Development of reference limits within the scope of biological effect monitoring. Interpersonal and intrapersonal variation
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9 APPLYING THE ESTABLISHED REFERENCE LIMITS

9.1 INTRODUCTION

The question is, if by using values of $A_n^2$ other measurements are detected as significant when critical differences (Costongs, 1984) or the autoregressive model (Harris, 1976) are used. For practical purposes the use of critical differences are more appropriate than the use of, e.g., the autoregressive model because critical differences are clear limits. In this section the values of $A_n^2$ of a series of Hb from a new group of workers (from the same industrial population as the reference population) have been calculated and compared to the values of $RA_n^2$. Moreover the critical difference ($d_{k90}$) between each successive value of Hb within each worker has been examined.
9.2 Method

- According to Costongs (1984) the $d_{k90}$ of Hb is 1.4 mmol/l. That means: “a change between two Hb results of 1.4 mmol/l Hb has a probability of being not pathological of 10%” (Costongs, 1984).

- Compute for each individual the value of his $A_n^2$ for series length $n$. Take the $k^{th}$ value as the first values of $n=1, 2, 3$ and 4. As long as the calculated values of $A_n^2$ do not exceed the reference limit ($RA_n^2$) the series length may increase one observation. Because $n=4$ is the maximum series length within the scope of this study, a second (third, fourth etc.) moving $A_n^2$ can be achieved.

If the value of $A_n^2$ of the $k^{th}$ value exceeds $RA_n^2$ (indicating a significant value) then the occupational physician has to make a decision about intervention. The next value is seen as the first value of a new series.

Note:

- The significant value (if analytically correct) could be coincidental or explained as a short-term reaction to a sudden stimulus (e.g. toxicological agents).

- If a significant value is not excluded from the next calculations, a significant value of $A_n^2$ may remain until the significant value does not take part in the calculations (see the definitions of $A_n^2$).
9.3 MATERIAL

Although environmental monitoring (EM) scarcely indicates an actual benzene load (the benzene values never exceed 1 ppm), values of Hb of 74 benzene workers (only men, mean age 38.6, sd 9.8 years) were sampled during the period July 1990 - January 1995.

The blood sampling conditions were the same as described in chapter 4 with one exception: the intervals within the blood sampling period were unequally spaced. The mean number of samples per benzene worker was 12. During the blood sampling intervals the individuals were evaluated by means of cross-sectional reference. The Hb data (in mmol/l) of 74 workers are presented in appendix 12.

The statistical characteristics of the Hb values of this group of workers were:

- the arithmetic mean value ($\mu$): 9.04
- the arithmetic mean value of the intrapersonal variances ($\tau_0^2$): 0.018
- the interpersonal variance ($\sigma^2$): 0.165

9.4 RESULTS

There were seven (p=0.95) workers with one or more Hb value(s) of which the values of $A_n^2$ were equal to or exceeded the reference values ($RA_n^2$), indicating significant values. Appendix 13 presents all values of $A_n^2$ per worker at significance level 95%.

The series of Hb (p=0.95) of seven workers is presented in table 41.
Table 41: The series Hb values of seven benzene workers (nrs. 24, 30, 37, 40, 51, 72, 73) (p<0.95, bold italic = significant)

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In the series, there were no values of Hb indicated by a critical difference of 1.4 mmol/l Hb ($d_{k90}$) for successive values of each benzene worker.

9.5 DISCUSSION

The use of values of RA$_n^2$ seems to be more sensitive than the use of $d_{k90}$. However, Costongs uses critical differences in combination with cross-sectional reference limits (7.5 - 11 mmol/l Hb).

The series and the significant values of Hb (p<0.95) of 7 workers are presented in table 41. These workers have one value of Hb equal to or greater than the value of RA$_n^2$ at least. Most significant values of Hb in table 41 are, as first values of a series, seen as mean values and, in comparison with $m$, significantly deviant. The reason might be that the arithmetic mean of the reference population was 9.5 mmol/l Hb, which differed significantly (t-test, p<0.05) from the arithmetic mean value.
of the 74 workers (9.0 mmol/l Hb). The difference may be due to selection bias between the two groups of workers.

The last Hb values of the employees indicated as number 24 and number 40 are outside the cross-sectional reference limits indicated by Costongs, while the last value of Mr "24" is not indicated as a significant value according to the proposed procedure. The last values of the employees numbered 37 and 73 are inside the cross-sectional reference limits, but are indicated as a significant value by the value of RA_n^2.

Except Mr "40", all workers were, according to their medical reports, in a healthy state. Mr "40" left the company because of a kidney disease.

Concerning Mr "24", his last value (7.4 mmol/l Hb) contributes to the last (8th) value of A_4^2 of the total series. The last value is not detected as a significant value because in the definition of A_4^2 the contribution of the difference between the mean of the values and m is relatively less important than the contribution of his intrapersonal variances, which seems to be not large enough to create a significant value of A_4^2.

The last values of Mr "37" and Mr. "73" (9.0 and 9.1 mmol/l Hb) are just detected as significant values because the contribution of their personal variances, concerning the last four values, is large enough to exceed the value of RA_4^2 by means of the values of the concerned A_4^2. The results demonstrate that applying the values of A_n^2 yields information useful to detecting early effects during BEM. However,
this statement has to be interpreted cautiously because, according to the discussion in section 8.5 several phenomena, which determine values of $A_n^2$, have not been examined.

9.6 SUMMARY

In light of the conclusions in section 3.3 a statistical framework has been used in order to follow the course of a longitudinal series of observed values of a quantity within a person, for our purposes a worker. The statistical procedure calculates the squared Mahalanobis distance ($A_n^2$). The values of $A_n^2$ of a worker are based on the $n$ individual absolute values of the quantity, the differences between the $n$ values and the estimated values of $m$, $\tau_0^2$ and $s^2$ of a reference population ($n=188$). Based on a reference population the reference limits are given for Hb.

The reference limits have been applied to data of a population of 74 workers who were exposed to a low level of benzene. There were seven ($p=0.95$) workers with one or more significant Hb values, whereas the method of critical differences (proposed by Costongs) in two successive values within the series of all 74 workers did not detect a single value of Hb. So the proposed method seems to be more sensitive than the cross-sectional-based reference limits and those according to Costongs’ method.