

FINAL PROGRESS REPORT

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Abstract:

Exposure measurements obtained at the workplace is a key component for developing appropriate strategies to monitor and improve occupational safety and health; in particular, for assessing health risks, for identifying cost-effective intervention strategies, and for developing exposure-response relationships that will enhance occupational health. Furthermore, the collection of exposure data involves considerable human and financial resources. Thus it is very crucial that the data be used effectively, and valid statistical methods be used for the data analysis. The goal of the completed project was the development of a comprehensive set of statistical methodologies to address some challenges in the analysis of industrial hygiene data.

The presence of non-detects being a very common phenomenon in industrial hygiene data, a significant part of the project dealt with the development of appropriate exposure data analysis strategies when non-detects are present. A set of accurate statistical methodologies have been developed to address the issue of non-detects; methodologies that can replace the ad hoc (and very often inaccurate) procedures that are currently being used. The new methodologies are applicable regardless of the sample size, and they comprehensively address a variety of problems in several models that are widely used for exposure data analysis. In particular, the newly developed methodologies can accurately analyze exposure data that are subject to multiple detection limits. Clear guidelines have been provided on sample size determination when non-detects are anticipated, so as to provide guidance while planning the exposure data collection. This is a problem that has never been addressed before. It is now possible to determine the increased sample size that is necessary (due to the presence of non-detects), so as to guarantee a specified level of accuracy in the data analysis. All of these were accomplished using novel methodologies that are available in the statistics literature. The work is in accordance with the consensus standard published by the AIHA, which includes two basic strategies for evaluating an exposure: those based on the mean exposure, and based on an upper percentile of the exposure profile. Estimation of an upper percentile is especially relevant in order to assess the likelihood of some upper percentile (say, the 95th percentile) exceeding a specified occupational exposure limit. Another output from the proposed research is the development of reference limits, suitable for making decisions concerning acceptable exposure levels in occupational health, and the development accuracy criteria for the quantification of the measurement accuracy of industrial hygiene data. As part of the output of the proposed investigation, computational algorithms and software codes have been provided, in order to facilitate the easy application of the newly developed solutions.

The work was carried out with consulting help from an industrial hygienist. The newly developed statistical methodologies have all been illustrated by applying them to the analysis of real exposure data. In order to disseminate the work among the industrial hygiene community, the work was published in industrial hygiene journals, and was also presented at several American Industrial Hygiene Conference Expo annual meetings.

Section 1

1.1 Significant Findings

A significant outcome from our investigation is the development of accurate data analysis strategies when industrial hygiene data include single or multiple detection limits. Accurate data analysis is now possible for analyzing a single exposure sample, or for comparing two exposure samples, when non-detects are present. Our work has also resulted in the accurate handling of non-detects under regression models that can be used to model the relationship between a health outcome and an exposure variable. Another finding is that industrial hygienists can plan their study by being able to determine the sample size when non-detects are anticipated. This is a significant outcome since sample size determination in the presence of non-detects has never been addressed in the industrial hygiene literature. A noteworthy finding is that the newly developed methodologies are applicable when the sample sizes are not large. This is especially important since large sample sizes are not typical. It should be noted that ad hoc, and very often inaccurate methodologies are sometimes employed for the analysis of exposure data when non-detects are present, for example the widely used methodology of replacing non-detects with one-half of the detection limit. Such inaccurate methodologies can now be replaced by the newly developed statistical techniques, which have been demonstrated to be accurate.

In the presence of non-detects, industrial hygienists appear to have developed appropriate methods to estimate various parameters (such as the mean exposure and an upper percentile of the exposures) relevant for the evaluation of an exposure profile. However, the computation of accurate upper confidence limits was never satisfactorily addressed; this has been noted in the industrial hygiene literature. Thus the completed project fills a void in terms of meeting the data analysis needs of the industrial hygienists, who routinely face the issue of non-detects in their data.

The availability of reliable data, along with statistically valid reference limits, is crucial in order to assess exposure levels and to make policy decisions. Such limits contain the central 95% of the values of the reference population. Such limits have been developed under the one-way random model, where the random effect captures the between-worker variability. In the occupational setting, such reference limits can aid in the analysis and interpretation of exposure data.

For quantifying the measurement accuracy of exposure data, the development of accuracy criteria is important. The NIOSH accuracy criterion for a sampler is based on the symmetric-range accuracy A , defined as the fractional range that includes a specified proportion of sampler measurements. In our work, an explicit expression for A is provided assuming that the sampler measurements follow a one-way random model so as to capture the variabilities among and within different laboratories, or among and within exposed workers. An accurate upper confidence limit for A is derived, and an accurate approximation is also provided for its computation.

1.2 Translation of Findings

In order to disseminate our work among the industrial hygiene community, we have published our work in industrial hygiene journals, and have also presented our work at the American Industrial Hygiene Conference and Expo. In all of our work, we have addressed the computational issues, and have provided

relevant computational algorithms, along with links to software codes with help files. These are posted at the website <http://www.ucs.louisiana.edu/~kxk4695>. We have also pointed out the implications of our work for exposure monitoring by applying them to actual exposure samples.

The industrial hygienist G. Ramachandran has been providing consulting help. For disseminating our research among the industrial hygiene community, we also collaborated with the industrial hygienist Dr. Paul Hewett, the founder and president of Exposure Assessment Solutions, Inc. Dr. Hewett includes our work in his professional development course on censored data analysis, and is programming some of our methodologies into his statistical analysis software.

1.3 Outcomes/Impact

Exposure measurements obtained at the workplace is a key component for developing appropriate strategies to monitor and improve occupational safety and health; for assessing health risks, for identifying cost-effective intervention strategies, for developing exposure-response relationships that will enhance occupational health. Furthermore, the collection of exposure data involves considerable human and financial resources. Thus it is very crucial that the data be used effectively, based on valid statistical methods for data analysis. However, exposure data analysis can present some unique challenges: small sample sizes and the presence of single or multiple detection limits being two major issues, and traditional approaches and practices fail to yield accurate and satisfactory solutions. The completed research is expected to have a significant impact, since it satisfactorily addresses all of these concerns. The completed work also includes sample size determination, in terms of providing clear guidelines on the increased sample size that is necessary in the presence of non-detects.

The completed research is in line with the consensus standard published by the AIHA for evaluating an exposure, which includes two basic strategies: those based on the mean exposure, and based on an upper percentile of the exposure profile (Ignacio and Bullock, 2006, *A Strategy for Assessing and Managing Occupational Exposures*, AIHA Press). These basic strategies are in fact a major focus of the completed research. Estimation of an upper percentile is especially relevant in order to assess the likelihood of some upper percentile (say, the 95th percentile) exceeding a specified occupational exposure limit.

The availability of statistically valid reference limits is crucial to assess exposure levels and to make policy decisions. The lack of such limits can be a hindrance to the analysis and interpretation of exposure data. Our work includes the development of such limits.

The quantification of the measurement accuracy of exposure data necessitates the development of accuracy criteria. The NIOSH accuracy criterion is based on the symmetric range accuracy A , and a measurement method satisfies the NIOSH accuracy requirement if a 95% upper confidence limit for A does not exceed 0.25. An accurate confidence limit calculation for A is addressed under the completed research for a model that takes into account between worker variability.

Overall, the outcomes from the completed research is expected to have a significant impact on the analysis of exposure data since we could successfully accomplish the goal of developing valid statistical methodologies that are applicable even for small samples.

Section 2: Scientific Report

2.1 Background

For evaluating an exposure profile, two basic strategies are included in consensus standard published by the AIHA: those based on the mean exposure, and those based on an upper percentile of the exposure profile (Ignacio and Bullock, 2006, *A Strategy for Assessing and Managing Occupational Exposures*, AIHA Press). Thus the problems of accurately estimating the mean and an upper percentile, and computing upper confidence limits for them, are very important. Such upper limits provide bounds on the unknown means and percentiles. Estimation of an upper percentile is especially relevant in order to assess the likelihood of some upper percentile (say, the 95th percentile) exceeding a specified occupational exposure limit. Very often, these problems have to be addressed assuming a log-normal distribution for the exposure data; in fact, the lognormal distribution plays a critical role in the analysis of environmental data and exposure data. Accurate data analysis based on the lognormal distribution can be challenging, especially when the sample sizes are not large: a typical scenario in industrial hygiene. The problems become especially challenging when the samples are subject to detection limits; once again, a very common feature of industrial hygiene data. The proposed research was targeted to address all of these peculiarities associated with exposure data analysis.

Industrial hygienists have highlighted the difficulties arising from these challenges, and have also noted the lack of accurate data analysis strategies. In an article commenting on the problems posed by non-detects, and published in the *Annals of Occupational Hygiene*, Helsel (2010, p. 261) notes that “Method evaluations for estimating a mean do not necessarily carry over to the more difficult issues of how to compute interval estimates, upper percentiles, a correlation coefficient, a regression slope and intercept, or a multidimensional surface when left censoring is present. There are many interesting issues still to be evaluated.” The goals of the proposed research included the investigation of the “many interesting issues” highlighted by Helsel (2010).

Industrial hygienists have noted that the lack of valid reference limit values can be a hindrance to the analysis and interpretation of exposure data; see for example, Gorny and Dutkiewicz (*Annals of Agricultural and Environmental Medicine*, 2002, p. 17) who highlight this problem in the study of indoor bioaerosols. The problems concerning reference limits proposed in the project were motivated by this observation.

The NIOSH accuracy criterion, based on the symmetric range accuracy A , has been investigated in the industrial hygiene literature; see Bartley (2008, *Annals of Occupational Hygiene*) for details. The literature on the problem shows that an exact expression for A is not available, and an accurate confidence interval is also not available. Furthermore, the symmetric accuracy range accuracy has not been investigated under models that involve random effects. The proposed problems in the project on this topic address these issues.

The overall goal of the project was to address the above problems in a comprehensive fashion: develop the required statistical methodology, address the computational issues, provide the necessary software codes, and illustrate the methodology using the analysis of real exposure data.

2.2 Specific Aims

A major aim of the proposed research was the development of accurate procedures for analyzing exposure data and health outcome data in the presence of single or multiple detection limits. The procedures were to be addressed in a comprehensive manner for a variety of practical scenarios: normal and lognormal exposure distributions, and regression models for modeling the relationship between two exposure variables, or between an exposure variable and a health outcome in occupational epidemiology studies. The case of multiple detection limits were also to be investigated. The emphasis of the proposed research was to come up with efficient procedures that are applicable regardless of the sample size. Specifically, it was proposed to address the following exposure data analysis problems:

- (1) Interval estimation for the arithmetic and geometric means, and exceedance fractions
- (2) Hypothesis testing regarding the ratio or difference of two lognormal means
- (3) Computation of confidence limits for percentiles.

It was proposed to accomplish the above using fairly recent and newly developed methodologies available in the statistics literature: the generalized inference approach, i.e., generalized p-values and generalized confidence intervals, as well as modified likelihood ratio procedures. It was also proposed to address

- (4) Sample size determination when non-detects are present.

Two other specific goals of the proposed research were:

- (5) The development of reference limits, suitable for making decisions concerning acceptable exposure levels in occupational health.
- (6) The development of accuracy criteria for the quantification of the measurement accuracy of industrial hygiene data.

2.3 Methodology

Here is a description of the methodologies used to address the various problems proposed in the project.

- (i) *Analysis of lognormally distributed exposure data in the presence of detection limits: single exposure sample*

Novel statistical methods were used to develop accurate data analysis procedures, i.e., tests and confidence intervals, concerning the arithmetic mean and the upper percentile of a single lognormal distribution. The methodologies used include the concepts of generalized p-values and generalized confidence intervals, as well as modified likelihood ratio methods. These are fairly recent methodologies in the mainstream statistics literature, and they turned out to be especially accurate to handle data that include single or multiple detection limits, and small samples. The methodologies also include computational details, and a source for the computer programs are given. It should be emphasized that the likelihood function only uses information on the number of values below each detection limit; no substitution values are used to replace them. An advantage of the proposed approach is the ease of computation and implementation. Examples with real and simulated data sets are given to illustrate the

methodology and its relevance for exposure data analysis.

(ii) *Analysis of lognormally distributed exposure data in the presence of detection limits: comparison of two exposure samples*

Similar to what is done under (i), modified maximum likelihood methodology has been developed for accurate data analysis procedures concerning the ratio of the arithmetic means, as well as the ratio of the geometric means of two lognormally distributed exposure populations. The work has resulted in confidence limits for the above problems, in the presence of multiple detection limits. Furthermore, based on simulation results, we have demonstrated the accuracy of the proposed solutions.

(iii) *Sample size determination in the presence of single or multiple detection limits*

The usual methodology for determining sample sizes is based on the requirement that a hypothesis testing procedure will have 80% (sometimes 90%) power. While we have also followed this well established approach, we note that such an approach is meaningful only if the test procedure itself is accurate. As noted under (i) above, the statistical methodologies we have developed are accurate, and hence the sample size determination is indeed meaningful. In our work, table of sample sizes have been provided so as to guarantee 80% power for the test procedures concerning various parameters of interest for exposure data analysis.

(iv) *Regression analysis in the presence of detection limits*

Regression analysis, appropriate for modeling the relationship between an exposure variable and a health outcome, was investigated in detail when the variables are subject to detection limits. The problems addressed include: (a) the estimation of parameters, and (b) computation of confidence intervals for the regression parameters and for the mean response. A simulation based methodology is developed for solving these problems. Also, algorithms are developed in order to facilitate easy implementation while analyzing exposure data.

(v) *The symmetric accuracy range under a one-way random model*

The NIOSH accuracy criterion, based on the symmetric range accuracy A , is taken up under this investigation and an upper confidence limit is computed using the methodology of generalized confidence intervals. Methodology is developed in both balanced and unbalanced data situations. The balanced data situation occurs when the same number of exposure measurements is available on each worker; if not, we have the unbalanced data situation. Monte Carlo evaluation indicates that the proposed upper confidence limit is satisfactory even for small samples. Especially important is the fact that we could develop an accurate approximation for computing the upper confidence limit. In other words, our proposed solution is both accurate and easy to compute.

(vi) *The development of reference limits*

Reference limits are useful for interpreting exposure data, and industrial hygiene literature has indicated

that reference limits should be calculated based on statistically well-defined confidence intervals or tolerance intervals. This has been noted, for example, in Heinrich-Ramm et al. (*Pure and Applied Chemistry*, 2000, pp. 385-436), where the authors deal with the application of biomonitoring for exposure to volatile organic compounds. Since reference limits are meant to include the central part of a population, we have used the concept and methodology of central tolerance limits for obtaining reference limits relevant to industrial hygiene applications.

The necessary computational algorithms and software codes for implementing our methodologies have been developed for each of the above problems, so that the industrial hygiene community can implement the newly developed methodologies without having to familiarize themselves with the statistical theory used in their development. The implementation was illustrated based on the analysis of real industrial hygiene data.

2.4 Results and Discussion

Samples that include measurements below an analytic detection limit are very common in industrial hygiene. A unified practical solution that is also accurate has been lacking for performing data analysis under this scenario, even in the situation of exposure measurements that follow a lognormal distribution. The results from our work has provided accurate solutions for a variety of exposure data analysis problems for lognormally distributed exposure samples in the presence of single or multiple detection limits. Only ad hoc procedures have been available in the industrial hygiene literature, and confidence limit calculation was not satisfactorily addressed. Sample size issues in the design of industrial hygiene studies were not addressed at all, in the detection limit scenario. For example, for estimating the mean exposure levels, what is the increased sample size necessary to guarantee the same accuracy compared to the situation of no non-detects? Even though sample size determination is a crucial part of any study, no sample size guidelines were available until our work on this problem; a major result of our investigation.

The investigations under the proposed project has resulted in data analysis strategies for analyzing a single exposure sample, or for the comparison of two exposure samples. The problem of comparing two exposure populations can come up, for example, in the context of evaluating the effectiveness of engineering controls or interventions for reducing exposures; the two populations consist of exposure levels before and after the installation of engineering controls or interventions. In particular, an appropriate hypothesis testing problem can be formulated for verifying if the mean exposure level was improved by an intervention. The problem can also come up if we want to compare two methods in terms of their efficacy in reducing exposures. Our results provide accurate methodologies for addressing such problems in the detection limit scenario.

We believe that the accurate analysis of exposure samples based on regression models has not received adequate attention in the industrial hygiene literature, when detection limits are present. We could make significant progress in addressing this important topic. We note that the conventional approach of replacing the non-detects with a single number (such as one-half of the detection limit) can distort the linear regression relationship, and is likely to lead to misleading conclusions. Given this observation, and given the importance of regression models for modeling the relationship between two exposure variables, or between an exposure variable and a health outcome, the results we have obtained should be of considerable practical interest for exposure data analysis. The results we have obtained in this context include the

development of algorithms for implementing a likelihood based methodology, and the development of confidence limits for the slope parameter in the regression model, and for the mean exposure level corresponding to a fixed value of an independent variable (for example, a biomarker). Numerical results show that the simulation based methodology that we have developed is indeed accurate.

The use of models that involve random effects is a convenient and practically useful approach to capture the heterogeneity among the exposed group. Such models have found extensive use in the industrial hygiene literature. Data analysis strategies under such models have immediate applications in industrial hygiene, and these include estimation of the mean and the percentiles. We have investigated two further issues under such models: the calculation of reference limits, and the development of accuracy criteria for the quantification of measurement accuracy. The results from our investigation of reference limits provide accurate limits that can be used for interpreting exposures. Results from our work on the symmetric-range accuracy problem is important due to two reasons: we could provide an exact expression for A under a random effects model; thus there is no need to use approximations. Furthermore, we could provide an accurate upper confidence bound for A . We believe that the ideas we have used can also be extended to investigate the symmetric-range accuracy and its upper confidence bound in the context of other models appropriate for exposure data analysis, for example, regression models.

2.5 Conclusions

The estimation of some rather complicated parameters comes up in many industrial hygiene applications. An added complexity is the presence of single or multiple detection limits, and the lack of large sample sizes. Our work dealing with the development of statistical methodologies has resulted in very satisfactory procedures for a variety of problems relevant to the analysis of industrial hygiene data. The methodologies are applicable regardless of the sample size, regardless of the number of detection limits, and regardless of the percentage of non-detects. In addition, sample size determination in the presence of non-detects has been addressed for the first time. The work relied heavily on the applications of some novel statistical concepts, namely, the concepts of generalized inference and modified likelihood ratio methods. It was necessary to use novel methodology since standard statistical methods were inadequate to address the challenges posed by industrial hygiene applications, especially the presence of non-detects. In our work, all the computational issues were carefully addressed, and the new methodologies were illustrated using the analysis of actual exposure data. Furthermore, computational algorithms and software codes have been provided. Even though some of the methodological developments in our work maybe beyond the reach of many industrial hygienists, this is no hindrance in applying the newly developed methodologies due to the availability of the algorithms and software codes. A final point to note is that the framework developed in this research maybe applicable to other models and problems where non-detects are encountered.

Publications

Journal Articles

Krishnamoorthy K, Mathew T, Xu Z: [2014]. Standardized Likelihood Inference for the Mean and Percentiles of a Lognormal Distribution Based on Samples With Multiple Detection Limits. *Journal of Environmental Statistics* 6:1-18.

Krishnamoorthy K, Mathew T, Xu Z: [2014]. Comparison of Means of Two Lognormal Distributions Based on Samples with Multiple Detection Limits. *Journal of Occupational and Environmental Hygiene* 11:538-546.

Krishnamoorthy K, Mathew T, Xu Z: [2013]. Tests for an Upper Percentile of a Lognormal Distribution Based on Samples With Multiple Detection Limits and Sample Size Calculation. *Annals of Occupational Hygiene* 57:1200-1212.

Krishnamoorthy K, Mathew T: [2013]. The Symmetric-Range Accuracy Under a One-Way Random Model With Balanced or Unbalanced Data. *Annals of Occupational Hygiene*. 57:953-961.

Krishnamoorthy K, Xu, Z: [2011]. Confidence Limits for Lognormal Percentiles and for Lognormal Mean Based on Samples with Multiple Detection Limits. *Annals of Occupational Hygiene* 55:495-509.

Krishnamoorthy K, Mallick A, Mathew T: [2011]. Inference for the Lognormal Mean and Quantiles Based on Samples with Nondetecteds. *Technometrics* 53:72-83.

Dissertations

Dong, X: [2011] Reference Intervals and Regions for Some Normal Populations, Ph.D. Thesis, University of Maryland Baltimore County.

Xu, Z: [2012] Inference for Lognormal Distributions based on Data with Multiple Detection Limits, Ph.D. Thesis, University of Louisiana at Lafayette.