FINAL PROGRESS REPORT

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Abstract. The proposed research was on the development of statistical procedures appropriate for analyzing exposure data, based on statistical models directly relevant for exposure assessment. The following topics were investigated: the univariate and bivariate lognormal distributions that describe exposure data, methodology for comparing several test methods or samplers, procedures to analyze samples that included values below the detection limit, and random effects models for describing variability among workers. Difficulties and limitations of some of the currently used statistical techniques were highlighted, and efficient alternatives were developed. Approaches based on the novel concepts of generalized p-values and generalized confidence intervals were successfully investigated for solving the proposed problems.

The problem of assessing occupational exposure using the mean of a lognormal distribution was addressed using the concepts of generalized p-values and generalized confidence intervals. The resulting methodologies are applicable to small samples and they are easy to implement. Power studies and sample size calculations have also been discussed. The procedures have also been extended for the purpose of comparing two independent exposure populations, as well as for comparing the means of a bivariate exposure population, following the bivariate lognormal distribution.

A model based "multiple imputation approach" was developed for analyzing exposure data with non-detects. The approach involves replacing the non-detects with randomly generated observations under the appropriate model, and then analyzing the data using complete sample techniques after adjusting for the imputation. The method has been described for lognormally distributed exposure data, and has been illustrated for computing prediction limits and tolerance limits, for setting an upper bound for an exceedance probability, and for estimating the arithmetic mean.

In many industrial hygiene applications, a model with random effects is used to account for the variability within an exposure group. Under this setting, statistical methods have been proposed for setting upper limits on (i) the probability that the mean exposure of an individual worker exceeds the occupational exposure limit (OEL) and (ii) the probability that the exposure of a worker exceeds the OEL. The proposed method for (i) was obtained using the generalized confidence interval approach, and the one for (ii) was based on an approximate method for constructing one-sided tolerance limits. The methods are conceptually as well as computationally simple.

The comparison of an alternative sampling device to an OSHA standard, or the comparison of two sampling devices, or that of several sampling devices and methods, is a problem that is frequently encountered while developing cheaper or more efficient exposure assessment strategies. A test procedure has been developed for making such comparisons. Performance of the test has been numerically investigated, and satisfactory performance has been noted.

Preliminary work has been completed to investigate the NIOSH accuracy criterion based on the symmetric-range accuracy, for the quantification of measurement accuracy of exposure data. The symmetric-range accuracy of a sampler is defined as the fractional range, symmetric about the true concentration, that includes a specified proportion of sampler measurements. An explicit expression has been derived for the symmetric-range accuracy when the sampler measurements follow a normal or a lognormal distribution. Confidence limits have been proposed for the symmetric-range accuracy using the generalized confidence interval idea. An accurate and convenient approximation has also been developed for computing the confidence limit.

The newly developed statistical methodologies have all been illustrated by applying them to the analysis of real exposure data. Computational algorithms and software codes have also been provided.

Highlights/Significant Findings. The proposed research was on the development of accurate statistical methodologies, appropriate for analyzing industrial hygiene data. Towards this, novel statistical methodologies, based on the concepts of generalized p-values and generalized confidence intervals, have been applied. Here are the significant findings:

1. Since the lognormal distribution plays a central role in industrial hygiene, several problems were addressed in this context. For estimating the arithmetic mean, accurate confidence intervals and test procedures have been developed. The problems were also investigated by taking into account the variability within the exposure group; this was done by including a random effect in the model. The issue of estimating an exceedance fraction was addressed. The problem of computing an upper tolerance limit–a limit below which most of the exposure levels are expected to lie, was investigated. Also addressed was the comparison of lognormal means in a bivariate lognormal exposure population.

2. Accurate methodology was developed for analyzing exposure data that contains non-detects. In order to handle the data analysis issues in this context, a well established statistical methodology, referred to as the imputation approach, was developed an implemented, and its accuracy was demonstrated to address a variety of problems, including the computation of confidence limits and tolerance limits.

3. Based on the OSHA criterion for establishing the equivalence of two sampling devices, statistical methodology was developed to test the equivalency of several sampling devices.

4. Recognizing the need to have reliable criteria for the quantification of measurement accuracy in industrial hygiene applications, work has been initiated to investigate the NIOSH accuracy criterion based on the symmetric-range accuracy. An exact expression has been derived for the symmetric-range accuracy, and an accurate confidence interval has been constructed by applying the generalized confidence interval idea.

In all of the above investigations, the associated computational details have been addressed in detail, and computational algorithms and software codes have been provided. All cf the new methodologies have been illustrated by applying them to the analysis of real exposure data.

Translation of Findings. In order to translate the findings among the industrial hygiene community, the results from the proposed research were published mostly in industrial hygiene journals. Furthermore, computational algorithms were provided, along with links to software codes with help files. The necessary algorithms and Fortran and SAS programs to carry out our procedures are posted at the web address http://www.ucs.louisiana.edu/~kxk4695. In addition, detailed analysis of several exposure data sets have been included in the publications.

Some of our findings were presented at the AIHCE conference in Chicago (2006). Since the proposed methodologies are fairly recent and novel, extensive applications of the proposed methods are yet to materialize. Dr. Stanley Shulman, who is with the Engineering and Physical Hazards Branch of NIOSH's Division of Applied Research and Technology (Cincinnati, Ohio), has been using the newly developed procedures concerning the lognormal distribution for the analysis of exposure data. The importance of the work on the symmetric accuracy range has already been noted by other researchers; see Bartley (*Annals of Occupational Hygiene*, 2008) and Bartley and Liden (*Annals of Occupational Hygiene*, 2008).

It should also be noted that most of the proposed work was done in collaboration with an industrial hygienist (Dr. Gurumurthy Ramachandran, University of Minnesota).

Outcomes/Relevance/Impact. The nature of some of the problems in exposure data analysis is such that the traditional approaches and practices fail to yield accurate and satisfactory solutions. The proposed research was based on this realization, and also based on the observation that accurate solutions can be obtained using novel methodologies that recently became available in the mainstream statistics literature.

The consensus standard published by the American Industrial Hygiene Association (AIHA) includes two basic strategies for evaluating an exposure profile: strategies based on the mean exposure, and those based on an upper percentile of the exposure distribution (see *A Strategy for Assessing and Managing Occupational Exposures*, Ignacio and Bullock, Editors, 2006, AIHA Press, Fairfax, Virginia). Thus the problems of estimating the mean and an upper percentile, and computing confidence limits for them, become important. Furthermore, an upper tolerance limit is precisely an upper confidence limit for an upper percentile. If the upper tolerance limit based on a sample of exposure measurements is less than an occupational exposure limit (OEL), then we conclude that majority of the exposures are below the OEL, and hence exposure monitoring might be reduced or terminated until a process change occurs. Since a major component of the proposed research dealt with the estimation of means and exceedance fractions, and the computation of tolerance limits, the outcomes of the proposed research have direct relevance as well as impact on the strategies recommended by the AIHA. An attractive feature of the proposed methodologies is that their validity and applicability do not require large sample sizes. This is especially important since exposure sampling is expensive, and large samples are seldom available. The outcomes of the proposed research also include data analysis strategies under random effects models. This is particularly relevant in industrial hygiene applications, since a large number of studies, reported in the industrial hygiene literature, use a random effects model for the data analysis. The inclusion of a random effect is a convenient way to capture between-worker variability within an exposure group.

Industrial hygienists often encounter left-censored exposure data, due to the presence of non-detects, i.e., sample values below an assay detection limit. The proposed research to deal with non-detects has resulted in satisfactory methodology to handle a variety of exposure assessment tasks, including the computation of confidence limits and tolerance limits, and the estimation of exceedance fractions. Furthermore, the proposed methodology is statistically sound, and holds promise to handle the non-detects issue under complex exposure models.

Equivalence testing of two more more sampling devices has obvious relevance in exposure sampling. OSHA has prescribed a criterion for testing such an equivalence. However, previous work in the industrial hygiene literature, dealing with testing this criterion, appears to be unsatisfactory since the statistical problem was not rigorously defined or solved, as pointed out in our proposed work on the topic. Our own work on this problem, under the proposed research, has resulted in statistically rigorous solutions based on the OSHA criterion.

Since reliable criteria for the quantification of measurement accuracy is crucial in industrial hygiene applications, our work on the symmetric-range accuracy will be relevant and useful in such applications. In fact, Bartley and Liden (*Annals of Occupational Hygiene*, 2008, p. 414) make the following comment on our new results on the symmetric accuracy range: "This discovery is expected to lead to a fresh fundamental understanding of the concept of accuracy as well as new means of calculating, for instance, confidence limits on the symmetric accuracy range."

Scientific Report

The statistical analysis of occupational exposure data is a critical component in the development of better and more comprehensive exposure assessment strategies. Specific aims of the proposed work were the development of (i) accurate statistical methodology for analyzing exposure data that can be modeled using the univariate and bivariate lognormal distributions, (ii) methodology for comparing several test methods or samplers, (iii) imputation methods for data analysis when exposure samples include non-detects, and (iv) tolerance intervals for exposure monitoring, especially in the context of random effects models. In particular, the proposed research emphasized the application of the concepts of generalized p-values and generalized confidence intervals for exposure data analysis.

Several attempts have been made in the industrial hygiene literature for drawing inferences concerning the arithmetic mean of a single lognormal distribution. To a much lesser extent, attempts have also been made to draw inferences for the ratio of the means of two lognormal distributions. These problems have certain inherent difficulties associated with them, and the available solutions were either approximate, or were applicable only to large samples, or were difficult to compute. In our work, we explored a novel approach for solving these problems, based on the concepts of generalized p-values and generalized confidence intervals. It turned out that these concepts provide a unified and versatile approach for the analysis of exposure data involving a single lognormally distributed exposure sample, or two such samples, and also for a bivariate lognormal distribution. Even though analytic expressions are not available for the resulting solutions, their computation is both easy and straightforward. In fact an added advantage of the new approach is the ease of computation and implementation. The necessary algorithms have been provided for their computation, and they have been illustrated using several examples dealing with the analysis of exposure data. In particular, the interval estimation of a lognormal mean was illustrated using a data set on air lead levels (obtained by NIOSH), for health hazard evaluation purposes. The procedure for comparing the arithmetic means of two lognormally distributed exposure samples was applied to data consisting of the total mass of metalworking fluids (MWF) obtained by thoracic MWF aerosol, and closed-face MWF aerosol.

Samples that include measurements below an analytic detection limit are very common in environmental sampling and industrial hygiene. A unified practical approach that also performs accurately has been lacking for performing data analysis under this scenario. Our work on the detection limit problem has been an attempt to fill this void by advocating an imputation approach that replaces the non-detects with an imputed value. For the normal and related distributions, confidence intervals, tolerance limits, prediction limits, etc., have been developed using the available standard procedures (after doing the imputation), and their performance has been numerically investigated. The confidence levels have been calibrated to improve the accuracy, and recommendations have been made for practical use. Two imputation approaches have been investigated in our work: one used approximate maximum likelihood estimates (MLEs) of the parameters, and a second approach used ad hoc estimates. The accuracy of the approaches has been verified using Monte Carlo simulation. Simulation studies showed that both approaches were very satisfactory for small to moderately large sample sizes, but only the MLE based approach was satisfactory for large sample sizes. The MLE based approach can be calibrated to perform very well for large samples. Applicability of the method to the lognormal distribution and the gamma distribution was also investigated. Simulation studies also showed that the imputation approach works well for constructing tolerance limits and prediction limits. The approach was illustrated using some practical examples, and the corresponding data analysis, for two data sets: data on oil mist measurements obtained from a machining workshop in France, and data on alkalinity concentrations in ground water obtained from a greenfield site (the site of a waste disposal landfill, prior to disposal of waste). The problem of computing tolerance limits, and that of estimating an exceedance probability, were both illustrated for the two examples. Our overall conclusion is that the imputation approach is quite satisfactory when samples contain non-detects. Furthermore, imputation is now a very standard procedure that is widely used, and our proposed methodology is applicable to small samples. The framework developed in this research should be applicable to other models and problems where non-detects are encountered.

The problem of testing the equivalency of an alternate sampling device to an OSHA standard, or that of two sampling devices, or that of several sampling devices or methods, is a problem that has received some attention in the industrial hygiene literature. Some of the investigators of this problem have used the t-test to compare the means of the log-transformed data, in order to establish equivalence. However, this is obviously not adequate to judge the closeness of the individual measurements from the two devices. The preferred approach toward solving the problem is to use an OSHA recommended criterion. OSHA regulations allow the use of an alternate sampling device for exposure monitoring, provided equivalence to the standard device can be established following the criterion that 90% of the readings of the sampling device be within plus or minus 25% of the readings obtained by the standard device, with a 95% confidence level as demonstrated by a statistically valid protocol (see OSHA regulation document 1910.1043). This criterion obviously requires that the actual observations, and not the means be compared. In an earlier paper, Krishnamoorthy and Mathew (*American Industrial Hygiene Association Journal*, 63, 567-571, (2002)), a method was proposed for testing if an alternative sampling device is equivalent to an OSHA standard, following the OSHA criterion. The necessary tables were also provided in this paper. In the proposed work on testing the equivalency of several sampling devices, we adopted the approach in the above article, and used the statistical methodology of intersection-union principle. The principle is simple to use in applications, and it does not require any new table values. Indeed, the same table values given in our earlier work can be used to carry out the intersection-union test. The proposed method was applied to a simulated data set for testing the equivalency of three sampling devices. Earlier, our methodology for two sampling devices was applied to establish the equivalence of an alternate cotton dust sampler to the Lumsden-Lynch vertical elutriator.

The use of a model that involves a random effect is a convenient and practically useful approach to capture the heterogeneity among the exposed group. In our work, we concentrated on the one-way random effects model for the log-transformed exposure data. Problems of interest for the purpose of exposure monitoring now reduce to problems concerning the unknown parameters of the model: the overall mean and the two variance components. As opposed to standard applications of the one-way random effects model, where the problems of interest deal with the individual parameters, exposure monitoring applications require inference on parametric functions that involve all the unknown parameters. Novel approaches were required to deal with such problems, especially since small sample procedures were desired. We once again investigated the generalized confidence interval idea to come up with confidence intervals and tests for two parametric functions of interest: the probability that the mean exposure of an individual worker exceeds the OEL, and the probability that the exposure of a worker exceeds the OEL. The latter parametric function also comes up in connection with the computation of tolerance intervals. The results were applied to a data set on nickel dust exposure measurements, made on a sample of maintenance mechanics at a nickel producing facility. The newly developed methodologies were applied to estimate the proportion of maintenance mechanics for whom the the exposure measurements exceeded the occupational exposure limit. For the problems we have investigated, large sample confidence bounds could be easily obtained using standard methods; however, numerical results have shown that the generalized confidence interval approach has a definite edge in terms of maintaining the type I error probability of the tests, and coverage probability of the confidence intervals. The computational algorithm mentioned in our work demonstrates that the generalized confidence interval approach is quite easy to implement.

The development of accuracy criteria for the quantification of measurement accuracy is clearly an important problem. The NIOSH accuracy criterion is based on the symmetric-range accuracy (denoted by A), and the NIOSH accuracy requirement states that a 95% upper confidence limit for A does not exceed 0.25; see NIOSH Manual of Analytical Methods, (Edited by Eller, P. M. and Cassinelli, M. E., fourth edition, National Institute of Occupational Safety and Health, Cicinnati, Ohio, 1994). In general, the symmetric accuracy range A is defined as the fractional range, symmetric about the true concentration, within which $100(1-\alpha)\%$ of sampler measurements are to be found. Assuming a normal distribution (for the original data, or the log-transformed data), some researchers have developed an approximation for A, and an approximate 95% upper confidence limit for A. The upper confidence limit is important since the measurement method satisfies the NIOSH accuracy requirement if the upper confidence limit is less than 0.25. The practical relevance of our results for estimating the symmetric-range accuracy was demonstrated by applying it to quantify the measurement accuracy of a data set consisting of measurements of carbon monoxide made by different monitors.

Our work on the symmetric-range accuracy problem is important due to two reasons: we could provide an exact expression for A; thus there is no need to use approximations. Furthermore, we could provide an accurate upper confidence bound for A using the generalized confidence interval idea. 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, a random effects models. This problem is currently under investigation.

In conclusion, our work dealing with the development of statistical methodologies for industrial hygiene has resulted in very satisfactory procedures applicable regardless of the sample size. The work relied heavily on the applications of some novel statistical concepts, namely, the concepts of generalized p-values and generalized confidence intervals. It was necessary to use novel methodology since standard statistical methods were inadequate to address the challenges posed by industrial hygiene applications. 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. A final point to note is that our work has actually provided the framework to investigate similar problems that may come up in the context of models that we have not addressed, but are relevant for the modeling and analysis of exposure data.

Publications

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