Development of reference limits within the scope of biological effect monitoring.
Interpersonal and intrapersonal variation
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10. GENERAL DISCUSSION

The ultimate aim of Biological Effect Monitoring (BEM), as a longitudinal periodical examination, is to prevent (chronic) negative effects within individual workers. The monitoring of personal variations of response parameters is essential for detecting significant values during BEM.

This study has been carried out to develop a procedure for estimating reference limits in order to be able to interpret the significance of a change or the difference in successive values (seen as long-term effects) within an individual worker by the occupational physician. Haematological and clinical chemical parameters are non-specific with respect to external, environmental influences or risk factors (e.g. physical demands, smoking habits). So, when developing reference limits these factors have to be taken into account. For this study this meant that, after classification of a population of ± 20,000 workers according to age, physical work demands and work schedule, 1,165 workers were available to be potential participants. Even then it was difficult to put together a study population of 200 workers divided into subgroups according to the criteria for classification. With very motivated participants and a very co-operative attitude on the part of
the local company management, we were able to complete the two year blood sampling period with 188 workers. A longer period of blood collection was not possible considering the constraint of loss of working time for the company. In two years we had to collect enough data in order to be able to estimate statistical characteristics of interpersonal and intrapersonal variations. Two years is a relatively short period of time, because in occupational health practice periods of monitoring occur half yearly, yearly or with even longer intervals. Blood collection was performed monthly, so this study was carried out with a large working population and under, relatively, ideal circumstances.

Based on nearly 24 bloodsamples per participant it was possible to calculate personal mean values, personal sd values and personal slopes for 15 haematological and clinical chemical parameters. Time-dependent effects (long-term trends) were found. However, these types of patterns could not be investigated in this study (the blood collection period was too short). The determinants of the blood parameters were examined by univariate analysis of variances.

Multivariate analysis of variance was not within the scope of this study because the purpose was not to study variances of blood constituents by determinants or combinations of determinants. The aim of investigating variances per constituent per determinant was to establish whether or not there was a need for separate reference limits. If statistically significant influences had been found then the phenomena involved should have been taken into account in developing reference limits (e.g. in assessing $s^2$ and $t^2$).
In this study which is based on statistical grounds, the examined determinants did not provide enough indication to use separate reference distributions of personal mean values and personal sd values. However, statistically significant influences of some determinants were found. Literature data on determinants of interpersonal and intrapersonal variations of blood parameters are often of limited value, as the blood sampling period, the periodicity of blood sampling or the classification of participants differ fundamentally.

Moreover, the assessments of determinants of blood constituents are based on cross-sectional instead of longitudinal studies. A fundamental problem encountered in this study was the "technical" quality (in terms of validity, reliability, precision) of questionnaires concerning e.g. psychological stress and smoking habits, so that they were suitable for longitudinal studies. A valid longitudinal assessment of such determinants is not only important for this kind of study but may also contribute to clarifying the personal coping capacity of e.g. enzyme induction expressed in longitudinal patterns of blood constituents in individual workers.

The use of the Mahalanobis distance combines the variation of periodic values of a blood constituent of an individual worker to interpersonal and intrapersonal statistical characteristics of the concerned blood constituent, found in a reference population. Neither the concept of critical differences, nor the concept of autoregressive models used in other studies, combines these elements of variation. Moreover, the procedure described in this study permits on
interpretation of a first value of a series of values of an individual worker in the light of interpersonal and intrapersonal variances of a reference population, in direct contrast to cross-sectional limits.

In general the usefulness of any reference limits as instruments for decision making is ultimately judged by their efficacy for preventive actions. This involves the discriminating power to establish two groups of ostensibly healthy workers: one which has specified signals of impending health risk and one which has not. The number of participants in each category depends on the statistical method applied, the physical overlap between the two groups and the reference limits chosen. In this study no attention was paid to the discussion about the efficacy of the proposed model. Because of the fact that the procedure for calculating values of $A_n^2$ and the procedure for establishing reference limits must be the subject of further investigation, it is necessary, in close co-operation with epidemiologists and experts in clinical medicine, to investigate and to define what should be regarded as physiological signals or early pathophysiological signals in order to prevent false positive or false negative decisions. According to Hatch (1973) it may be possible to recognise some effects before "breakdown" occurs. This would be in the zone of homoeostasis and compensation, which is the area of BEM. It is the area in which the response in the dose-response relationship will be mostly non-specific, reflecting a kind of general response. Moreover, the same value of $A_n^2$ (below or above the reference value) of several workers may not indicate the same
individual regulations of homoeostasis and compensatory mechanisms due to acquired and genetic predispositions.

The present study should be considered as a contribution to the pioneering stage of improving the methodology of periodic medical monitoring of individual workers by identification of signals of early deviation from his/her personal background reference values including their physiological variation.

The study is only one step of still many to be taken in the future, e.g. with respect to the meaningfulness of using liver and kidney protocols, proposed in 1995 by the Dutch Ministry of Social Affairs and Employment. Both protocols meet and indicate the problem of inter- and intrapersonal variation for occupational medicine as a preventive medicine.