the methods of subject selection used by Austin and Reynolds were standard and probably did not result in selection bias. All malignant melanoma cases who were diagnosed while working at LLNL between 1969 and 1980 were identified through the California Tumor Registry (one case did not participate). A possible source of bias could have been the exclusion of cases who were diagnosed after terminating employment at LLNL. If the exposures of these cases differed from those cases who remained at LLNL, then their exclusion from the study could have distorted the odds ratio estimates.

The strongest evidence for the lack of selection bias is the general agreement of the odds ratios for the non-occupational variables with those from other case-control studies. Although it is possible that these other studies share the same unidentified errors of selection bias as the A/R study, it is more likely that these studies (as well as the A/R study), each based on different methods of study subject selection, are also free from selection bias. By agreement among studies, we refer to a qualitative agreement among the odds ratios rather than an exact numerical correspondence. An exact correspondence of the odds ratios among studies is not to be expected because information is ascertained from different populations using different questionnaires and methods of analysis. Given these limitations, Table 1 shows that the odds ratios for three non-occupational factors found by Holman et al. (1986) in their study of 511 melanoma cases and their 511 matched controls are similar in magnitude to those observed by Austin and Reynolds.

Not only does the cutpoint for the first variable ("the number of nevi") differ between the two studies, but A/R asked the study subjects to estimate the number of moles the same size or larger than a #2 pencil eraser on their bodies, while Holman et al. counted the number of raised nevi on each study subject's arms. Yet, both odds ratios are large (>5), indicating the importance of benign nevi as a risk factor. The difference in the magnitude of the odds ratios for having a "previous diagnosis of non-melanotic skin cancer" may be due to the greater prevalence of this condition among the Australian, than among the Californian, controls. Since the "susceptibility to sunburn" variable is defined somewhat differently between the two studies (as is shown in the definitions in Table 1), the similarity between the two odds ratios is striking.

Information Bias

We follow Kleinbaum et al. (1982) in defining information bias as a distortion of the estimated odds ratio resulting from a systematically inaccurate measure of either disease or exposure. Both the sensitivity (the probability that a person having melanoma will be so defined) and the specificity (the probability that a person free of disease will be so defined) of the A/R case and control designations have been questioned. During the course of the investigation, the LLNL pathologists have identified melanoma cases which have not been reported to the California Tumor Registry (cited in, IFP, 1253403). Thus, there may have been false negatives (individuals with melanoma) in the potential control group. However, none of these individuals were included in the actual control group. Had they been included, the questionnaire would have identified such individuals (Q # 507), and they would have been excluded from the analysis. It is possible, but unlikely, that there were individuals in the control group who were diagnosed as having melanoma but were not told their diagnosis, and they were also not reported to the California Tumor Registry. Somewhat more likely is that individuals who were subsequently diagnosed with malignant melanoma were included in the A/R control group. In either of these hypothetical situations, if the proportion exposed among the false negative cases was the same as that among the true positive cases, then including such individuals in the control group would have pulled the estimated odds ratio somewhat closer to one.

A charge made by Shy and others (1986) was that the early stage melanomas might have regressed had not the population of LLNL been "screened" (self-

screened). "In this case, the intensive surveillance itself would increase the observed number of moles in the absence of a physical or chemical causal agent. The possibilities that early stage melanomas regress spontaneously and that intensive surveillance has generated the excess of melanomas among Laboratory employees remain the central questions." Although there is no evidence in the literature for the large scale spontaneous regression of early stage malignant melanoma, even if we assume that the 1977 to 1980 cases "would never have been biopsied or clinically detected", or that they are almost false positives (they are, strictly speaking, melanoma at a sub-clinical stage), the effect of including these individuals in the case group would have been to pull the estimated odds ratios slightly closer to one. That is, if these "false positive" cases could have been excluded from the study sample, the estimated odds ratios could have been somewhat farther from one than those reported by Austin and Reynolds.

Recall Bias

Usually recall bias manifests itself as the over-reporting of exposure by the cases due to their knowledge of their disease status. However, it can be more broadly understood as the systematically inaccurate reporting of exposure by either cases or controls. Although the recall bias of the cases (when the occurrence of the disease leads them to report more exposure than they actually had) causes the odds ratios to be larger than they should be, recall bias as (broadly defined above) can produce distortion of the odds ratio in either direction. The only way to accurately determine whether recall bias exists is to validate the information obtained from the study subjects in some objective fashion, preferably documented before the diagnosis of the disease

for the cases or the reference date for the controls. One method of determining whether recall bias exists is to place a "dummy" question on the questionnaire which is not expected to vary between cases and controls. If the odds ratio for this item differs from one, then either recall bias exists for this item, or the variable actually differs between the cases and controls. Since the A/R questions represented exposures which were thought to differ between cases and controls, we cannot use one of these questions to ascertain the presence of recall bias. Further, it may be that, while there is no recall bias for an innocuous dummy variable, an important exposure may be subject to this bias.

Klemetti and Saxen (1967) conducted an empirical investigation of recall bias by comparing information they obtained by interview prospectively with that collected retrospectively. A group of pregnant women were interviewed before the birth of their children. After delivery, a group of 203 women who gave birth to dead or malformed children, and a group of 203 mothers of normal children, were re-interviewed. The central feature of the retrospective results was the under-reporting of the exposure in the retrospective interview compared to the prospective interview. Although the degree of under-reporting varied by item, at least 85 per cent of the positive responses to exposure reported in the prospective interview were not reported in the retrospective interview. Further, responses indicating no exposure in the prospective study were changed to suggest exposure in the retrospective study. The authors report small differences in recall between cases and controls (generally, cases recall somewhat more information); however, it is difficult to evaluate the results because they are reported by response rather than by individual. If the trends observed by Klemetti and Saxen also hold for the A/R study, then

both cases and controls may have under-reported constitutional and occupational exposure.

While Klemetti and Saxen observed no association between the proportion of agreement between the prospective and retrospective responses and the time of interview, the time between the delivery and the interview was relatively brief. Fifteen months was the maximum time between delivery and the interview about previous exposures. In the A/R study, the maximum time from the date of the cases' diagnosis to the interview for study subjects was twelve years. In Chapter VII, Figure 2 shows that the odds ratios for exposure to radioactive materials and to working at Site 300 are higher in the earlier reference years, and that they decrease as they approach the time of the interview. These graphs might provide evidence of recall bias in the early reference years, or they may reflect a true time-related phenomenon. It is not possible using only these data to discriminate between these two interpretations.

It may be possible to bring some indirect evidence to bear on the possibility that recall bias is responsible for the large odds ratio for the factor "having worked around radioactive materials". Respondents were asked both if they had worked around each of the items on the occupational exposures lists and if the respondents had had direct contact with the items. If the effect estimate of the factor "worked around radioactive materials" was high due to recall bias, one might expect that the factor "directly contacted radioactive materials" would be similarly subject to recall bias. We estimated odds ratios for a dichotomous variable that takes the value 1 if a respondent had direct contact with radioactive materials, and the value 0 if they had not, in twelve different conditional logistic regression models. Each of six of the models included the "directly contacted" variable and one

of six different confounder sets, and each of the other six models included both the "worked around" radioactive materials and "directly contacted" variables, as well as one of six confounder sets. In no model was the effect estimate for the "directly contacted" variable significantly different from one. This would seem to suggest that the large odds ratio for having worked around radioactive materials is not due to recall bias.

Another useful approach for checking for possible recall bias is to determine the odds ratios for variables that would not be subject to recall bias, but which are suspected to yield information similar to that contained in the variable "worked around radioactive materials". So, for example, we can calculate odds ratios for a dichotomous variable derived from badge readings, or for the variable JCAVG, which identifies radiation-related job categories, described in the "Selection of Controls" chapter of this report. In the chapter "Ionizing Radiation and Melanoma at LLNL" of this report, we discussed whether badge readings added information about melanoma risk over and above that contained in the variable "worked around radioactive materials", and we concluded that it did not. Although we will not detail the results here, we also found that badge readings by themselves are not a significant predictor for melanoma risk, although the odds ratio is greater than one for a variable that takes the value one if a person's total badge reading during the ten years before the reference date was greater that 200 mrem and zero otherwise. This result could indicate that there has been recall bias, since the result for this badge-reading variable differs from the result for "worked around radioactive materials", or it might simply indicate that there is insufficient power to show that the effect of this badge-reading variable is greater than one. If there was an increased risk of melanoma

associated with working around radioactive materials that was not due to exposure to ionizing radiation, then any variable that was related to ionizing radiation would not classify the "true" risk factor correctly, since it is quite possible to work around radioactive materials without accumulating appreciable radiation exposures. The general effect of this kind of misclassification would be to reduce the odds ratio for the relationship between a variable based upon direct exposure to ionizing radiation and melanoma from the (hypothetically greater than one) odds ratio for the relationship between some other measure of having worked around radioactive materials and melanoma.

JCAVG (described in the chapter of this report on the selection of controls) takes the value one for a subject if the average badge reading for a ten year period for an employee at LLNL with the same job classification is greater than 200 mrem, and zero otherwise. Thus, JCAVG measures the likelihood that a person would work around radioactive materials. As shown in the chapter on the selection of controls, JCAVG is a significant predictor of melanoma case status. This result argues that, even if there is some recall bias, there is something associated with working with radioactive materials (or potentially working with radioactive materials) that is correlated with melanoma case status.

If recall bias is responsible for the large odds ratio for "worked around radioactive materials", then cases will have been more "eager" to claim to have worked around radioactive materials than will have controls. Since the question "Did you work around radioactive materials?" is ambiguous (for example, how close to radioactive materials would one have to work to answer this affirmatively? How frequently? How intimately associated with one's

job? What kind of radioactive materials?), it is possible that cases, in the course of trying to explain their disease, might well say that they had worked around radioactive materials in jobs that controls would typically say that they had not. This suggests that cases who said that they had worked around radioactive materials would say so about more of their job assignments than would controls. Furthermore, controls who said that they worked around radioactive materials might truly be in more such radiation-associated jobs than would cases.

We tested these two hypotheses. Since, for each job a subject held at LLNL, we know whether or not that subject said that he or she worked around radioactive materials on that job, we calculated the proportion of jobs each subject held in which they said that they had worked around radioactive materials. If this proportion is greater among cases than among controls, we would have evidence that recall bias might be operating. The average proportion of such jobs among the 21 controls who ever claimed to have worked around radioactive materials is in fact 0.752; in contrast, among the 11 cases, the average proportion is only 0.560. These two numbers are not statistically significantly different, based on a Mann-Whitney U test comparing the two distributions of proportions (P-value for the test is 0.182).

We tested the second hypothesis by determining whether controls who claim to have worked around radioactive materials have higher badge readings than do cases, and whether controls reported that they had used clothing designed to protect against ionizing radiation more frequently than did cases. The difference for radiation badge readings is at least in the right direction for recall bias: the average badge reading among controls who said that they

worked around radioactive materials is 0.300 rem, whereas it is 0.844 among cases who said that they worked around radioactive materials. However, again, these two values are not significantly different (P-value for a t-test on log-transformed data equals 0.56). Five of 16 cases (or 31.25% of the cases who said that they worked around radioactive materials) and six of 16 controls (or 37.5% of the controls who said that they worked around radioactive materials) said that they had used clothing designed to protect against radiation.

That the odds ratios for non-occupational factors, particularly the number of benign nevi ("number of moles"), are roughly consistent with those estimated in other studies is further evidence that recall bias is not important in this data set (at least to the extent that one can generalize from one variable to another about recall bias). Since there have been few case-control studies of occupational risk factors, the validity of the reporting of the occupational exposures cannot be similarly evaluated.

We need to beware of one intuitively appealing approach to testing for recall bias. Suppose we believe that there is a variable (call it T) whose value is one if a person really worked around radioactive materials. We are really interested in the odds ratio for the relationship between T and case status, but we can only measure the odds ratio for the relationship between "worked around radioactive materials" and melanoma case status. Since persons who work around radioactive materials are more likely to get large badge readings than persons who do not work around radioactive materials, it might seem reasonable to argue as follows: "If we look only among persons who have "large" badge readings, we ought to be looking mainly at people for whom the variable T takes the value one. Therefore, among this subgroup of cases and controls, anyone who says that he or she did not work around radioactive

materials is probably misclassified. Thus, among this subgroup of subjects, we can directly compute the fraction of misclassified cases and controls. If the fraction is less than one, then there is some misclassification; and, if the fraction is different between cases and controls, then there is differential misclassification, probably due to recall bias."

We made a mathematical analysis of this problem which shows that this argument is only partially correct. If there is recall bias, then among persons with large badge readings, the fraction of cases and controls who say they work around radioactive materials will differ. Furthermore, if we look among people with badge readings so high that their value of T must be one, then recall bias is the only thing that can cause cases and controls to differ in this regard (taking into account sampling error, of course). However, if it is possible for a person to have a badge reading as large as the cutoff we choose, but not to have worked around radioactive materials (for instance, if there have been some accidental exposures while carrying out activities not associated with a person's normal work assignment), then cases and controls can differ in the fraction claiming to have worked around radioactive materials if, in fact, persons who work around radioactive materials are at an increased risk for melanoma.

To demonstrate this, we have plotted in Figure 1 six graphs. In each of the six graphs, for each distinct badge reading in the data set greater than 200 mrem, we have plotted the proportion of cases with badge readings greater than that value among those who claimed to have worked around radioactive materials, and the proportion of controls with badge readings greater than that value among those who who claimed to have worked around radioactive materials. Superimposed upon those graphs are theoretical curves computed for

different assumptions about the values of the probabilities of misclassification of the variable that codes "worked around radioactive materials" and different assumptions about the true odds ratio for the relationship between melanoma case status and T. The theoretical curves in the left three panels all depict situations in which the true odds ratio for T is one, and the difference between cases and controls is due entirely to recall bias. The theoretical curves in the right three panels all depict situations in which there is no recall bias; the odds ratio for T is greater than one in each of these panels. The purpose in constructing these graphs is to demonstrate that it is possible to produce curves very much like that in the data at hand with very different assumptions about recall bias and risk associated with the true value of "worked around radioactive materials".

In summary, we have not found clear evidence that recall bias has been operating, and have found that cases were more likely to be working in jobs in which they might come into contact with radioactive materials than were controls. Thus, it is unlikely that the large odds ratio for "worked around radioactive materials" is due solely to recall bias.

An Evaluation of the Measurement of Non-Occupational Factors

1. The number of large benign nevi

The method of measuring this variable was questionable. The study subjects were asked to estimate the number of moles on their body the size of a number-two pencil eraser or larger (> 1/2 cm.). Moles were not described or defined; it was believed that the size itself would exclude freckles and other pigmented lesions. If any question was to be subject to recall bias, this

would be such a question, being both subjective and related to pigmented lesions which might resemble the malignant melanoma itself. However, Austin and Reynolds found that LLNL medical records which were made prior to diagnosis, and a dermatologist's examination of some of the cases, show that this variable probably provides a qualitative measure of the number of moles. That is , those who report "alot" of moles seem to have more than two or three, and so on. Unfortunately, one does not know where the true cutpoint should be (i.e., the point which separates "a few" from "a lot"). In spite of the crude method of measuring the number of benign nevi on the body, we note in Table 1 that the magnitude of the odds ratio for the variable "number of benign nevi" is not inconsistent with those reported in the literature. The variable "number of benign nevi" in the literature has been measured both by counting the study subjects' moles and by the self-assessment of the number of moles.

2. Sunburning with previous exposure

The information for measuring this variable is based on the following hypothetical situation: "After your skin has been exposed to the sun for a few days, what would happen if you were to go out in the summer noonday sun for a half hour... would you usually burn with no tanning, or... usually tan with no burning, or never burn or tan?" The reliability or validity of this question has not been empirically examined. Whatever it is that this variable measures, and it may measure exactly what it claims to measure (susceptibility to sunburn), this variable or one similar to it has been reported by Holman et al. (1986). Their results are comparable to those observed by Austin and Reynolds (see Table 1).

3. Indoor days

This variable is based on a question which asks the study subjects to remember the average number of days during a typical year from age 21 to the reference year that he or she participated in particular outdoor recreational activities. The purpose of measuring this variable is to estimate the number of days each study subject was exposed to UV light from natural sources. Austin and Reynolds dichotomized this variable, coding 1 for individuals who had reported more than the median number of indoor days and 0 otherwise. There are two aspects of this question where errors might occur. First, a respondent, rather than selecting a typical year, may select a year close to the time of interview. Second, the respondent may not accurately report the amount of time spent indoors. The measurement of lifetime solar exposure is difficult and needs to be further refined.

4. Parent with skin cancer

Reporting having a parent with skin cancer may be more prevalent among the cases because of their own diagnosis of malignant melanoma. That is, a parent might be more likely to tell a child of his or her diagnosis of skin cancer if the child reports that he or she has been similarly diagnosed.

5. Previous diagnosis of skin cancer, and having an advanced degree

Of the non-occupational variables, these two variables appear to be the easiest to measure and are therefore less likely to be biased. As noted in the literature review chapter, both of these variables have been reported as risk factors for malignant melanoma.

An Evaluation of the Measurement of Occupational Factors

1. Working in a building built in 1969 ten years prior to the reference date.

Study subjects were mailed questionnaires requesting information on jobs held at LLNL since age 16, and on the laboratory at LLNL in which the work was performed. During the personal interview, the subject re-examined the work history for the ten years prior to the reference date which he or she had reported on the mailed questionnaire. The study subjects thus had two chances to recall the laboratories in which they had worked. Although the method of reviewing the occupational history twice is a good method of measuring information on work, there were still many individuals who did not remember where and when they worked at LLNL (i.e. this variable had missing values). Here the problem is that those who remembered where they worked might differ in other ways from those who did not.

2. Have you ever (in the 10 years prior to the reference date) worked around radioactive materials, volatile photographic chemicals, or fumes from high explosives?

This variable was measured by asking the respondent (for each job he or she had listed at LLNL on the mailed questionnaire which was also within ten years prior to the reference date) whether he or she had worked around any of the substances on three lists, with which the study subject was presented. "Radioactive materials (e.g. uranium, plutonium)" was the fifth item on the third list of eight items. Volatile photographic chemicals and fumes from high explosives were on a list together with 17 additional items which may have been inhaled. The measurement of the variables which were obtained by

showing the study subjects lists could have been improved by having the interviewer read the name of each variable, describe it (color, form etc.), state its common names, and give examples of its use. By not describing the substance in more depth, the measurement of these occupational exposures may have been biased toward the better educated study subjects who would recognize the technical names of these substances.

Although the occupational exposures listed may have been easier to recall if better descriptions had been given, they were probably not as difficult to recall as the non-occupational exposures which were more abstract (number of days during a "typical" year spent swimming, etc.). That the responses to the question regarding exposure to radioactive materials are not consistent with the cumulative radiation exposure as measured by the badges may indicate that the question asked is not the same as the exposure measured by the badges.

3. Have you ever, during your whole life-time work history, worked at any of the Pacific Nuclear Test Areas, or been to Site 300?

These questions are straightforward and should not be difficult to answer.

4. Job Classifications, Scientist and Chemist

The job classifications of scientist and chemist were objectively measured and came from the study subjects' personnel files. When individuals were asked in the personal interview about their job descriptions, the odds ratio for the variable, chemist, was similar: the odds ratio for chemist based on the job classification was 4.39 (95.% CI, 1.16 - 16.55); the variable, chemist, based on history was associated with an odds ratio of 8.0

[CI not given]. The similarity of the objective measure and the self-reported measure for this variable validates the self-report. The odds ratios are not identical because the job classification is made for payroll purposes, while the study subjects described their actual duties.

Confounding Bias

Confounding is a bias which results from failure to control for a variable which is associated with both the disease and the exposure of interest. In the A/R study, we were concerned that the occupational exposures may have erroneously appeared to be statistically significant due to the improper control of non-occupational confounders. In Chapter V, we examine the question of confounding bias by controlling confounding variables previously identified in the literature and determining whether this alters the estimate of the effect of the occupational variables on melanoma. As shown in Chapter V, Figure 1, the occupational variables: radioactive materials, Site 300, and exposure to photographic chemicals remained significant when adjusted for confounding variables noted in the literature; high explosives, 1969 building and chemist duties were generally not statistically significant. Less than half of the regression coefficients for the variables Pacific Test Site and scientist were statistically significant. Figure 1 should not be "over"-interpreted for several reasons. First, the variable chemist duties is associated with the variable scientist; in those models where both are included, neither one may be statistically significant.

This does not indicate that both are unimportant, but rather that one or the other should be selected to be included in the same model. Second, it is possible that the surrogate variables which we used to estimate the confounders were such poor estimates of the confounders that they did not adequately control for confounding. For example, to estimate solar exposure during youth, we used the variables "study subject born in California" (a dichotomous variable, 1 = yes, 0 = no) and the "average number of times per year a subject was sunburned before the age of 21". Third, we do not know enough about the biology of melanoma to be certain that we have not "over - adjusted" the models on which Figure 1 is based. That is, if an occupational exposure is producing benign nevi rather than melanoma, then adjusting for "benign nevi" will falsely obscure the apparent influence of that occupational factor.

Type I and Type II Error

In the critiques of the A/R study, the Type I error (the probability of falsely rejecting a true null hypothesis, or, in the context of the A/R study, saying a particular variable is a risk factor for melanoma at LLNL when, in fact, it is not) was given as a reason for discrediting the results (Shy et al. [1986], Moore et al. [1984]). Although, in general, if the alpha level is .05, then, for every 100 variables tested, 5 (on the average) will be falsely significant, the Type I error for the A/R study is much more difficult to assess. First, many tests were conducted on the same variables and there

is no single satisfactory method to adjust for these tests (Thomas et al., 1985). In general, multiple tests increase the Type I error. Second, even if we were able to accurately estimate a Type I error, we could not say whether the result of any particular hypothesis test was really correct. Of course, we would be more likely to believe significant test results on variables which had been previously identified in the literature as being important. The possibility that a Type I error may have been committed is not reason to reject outright any particular significance test. In fact, any variable in the A/R study which is statistically significant must be carefully considered because of our relative ignorance about the occupational etiology of malignant melanoma. Because we are evaluating substances which may be harmful, we must, until better evidence appears, treat the risk factors found by A/R and confirmed in the re-analysis of these data as being worthy of further study.

A Type II error for the A/R study is the probability that a particular variable is not found to be a significant risk factor for melanoma when it is truly associated with melanoma. The smaller the sample size and the smaller the true odds ratio, the greater the probability of making a Type II error. Because the A/R study had only 31 cases there may be some exposures which are truly associated with melanoma, but which were not identified as statistically significant. We cannot say which variables these are; still, we must acknowledge that this problem exists.

Combining consideration of both Type I and Type II errors, Peto and others (1976) point out that a significant hypothesis test from a small study is more likely to represent an error than is a significant result from a large study (Peto and others, 1976; Royall, 1986). At the same time, any particular P value could be considered to be stronger evidence against the null

hypothesis in a small study than is the same P value in a large study (Lindley and Scott, 1984; Royall, 1986).

Summary

There is no meaningful evidence of selection bias in the A/R case-control study. If cases who were not actually cases, or controls who were diseased, were erroneously included in the study population, the exposure odds ratios presented in the A/R study would tend to underestimate the true effect. No evidence of recall bias exists, although, without objective measures of exposure, such bias is difficult to detect. The similarity of the non-occupational odds ratios to those reported in the literature is the strongest evidence for lack of recall bias. Our investigations of the confounding of the occupational odds ratios by the non-occupational variables suggests that the occupational odds ratios for "radioactive materials", "Site 300", and "photographic chemicals" are resistant to numerous control methods, and hence must be considered as robust. While the probability of falsely declaring a variable significant was undoubtedly high, we cannot say whether this error operated for any particular variable. Similarly, we may have lost power because of the relatively small number of cases (31). The A/R study was carefully conducted but is subject to the limitations in all observational case-control studies. A case-control study such as this, is, however, the only appropriate study design for investigating risk factors for malignant melanoma of the skin at LLNL on an individual level.

References

Holman CDJ, Armstrong BK, Heenan PJ et al. The causes of malignant melanoma: results from the West Australian Lions Melanoma Research Project. In Epidemiology of Malignant Melanoma, Gallagher, R.P. (ed.). Springer-Verlag: Heidelberg, 1986b.

Invitation for proposal 1253403. Study of unreported incidence of cutaneous malignant melanoma, 1986. LLNL.

Kleinbaum DG, Kupper LL, Morgenstern HL. Epidemiologic Research: Principles and Quantitative Methods. 1982, Lifetime Learning, Inc. San Francisco, CA.

Klemetti A, Saxen L. Prospective versus retrospective approach in the search for environmental causes of malformations. Am J Pub Health 1967; 57:2071-2075.

Lindley DV, Scott WF. New Cambridge Statistical Tables, Cambridge University Press: Cambridge, U.K., 1984.

Mason TJ, McKay FW, Hoover R et al. Atlas of Cancer Mortality for U.S. Counties: 1950-1969. DHEW Publications no (NIH) 75-780. US Dept of Health, Education and Welfare, 1975.

Moore D. Bennett D, Mendelsohn M. Melanoma among LLNL employees: an epidemiologic puzzle. Preprint, UCRL - 91475.. 1984.

Peto R, Pike MC, Armitage P. et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient, I: Introduction and design. Br J Cancer 1976; 34: 585-612.

Rogers GS, Kopf AW, Rigel DS et al. Hazard - rate analysis in stage one malignant melanoma. Arch Derm 1986; 122: 999-1002.

Royall RM. The effect of sample size on the meaning of significance tests. Amer Stat 1986; 40: 313-315.

Shy C, Checkoway H, Marshall EG. Malignant melanoma at a scientific laboratory: a synthesis of reviewers' comments on the Austin and Reynolds' study of employees at the Lawrence Livermore National Laboratory. October 7, 1985.

Thomas DC, Siemiatycki J, Dewar R et al. The problem of multiple inference in studies designed to generate hypotheses. Am J Epid 1985; 122: 1080-1095.

Table 1

Comparison of the odds ratios for selected exposures from the Austin/Reynolds study with those observed by Holman et al. (1986b)

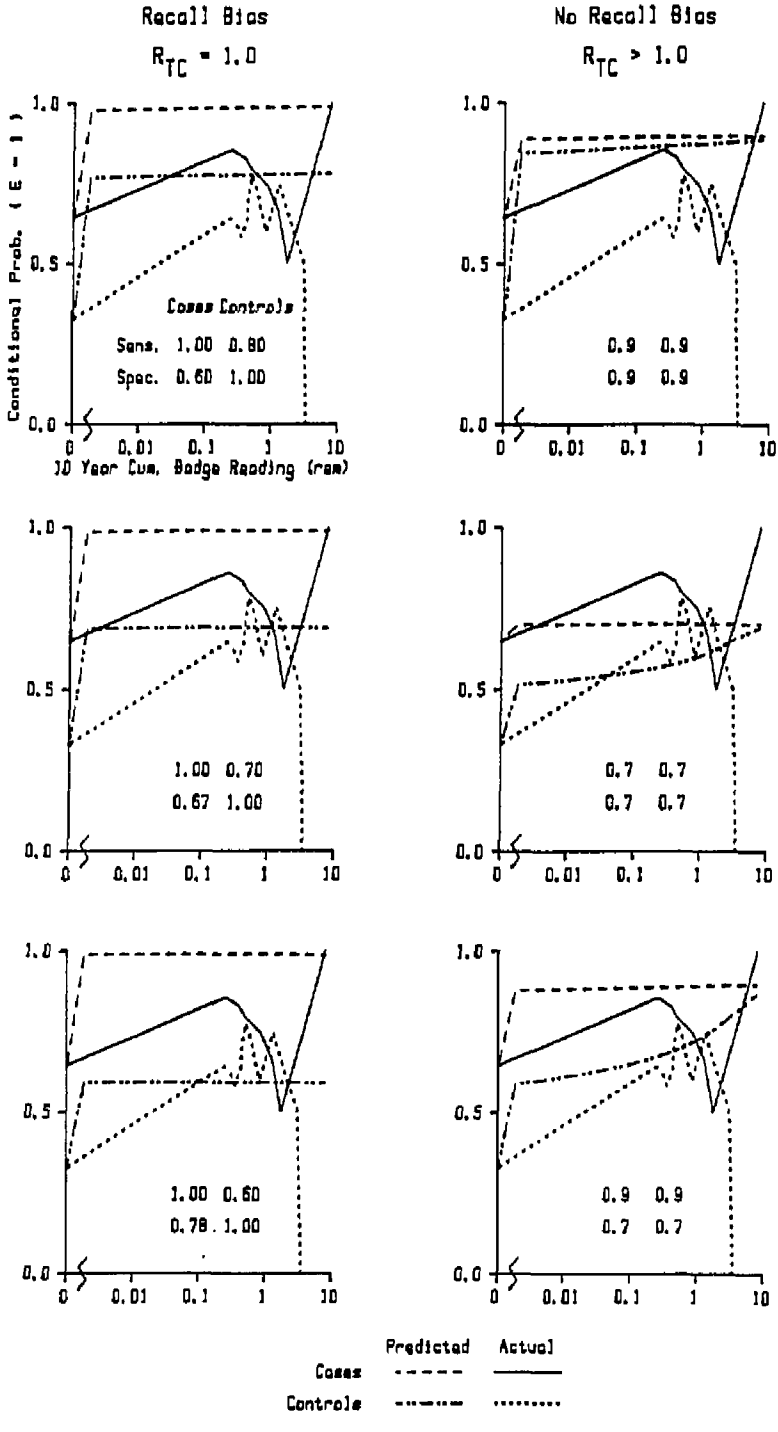
Austin/Reynolds[1]		Holman et al.	
VARIABLE	ODDS RATIO[2]	VARIABLE	ODDS RATIO[3]
1. (a) >6 nevi > 0.5 cm on the body=1	7.4	(a) >10 raised nevi on the arms=1	11.3 (CI not given)
(b) <6 nevi > 0.5 on the body=0		(b) No nevi on the arms=0	
2. (a) Reporting previous dx of non-melanotic skin cancer=1	12.0	(a) Reporting previous dx of non-melanotic skin cancer=1	3.0[4] (95% CI: 1.0-9.4)
(b) No previous non-melanotic skin cancer=0		(b) No previous non-melanotic skin cancer=0	
After previous solar exposure:		After previous solar exposure:	
3. (a) Burn with little or no tan=1	2.7	(a) No tan=1	2.8[4] (95% CI: 1.2-6.6)
(b) Burn with tan, tan, neither tan nor burn=0		(b) Deep tan=0	

1. Table 34 of the A/R Report
2. Matched on age, race, sex and employment at time of diagnosis
3. Matched on electoral subdivision, 5 year birth period, sex
4. For superficial spreading melanoma (SSM) only; 61% of the A/R cases were SSM.

Figure 1

Observed and predicted proportions of subjects with badge readings greater than x who would claim to have worked around radioactive materials. The predicted proportions are calculated based upon six different assumptions about R_{TC}, the odds ratio that measures the association between the "true" status of whether a person had worked around radioactive materials, and the sensitivity and specificity for "worked around radioactive materials" for both cases and controls. Sensitivity is the probability that a person claimed to have worked around radioactive materials, given that he or she actually did work around radioactive materials, and given that he or she is a case or control. Specificity is the probability that a person said that he or she did not work around radioactive materials, given that he or she actually did not work around radioactive materials, and given that he or she is a case or control. Only if the sensitivity for the cases does not equal the sensitivity for the controls and/or the specificity for the cases does not equal the specificity for the controls is there recall bias. Otherwise, there is only misclassification of the exposure variable (which biases the observed odds ratio towards one).

Figure 1
Probability of Claiming to Have
Worked Around Radioactive Materials
Conditional on Badge Reading and Case Status



X. Conclusions and Recommendation for Future Studies of Malignant Melanoma of the Skin at LLNL

Conclusions

The conclusions of the individual analytical chapters of this report are summarized here. The data have been collected and recorded in such a manner that the data tapes faithfully reflect the information collected on the self-administered questionnaire and the personal interview. The controls were shown to be a representative sample of the relevant portion of the undiseased LLNL population. Also, we found that the calculations in the Austin and Reynolds report have been carried out properly, and that their estimates for the most important occupational risk factors are not influenced unduly by outlying observations. When the five occupational factors identified in their report were examined for resistance to confounding, three of these proved to be quite reliable: "working around radioactive materials", "presence at site 300", "and working around volatile photographic chemicals". We also analyzed the LLNL radiation badge data, and found no association between exposure to ionizing radiation and melanoma. However, this analysis assumed that the linkage between LLNL's personnel data and the case-control data set was carried out correctly, that the badges measured relevant radiation exposure, and that the exposure occurred at LLNL. We also investigated the time factor in the A/R study, and found suggestive evidence that "working at site 300" and "worked around radioactive materials" were stronger risk factors for cases

diagnosed before the year 1974. The variable "worked in a building constructed in 1969" followed a similar pattern. We also examined the possibility that the odds ratios estimated for occupational factors in this study are subject to some form of bias. Although this possibility could not be ruled out, there was no obvious evidence in favor of either selection or of recall bias.

Therefore, as a working hypothesis, we can assume that the estimates reported by Austin and Reynolds represent valid effect estimates for their corresponding occupational factors. It is our opinion, then, after extensive examination of Austin and Reynolds's Report #3, and the data upon which it was based, that their study was generally well conceived, well conducted, and well analyzed, although somewhat overinterpreted. Our basic disagreement is with their insistence upon the causal nature of the factors they identified. We would like substantially more evidence from other studies before concluding that the factors they identified may be true risk factors. However, if there are factors truly associated with malignant melanoma at LLNL, the Austin / Reynolds report has identified the best candidates for such factors among the occupational factors they measured.

On the basis of our own investigations, of our interpretation of the Austin / Reynolds report, and also our impressions of other studies in the epidemiological literature, it is plausible that (if there is an occupational risk factor for melanoma) the relevant exposure is a substance that employees who either work around radioactive materials, who have worked at site 300, or who work around volatile photographic chemicals are more likely to encounter than are other employees. This exposure could be present now, or possibly could have been present mainly in the late 1960's or early 1970's. The recent

epidemiological literature on melanoma and chemical exposures suggests that this relevant exposure may be some type of chemical (see, for example, Hoover & Fraumeni, 1975, Bahn et al., 1976, Pell et al., 1978, Thomas and DeCoufle, 1979, Hoar and Pell, 1981, Elashoff et al., 1982, Wright et al., 1983, Holmberg, et al., 1983, Heldaas et al., 1984, and Vagero et al., 1985). Finally, we conclude that, although there is a good possibility that ionizing radiation is not a risk factor for melanoma, further investigation of this factor should be continued.

Recommendations for Future Studies

Current research at LLNL is focused on the question of whether or not there is truly an excess of malignant melanoma at LLNL. One way to address this question is to search the surrounding counties for cases of melanoma which were not reported to the California Tumor Registry (IFP 1253403, 1986). While enough information may be obtained from this exercise to show that the excess of melanoma at LLNL was not as great as previously thought, it will be difficult to duplicate in the surrounding community the intense case finding effort which has taken place at LLNL. For example, there will be no A/R report to produce concern about benign nevi, no screening program, and no heightened awareness in general.

Even if it is found that there is no excess of cutaneous malignant melanoma at the Lab, and that the reported excess was due to heightened awareness, it is still possible that some of the cases at LLNL may have been

occupationally induced. There could also be such cases in the surrounding community (associated with the workplaces of these individuals). An unknown proportion of the "background" rate may have an occupational etiology. For example, Elashoff and others (1982), in a case-control study of oral contraceptive use and malignant melanoma, found that women who had been exposed to certain occupational chemicals had a five times greater risk of melanoma than did those who were not so exposed.

Since LLNL has the opportunity to examine the occupational etiology of melanoma, we propose that the Lab continue their study of individual cases and controls at LLNL. In this follow-up case-control study, the Lab will have an opportunity to investigate some of the issues raised in the A/R study.

We propose that the Lab have four groups of cases (which could first be analyzed separately, and, if they are similar, ultimately analyzed together). The first would consist of individuals identified by Moore et al. (1984) who developed melanoma subsequent to leaving LLNL. (Living cases only should be interviewed because surrogate respondents would probably not know the details of the subjects' job histories). Cases identified by A/R would compose the second group. Cases identified subsequent to the A/R study, but not by the LLNL screening program, would be included in the third group. Finally, cases identified by the LLNL screening program would comprise the fourth group. The controls for each group would come from the same population at risk from which the corresponding cases developed. For example, cases identified by screening would be matched to controls who were screened but did not have melanoma.

The central purpose of this study would be to allow further systematic investigation of occupational factors identified by Austin and Reynolds. To avoid possible sources of error, we address each possible source of bias

presented in the chapter on sources of bias.

First, to make certain that no selection bias occurred due to the exclusion of cases who developed malignant melanoma subsequent to employment at LLNL, we include these individuals in the combined case group. We could also identify surrogate respondents for the deceased cases; however, surrogates could probably not complete the occupational exposure history accurately. We could compare the living cases to the deceased with respect to demographic details; however, if we found that they differed, there would be little we could do to correct the results. Further, we would not know whether the difference was due to the use of surrogate respondents or to true differences between the living and deceased cases. The method of selection of the control sample should be carefully recorded.

The definition of cases would be agreed upon by a panel of pathologists and a decision would be made whether to include cases of melanoma in situ (it would seem reasonable to do so, for these early cases might provide clues to the etiology of the disease). If there is an occupational carcinogen, we do not know at what stage in the disease process it operates.

Recall bias might be a problem because of the quantity of information which has been published about malignant melanoma at LLNL. Since it is no longer possible to keep the cases and controls ignorant of the A/R risk factors, each study subject (both cases and controls) should be given the same brief, but understandable, summary of the A/R results. This could be done in classes, or at the time of the interview. We also recommend that certain improvements be made in the measurement of the occupational and non-occupational exposures. First, we suggest that the number of benign nevi on the entire body be counted by a dermatologist for both cases and controls. It

is important that confounding variables be carefully measured (Kupper, 1984). We suggest that questions about solar exposure be extended to include exposure during youth. Holman's dissertation questionnaire (1982) could be used as a model for these questions. Also, it would be important to obtain a complete residence history from birth to the reference date for each study subject. The residence history can be used as a surrogate for solar exposure and should be examined because of the difficulty of measuring this variable. The study subjects' physicians should be questioned about previous diagnoses of non-melanoma skin cancer and related medical diagnoses.

As discussed in the chapter on the sources of bias, occupational exposure questions should be more detailed. Although lists should not be given to study subjects, each potential occupational exposure should be separately described. This part of the questionnaire would benefit from the collaboration of an industrial hygienist who could examine each occupational risk factor identified in the A/R study for its association with known carcinogenic chemicals. Special attention should be given to past work environments at LLNL (see Chapter VII on time). Where possible, occupational exposures must be evaluated by objective external comparisons. A disagreement between subjective and objective measures of exposure may mean that the objective measure did not contain sufficient information. For example, a medical record may contain information that a particular drug was prescribed (objective), but the study subject may correctly insist that he or she never consumed the medication (subjective) because the prescription was not purchased. There are similar disparities between official and actual tasks at work.

In preparation for a second case-control study, it would be valuable for an industrial hygienist to consider the specific chemical exposures to which

persons who worked around radioactive materials, worked at site 300, or worked around volatile photographic chemicals were more likely to be exposed than were other LLNL employees. It may be possible to screen such a list, once narrowed, using studies of melanoma among populations of employees in other industries.

Imperfect control of confounding of the occupational risk factor effect estimates may have occurred because there were few non-occupational questions on solar exposure during youth. This problem could be addressed via a second case-control study.

If the four case groups discussed above seem to be similar with respect to the associations of interest, they can be combined to increase the sample size. Also, the second study (excluding the A/R cases) can be an hypothesis-testing study of the occupational factors identified by Austin and Reynolds. Finally, it is imperative that existing screening programs be continued. Although the occupational factors identified by Austin and Reynolds cannot be claimed as causal, it would be prudent to make an effort to insure regular screening of persons identified as having these occupational exposures.

Summary of Recommendations

We recommend that, along with its investigations of whether there is a true excess of malignant melanoma of the skin at LLNL, the laboratory fund a second case-control study. We have suggested several ways in which the design of the A/R study may be improved. The purpose of this follow-up study would

be to examine the occupational exposures in further detail, and to assess whether or not one or more occupational exposures in the environment at LLNL are associated with the development of malignant melanoma of the skin among some employees. Current screening programs should be continued, with an effort made to insure regular screening of persons identified as being at higher risk for melanoma due to occupational exposures identified in the Austin / Reynolds case-control study.

References

Bahn AK, Grover P, Rosenwaike I, O'Leary K, Stellman J. PCB? and melanoma. New Eng J Med 1977; 296:108.

Bahn AK, Rosenwaike I, Herrman N, Parkash G, Stellman J, O'Leary K. Melanoma after exposure to PCB's. New Eng J Med 1976; 295:450.

Elashoff RM, Hunter TD, Mohilef E. Final report on epidemiology of melanoma, NICHD Contract, HD-8-2803, 1982.

Heldaas SS, Langard SL, Andersen A. Incidence of cancer among vinyl chloride and polyvinyl chloride workers. Br J Ind Med 41: 25-30.

Hoar SK, Pell S. A retrospective cohort study of mortality and cancer incidence among chemists. J Occup Med 1981; 23:485-494.

Holman CD. Risk factors in the causation of human malignant melanoma of the skin. Ph.D. thesis, Perth: University of Western Australia, 1982 (available through University Microfilms International, Ann Arbor, Michigan)

Holmberg B, Westerholm, Maasing R. Retrospective cohort of two plants in the Swedish rubber industry. Scand J. Work Environ Health 9 [Supppl 2]: 59-68.

Hoover R, Fraumeni JF. Cancer mortality in U. S. counties with chemical industries. Environ Res 1975; 9:196-207.

Invitation for proposal 1253403. Study of unreported incidence of cutaneous malignant melanoma, NICHD Contract, HD-8-2803, 1982.

Kupper, L. Effects of the use of unreliable surrogate variables on the validity of epidemiologic research studies, American Journal of Epidemiology, Vol. 120 (4), 643-648, 1984.

Moore D, Bennett D, Mendelsohn M. Melanoma among LLNL employees: An epidemiologic puzzle. Preprint, UCRL - 91475., 1984.

Pell S, O'Berg M, Kareh BW. Cancer epidemiologic surveillance in the DuPont Company. J Occup Med 1978; 20:725-740.

Thomas TL, Decoufle P. Mortality among workers employed in the pharmaceutical industry: a preliminary investigation. J Occup Med 1979; 21:619-623.

Vagero D, Ahlbom A, Olin R et al. Cancer morbidity among workers in the telecommunications industry. Br J Ind Med 1985; 42: 191-195.

Wright WE, Peters JM, Mack TM. Organic chemicals and malignant melanoma. Am J Indust Med 1983; 4:577-581

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Corrections

The following corrections were added after this report was printed.

Throughout, replace "worked around photographic chemicals" with "worked around volatile photographic chemicals".

p9. In the sentence, "In a previous study, Austin and Reynolds had reported a lack of association between ionizing radiation and melanoma.", insert "dose" between "radiation" and "and".

p13. In the sentence, "To further improve the study, an industrial hygienist should be involved in planning the questionnaire for this future study.", insert the phrase, "familiar with laboratory operations" after "hygienist".

p39. In the sentence, "JCAVG seems to contain all the information about melanoma risk that 'worked around photographic materials' contains, and some (but not all) of the information that the other two variables contain.", replace "'worked around photographic materials' with 'worked at site 300'.

p85. Replace the sentence "Employees who are likely to be exposed to ionizing radiation routinely wear radiation badges and LLNL keeps a permanent..." with "LLNL employees routinely wear radiation badges and LLNL keeps a permanent...". The point is that all LLNL employees wear radiation badges.

p143. Replace the sentence "As noted in the literature review chapter, both of these variables have been reported as risk factors for malignant melanoma." with "Both of these variables have been reporeted as risk factors for malignant melanoma in the literature (see, for example, Holman and Armstrong (1984) and Graham et al. (1985))."

p150. Additions to references:

Graham, S., Marshall, J., Haughey, B., Stoll, H., Zielezny, M., et al. An inquiry into the epidemiology of melanoma. Am. J. Epidemiology. 1985; 122: 606 - 619.

Holman, C.D., Armstrong, B.K., Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: An analysis separating histologic types. JNCI 1984; 73: 75 - 82.