Eisen and colleagues have provided a good example of the use of smoothing splines in a thorough analysis of exposure-response data, for a study of lung cancer in relation to silica exposure. Exposure-response data are increasingly important for two reasons. First, as noted by Bradford Hill, a positive exposure-response provides support for a causal interpretation of an association. In the case of silica and lung cancer, evidence of a positive-exposure response in several studies has provided important support for the original 1997 IARC judgement that silica is a class I (definitive) carcinogen. That judgement has remained controversial because in some studies the exposed population has not had a higher lung cancer rate than the non-exposed comparison group. Some have argued that this may be because the surface properties of silica change in different settings and may have different toxicities, so that in some cases silica may not increase lung cancer risk. However, the explanation may simply be that in some cohorts there were not enough highly exposed subjects. Our own exposure-response analysis of 10 silica exposed cohorts (60,000 workers) indicated that indeed there is a positive exposure-response for silica but that the increase in risk is seen primarily at higher exposures, and the overall slope of the exposure-response curve is relatively low compared to classic lung carcinogens such as nickel and asbestos. This relatively low slope may be the reason why it has been difficult to show that silica does indeed cause lung cancer.

Second, exposure-response data provide necessary data for regulators to conduct quantitative risk assessment. Regulators want to know the amount of excess risk incurred due to exposure at different levels, and only good exposure-response data can answer this question. For example, the US OSHA typically sets limits based on a level of exposure over a working lifetime which permits an excess risk of at most 1 per 1000 (0.1%) above background risk. The background lifetime risk of lung cancer is about 5%. OSHA would therefore seek a permissible limit for silica exposure which would allow a lifetime risk of no greater than 5.1%. The current limit for silica exposure is 0.1 mg/m³. It is clear from exposure-response analyses of silica, including the paper by Eisen and colleagues, that the current limit is too permissive. Several analyses indicate that the lifetime risk of lung cancer after 40 years of exposure at the standard results in an excess risk of the order of 1–2% rather than the goal of 0.1%.

Splines and other types of smoothing functions are a middle ground between traditional categorical analyses of exposure, which avoid any parametric assumptions and let the “data speak for itself”, and the also traditional parametric analysis which uses exposure as a continuous variable in a model in which—the investigator imposes a shape on the exposure-response curve. For example, in using logistic or Cox regression, the investigator is assuming the log of the rate ratio is a linear function of exposure. Yet this assumption requires justification, as this model may not fit the data, and a thorough search for the best model, with the best fit to the data, needs to be conducted.

Categorical analyses have their own limitations. The investigator must choose the number and placement of the cutpoints defining the categories, which may be arbitrary and which may heavily influence the apparent “shape” of the exposure-response. Furthermore within each category a categorical analysis assumes that there is a single exposure effect—that is, the rate ratio is constant across the exposure category, an obviously false assumption when the category is reasonably wide.

Smoothing functions do not impose a particular form of a simple parametric model on the data, yet avoid some of the pitfalls of categorical analysis by being less dependent on the choice of cutpoints and by providing a continuous curve which is not a step function. They are primarily useful graphically, for seeing the shape of the exposure-response curve. The shape of the curve may help provide a hint for choosing the best simple parametric model which will provide a concise summary of the exposure-response and be useful for quantitative risk assessment. One type of smoothing function, splines, may themselves be used for quantitative risk assessment, because they permit a quantitative estimation of risk for any specific level of exposure.

The idea of smoothing functions stems from using a simple moving average of ”y” across local regions of ”x”, often a weighted average in which the centre points in the region have more weight than the outermost points, and the average is calculated for one region after another as one moves across the x-axis. This produces a smooth curve in which the investigator imposes minimal constraints on the shape of the curve. Such curves have a long history, including, for example, the common moving average of the stock market calculated across time. These are non-parametric curves, in that there is no simple function with a few parameters which can summarise the curve.

Splines are an extension of this idea in which a regression of ”y” on ”x” is carried out in each local region as one moves across the ”x” axis. Cubic splines are one common type of spline in which the effect measure (for example, the log of the rate ratio) is regressed on a cubic function of exposure (the x-axis), across several different regions or categories of exposure, spanning the entire range of exposure. A single smooth curve across these regions is then produced. Penalised splines, as used by Eisen and colleagues, are another variant of splines in which there is a penalty for rapid change in slope of the curve in any given region of the x-axis. At this point it is not clear whether they offer any particular advantage over more traditional cubic or quadratic splines. The details of the difference between different types of spline functions need not overly concern investigators, as long as they understand the basic idea. Essentially the software increasingly makes spline functions available to investigators, although the epidemiologist may need a statistician’s help for such programming.

One important point of the analysis by Eisen et al is the influence of outlier observations, in this case the influence of two non-cases with very high high.
exposure values. These two controls resulted in the downward shape of the exposure-response curve in the highest regions of exposure. Eisen et al analyse their data with and without these two outliers. Without them, the curve tends to continue to increase at the highest exposures. They note that the shape of the curve at the low and medium dose region does not really change whether the outliers are included or not. This is important because it is this relatively low and medium dose region that in practice is of importance to risk assessors. It is quite likely that measurement error is greater in such extreme high dose regions where there are little data. An alternative approach, also illustrated by Eisen et al, is to consider the log of exposure rather than exposure itself. Taking the logs tends to reduce the influence of the highest exposures. A log transformation of exposure tends to result in curves in which the rate ratio tends to stop increasing or plateau at the highest exposures, a phenomenon which seems consistent with data observed for a large number of occupational carcinogens. There are a number of plausible reasons for such a plateau, including mismeasurement at highest exposures, an exhaustion of susceptibles at high exposure, and saturation of biological pathways.

Clearly it is incumbent on epidemiologists to collect as good exposure data as possible. But then the job is not over. We must use the rich exposure data to find the fullest in our exposure-response analyses, and new analysis techniques have become available for this. 


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Exposure assessment in ergonomic epidemiology: is there something specific to the assessment of biomechanical exposures?

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In recent issues of OEM, the authors of two articles in “ergonomic epidemiology” stress several necessary qualities of exposure data: they must be accurate and precise;1 and the method of exposure measurement must be reliable.2 All epidemiologists in occupational epidemiology would agree with that: absence of systematic or random error is important, stability of the measure if repeated under identical conditions is important too. Among the expected qualities of exposure data one could add “relevant”; we expect that the exposure data are consistent with what is known (or suspected) about the mechanisms underlying their effect on disease. This is less obvious than it seems; for example, in many situations one can wonder whether the relevant exposure is that of today, or that of last week, or that of 20 years ago, or the cumulative exposure over the last 20 years. Another quality (or limit) has to do with feasibility. If exposure assessment, at an individual level, is very expensive (in terms of money or time), alternative solutions have to be found if the study sample is large.

All this is common to all the fields of occupational epidemiology. However, is there something specific to the assessment of biomechanical exposures? Are the problems met when recording the time spent with the upper arm elevated above 90° very different from those met when assessing the level of past
exposure to (for example) formaldehyde or electromagnetic fields, considered as potential carcinogens?

At least the history of research in these domains is different: a decade ago, in the field of occupational risk factors for musculoskeletal disorders, some questions were not discussed: there was no debate on how to use the expertise of ergonomists or specialists in biomechanics for epidemiological studies; and there was almost no research activity on other methodological aspects such as comparisons between questionnaires and direct observation. These questions were almost absent from the first PREMUS (Prevention of Work-related Musculoskeletal disorders) conference in 1992 in Stockholm. One exception was an abstract by Winkel and colleagues from the MUSIC project, who had evaluated a questionnaire estimating physical workload.1 The situation was very different in occupational cancer research. The concept of JEM (job exposure matrix) covering an array of chemical substances, job titles, and industries, was described as early as 1980.2 Ten years ago cancer epidemiologists applied specific methods for sampling and analysis of exposure data.3 In the presentation of the results of a European concerted action on the retrospective evaluation of occupational exposures in epidemiology in 1993, Goldberg and Hémon gave more than 50 references discussing the measurement of occupational exposures in epidemiological studies.4 A reason for that early development of methods for exposure assessment could be that, for cancer, difficulties dealing with (past) assessment of exposure were obvious, which motivated occupational hygienists, epidemiologists, and also biostatisticians to find adapted solutions.

For biomechanical exposures, the (false) idea that it was enough to use the tools provided by ergonomists and specialists in biomechanics was probably widespread. However, in the last 10 years, there has been a remarkable development of research on methodological aspects of assessment of exposure to biomechanical risk factors. Several subjects have been widely studied and discussed: the limits of using job titles to assess exposure6 and various other aspects of variability of exposure measures,7 the validity of questionnaires versus observation or measures,8 the use of aggregated measures,9 the retrospective assessment of exposure,10 and others such as bias due to the presence of pain.

The two articles published recently in OEM bring interesting results in this field of research: Heinrich and colleagues’11 compared, in a study population of 87 computer workers, questionnaire data about exposure to postural load and duration of computer use with an observation of the workstation design and posture by a trained observer. They found a low agreement between the two approaches. However, they raise the question of whether the “gold standard” for postural load is the observation technique, since observation is based on short periods of time, and being observed might modify the posture.

Svendsen and colleagues12 explored an attractive approach to the assessment of upper arm elevation above 90° in machinists, car mechanics, and painters. Workers filled diaries with approximately 10 preprint tasks, and exposure was evaluated using a TEM (task exposure matrix). The diary worked well, and could be used to take into account the variability of tasks between subjects in the same job, which is a positive result. However, there was considerable within-task variability; in addition the exposure contrast between tasks was relatively small in these jobs. In this situation, spending resources on obtaining task information does not seem to be the optimal strategy.

These two studies suggest important directions for future research. The first is the development of simple techniques for assessing biomechanical exposures. There is still no consensus about the validity of questionnaire data to assess postural load.13 Improving the questionnaires by adding pictures to the questions is probably a good suggestion. It is also necessary to think about the qualities expected from a tool (such as a questionnaire) in the context of epidemiological studies. The most important qualities are not necessarily the same in epidemiology, ergonomy, or biomechanics.

The second direction deals with indirect measures such as JEMs (job exposure matrices) or TEMs (task exposure matrices). The main limitations in the development of matrices for biomechanical exposures is the variability of exposures within a job and within a task. However, this is probably the case more for some risk factors than for others. In large scale studies, JEMs might be useful to evaluate levels of exposure among all the subjects in a first step, possibly in combination with more precise assessments in specific subsamples.

In addition, adapted statistical methods should be used and developed. Multilevel models should be more widely used.14 They are adapted to situations where some data were collected at a group level, and also for repeated measures.15 Methods have also been proposed for combining expert ratings and exposure measurement techniques.

For these three aspects, the research needs are partly specific to the field of “ergonomic epidemiology”, but are also common with other fields in occupational epidemiology.

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