Development of reference limits within the scope of biological effect monitoring.
Interpersonal and intrapersonal variation
van Geen, F.

Citation for published version (APA):
van Geen, F. (2000). Development of reference limits within the scope of biological effect monitoring. Interpersonal and intrapersonal variation

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)

Download date: 22 Dec 2018
1 INTRODUCTION AND PROBLEM DEFINITION

1.1 INTRODUCTION

In the occupational health services field clinical laboratory blood parameters are measured in monitoring programs. When using clinical laboratory parameters the reference distribution most widely utilised is the distribution of the values of these parameters in a population of apparently healthy persons at a certain point in time. If the values can be described according to a normal distribution, the information presented to the physician usually consists of an estimate like the mean value ± twice the sd indicating the "normal" range. If the values are not normally distributed, percentiles can be used to derive reference values (Bezemer, 1981; Naus, 1982).

The primary objective of monitoring programs is prevention with an emphasis on early detection of biological effects or health impairment, causally related to the work task or working conditions such as the identification of an effect of exposure to toxic agents. The term
"effect" is defined as an exposure related biological change (WHO, 1973).

However, such monitoring programs are not equipped with a set of criteria to assess adequately the relevance of an actual level of a clinical laboratory parameter as indicator of an effect in a single worker, even when his/her value is clearly outside the above mentioned normal range e.g. of two (5% and 95%) percentiles. What to do for a single subject with an actual value much higher or lower than his/her preceding results but still within the "normal" range? The decision made by the physician is primarily of interest in the perception of the person who has been examined:

- if the decision is to take no action, then the worker will tend to perceive this as a "clean" bill of health, although the deviation might be a biological effect of exposure;
- if the decision is to take some kind of action, then the worker becomes concerned about his health (with potential negative side effect of this action), although the deviation might be a random fluctuation.

Because some variation among the values is considered acceptable from a health or from a monitoring point of view, the occupational physician should be able to interpret this variation within and between workers by means of reference limits. However, he/she will be confronted with crucial questions: how shall he/she establish acceptable standards of variation, and how will he/she establish acceptable limits to this standard by indicating the reference interval?
The definition of monitoring is: "a systematic, continuous or repetitive health related activity, designed to lead, if necessary, to corrective action" (Berlin, Yodaiken, Henman, 1984).

There are many types of monitoring. One type is Biological Effect Monitoring (BEM): "the measurement and assessment of early biological effects, of which the relationship to health impairment has not yet been established, in exposed workers to evaluate exposure and/or health risk compared to an appropriate reference" (Zielhuis, Henderson, 1986).

The description of BEM includes at least three key terms, which need to be discussed in greater detail before the BEM concept can be applied:
- early biological effects
- health
- an appropriate reference.

To show the essence of the problems surrounding BEM, it may be helpful to contrast BEM with another type of monitoring, known as Health Surveillance. Health Surveillance (HS) is "the periodic medicophysiological examination of exposed workers with the objective of protecting health and preventing occupational diseases. The detection of established disease is outside the scope of this definition." (Berlin, Yodaiken, Henman, 1984) The essential difference between the descriptions of BEM and HS is the point of departure; for HS this is the assumed presence of known (possibly
adverse) effects (including morbidity), whereas for BEM it is the
detection of "changes in physiological or biochemical functions"
which are a priori considered non-adverse, although in the context of
all data observed they may a posteriori have to be considered adverse.
According to the WHO definition (1973) of early detection of health
impairment, the detection of "changes" in physiological or
biochemical functions, can be seen as "the detection of disturbances of
homoeostatic and compensatory mechanisms while biochemical,
morphological and functional changes are still reversible."
During BEM the search for non-adverse effects implies the detection
temporary changes of physiological and/or biological functions of
self-regulatory subsystems, while there may be no interference or
impairment of functional capacities of the system. For instance,
increased enzyme-activity in the liver may indicate a cellular effect,
while the specific liver function is not (yet) impaired.
The description of non-adverse effects as a temporary change of
physiological or biochemical functions agrees very well with the
concept of homoeostasis in the physiological sense as formulated by
Claude Bernard and as a term introduced by Canon (1929):
"The constant conditions which are maintained in the body might be
termed equilibrium. That word, however, has come to have a fairly
exact meaning as applied to relatively simple physiological states in
closed systems where known forces are balanced. The co-ordinated
physiological processes, which maintain most of the steady states in
the organism that are so complex and so peculiar to living beings -
involving as they may be the brain and nerves, the heart, the lungs,
kidneys and spleen, all working co-operatively - that I have suggested a special designation for these states, homoeostasis. The word does not imply something set and immobile, a stagnation. It means a condition - a condition which may vary, but which is relatively constant."

So during BEM one acknowledges a constant dynamic interaction around a varying equilibrium within an ostensibly healthy human body. It is very difficult, however, to distinguish between random fluctuations, non-adverse effects and adverse effects due to exposure in the early phase of health impairment.

Moreover, when using for instance haematological and biochemical parameters in industrial toxicological monitoring activities, the biological response is usually not agent-specific: it usually reflects a non-specific response to toxicological and/or non-toxicological agents at and off work. A significant event may often not reflect a disturbance brought about by a single occupational agent.

In ideal circumstances BEM assumes knowledge of the conversion from physiology, including biochemistry, to the starting point of pathology. Unfortunately, this knowledge is hardly available.

In Health Surveillance the detection of an expected (possibly adverse) effect refers to the detection of impairment of functional capacities of a self-regulatory system. In accordance with this, Sherwin (1983) defined the term "adverse effect" as "the causation, promotion, facilitation and/or exacerbation of a structural and/or functional abnormality, with the impact that the abnormality has the potential of
lowering the quality of life, causing a disabling illness or leading to a premature death".

The concept of "health" in the definition of BEM can be approximated according to the criterion of workers' health applied by the Dutch National MAC Commission (1978): "a non-stable condition of the human organism, of which the functional capacities leave nothing to be desired in the worker's own opinion and/or according to health experts: pre-existing physical and mental capacities, depending on for instance age and sex, have to be taken into account; the functional conditions should be comparable to that in non-exposed, otherwise similar groups of workers in the same society: allowance should be made for the present state of the art, present-day objectives of health care, social acceptability and social habits."

In the clinical setting, measurements of e.g. blood quantities are called "normal" if the values of these measurements do not deviate from a "normal" range. However, for many clinical laboratory parameters the upper/lower limit of the "normal" interval is too insensitive to detect mild stages of a specified effect within a subject, because of the physiological/biochemical variation within and between subjects. In order to narrow this interval or range Gräsbeck and Saris (1968), (quoted in Gräsbeck R, Alström T, 1981) proposed to categorise healthy individuals. They introduced the term "reference values" in
order to discriminate between healthy and (potentially) not healthy individuals. Thus reference values have to be chosen carefully. Therefore Grärsbeck and Saris formulated conditions: "This term 'reference values' implies that the user is clearly informed how the values are generated, that is, all essential details regarding the characterisation of the reference population (for instance age, sex, genetic, social and environmental factors of the subjects), how these subjects were selected and how their health or disease was assessed, the physiological and environmental conditions under which the population was studied, the specimen collection procedure, the subsequent handling of specimens, the analytic methods used including their accuracy, sensitivity (detection limit), specificity and precision, and the calculations used."

Then the next step could be to select and describe a subpopulation.

In 1978 The International Federation of Clinical Chemistry Committee (quoted in Grärsbeck R, Alström T (1981)) introduced several definitions about references (Appendix 1).

Williams et al (1978) tested the assumption that a reference population, categorised by age and sex, yields a narrower range of variation than a larger mixed population. If this would be true, then figures based on demographic categories would yield more appropriate reference intervals or ranges than the common "normal" interval. However, their conclusion was: "the results imply the need for individual rather than population based reference ranges, even if the
latter are from persons of similar age and the same sex". This conclusion confirms Young et al's statement (1971): "Certain blood parameters depend more on personal characteristics than on broad demographic factors."

From a clinical point of view some authors (Gräsbeck and Alström, 1981) also emphasise the importance of individuality as a significant factor determining a medical fate. This statement has even greater importance in occupational medicine, which is a preventive discipline, because ideally the starting point is the description of the biological state of a person at risk before exposure.

1.2 STATEMENT OF THE PROBLEM

In monitoring a worker, using clinical laboratory indicators, deviating test results may be signals of an incompatibility between workload and human capacity. In the context of BEM these signals are seen as early effects with a priori no clear significance concerning damage to health. In this study the emphasis is on single workers in order to assess appropriate reference limits for the detection of deviating test results during BEM.

To meet this objective the following question has to be answered:
Given a series of test results of a constituent within a single person: when is it correct to conclude that an increased or decreased value of a test result is "abnormal".

This main question induces the following subquestions:

- when to use group-based cross-sectional or longitudinal reference limits and when to use individual subject-based longitudinal reference limits?
- which statistical tools are available to follow the course of a series of measurements of a single worker?
- which factors influence workers' variation of results?
- To what conditions does a reference population have to comply?
- Which adequate statistical methods are available to meet the main question?
- If there are no adequate statistical methods, what to do?