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Announcement by the Federal Environment Agency

Addendum to the Concept of Reference and Human Biomonitoring Values in Environmental Medicine

Opinion of the Human Biomonitoring Commission of the Federal Environment Agency

1 Introduction

In 1996, the Human Biomonitoring Commission of the Federal Environment Agency presented its concept for reference and human biomonitoring (HBM) values in a background paper [1]. In this paper, it is stated under “Definition of reference value”: “The reference value for a chemical substance in a body matrix (such as blood, hair, urine) is a value derived from a series of measurement results obtained from a sample of a defined population, using a predefined statistical method. This value is defined purely in statistical terms and expresses the concentration of that substance in the relevant body matrix for that group of the population at the time of analysis. It is not per se health-relevant. … Generally, it is assumed that reference values are dependent *inter alia* on the age and sex of the persons investigated and that they change over time due to a changing environmental exposure. It is necessary to consider carefully where they can be meaningfully applied.”

Under “Characterisation of the reference population”, the Commission states: “The extent to which available data from studies meet the criteria for determination of reference values must be assessed on a case-by-case basis. … Where studies with representative population samples are available, the Commission will determine reference values for the entire population. The studies used for this purpose must be based on a sufficient sample size. The sample’s characteristics must be described in detail. If these requirements are not fulfilled, the Commission will evaluate the available data set and derive, if justified, provisional reference values of questionable representativity. … Where appropriate and possible reference values will be determined for sub-groups with or without specific exposures (for example, mercury in urine of persons treated with dental amalgam, cadmium in the blood of smokers and non-smokers, lead in the blood of children and adults, blood PCP levels in case of exposure to wood preservatives in the home).”

After more than 10 years a review generally confirms the applicability of the reference value approach. The reference value concept has received international attention. Reference

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values have proved their usefulness as a basis for evaluation, they are applied as a basis for assessment and they are widely accepted in scientific community.

Nevertheless, there are some problems that have emerged in the course of the Commission's work. Limitations are related to the degree of the representativity and timeliness of the data as well as the possible need for action when the reference value is exceeded while the HBM I value is not.

2 Representativity and timeliness

A reference value indicates, by definition, the exposure of a defined group of the population at a certain point in time (i.e., the time of the study whose data were used as a basis for its derivation).

It is defined as the 95th percentile. This means that (approximately) 95% of measured values do not exceed it. The reference value should be expressed as a simple numerical value. For greater "confidence" of the 95th percentile estimate, it is recommended that the 0.95 confidence interval should be determined and indicated along with the value. Reference values should be rounded within the confidence interval [1]. The German Environmental Survey (GerES) conducted by the Federal Environment Agency provides a representative data base for the derivation of up-to-date reference values.

High variance in population exposure results in high variance in body burden and human biomonitoring measures. Under these circumstances statistical questionnaire and field investigation should be able to identify relevant sources and pathways of exposure. But, this situation is the exception, not the rule. For many substances the sensitivity of laboratory measurement has increased, the level of detection (LOD) has decreased. In consequence, the range of measurements includes more distinct low values, and for well-regulated substances a low degree of variance. In this situation it gets difficult to differentiate between exposure sources. If measurement and analytical quality of HBM values is sufficient, we might differentiate between different evaluation approaches: (a) The distribution of exposure follows a homogenous random process, i.e. the values are distributed more or less randomly (e.g. following a lognormal distribution). If the variance is low and the upper tail is far below any level of concern, there is no need for action (warning, separate information, examination). A reference value might be valid for all. (b) The distribution of analytical values indicates for two or more subgroups due to subgroup specific exposure patterns. If group membership might be identified, a stratified analysis might clarify the influence structure. It depends on the means and variances whether a unique reference value might characterize

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the total population. If one subgroup dominates the right tail of the distribution, this group should be looked at for specific exposure.

The data from each survey will become outdated over time. In addition, due to new problems the study programmes did not always include those parameters for which it would have been desirable to derive reference values. That is why the Commission in some cases had to rely on data from studies which do not fulfil the sample size and representativity criterion. The Commission has therefore called on several occasions for a periodic schedule of representative surveys generating HBM population exposure data. It has derived “reference values of questionable representativity” [1] from insufficient data.

Routinely generated data, being collected over a long period of time, are one data source used for this purpose. Such studies might reflect exposure trends over time. The available sample size is often small. An example is the data set for pesticides and some organochlorine compounds in human breast milk specimens. The available specimens do not come from a representative survey – instead they stem from females who had agreed spontaneously to take part in the study. The analyses give indication of a decreasing trend in exposure levels. Likewise, data from the German Environmental Specimen Bank only reflect a small and not representative part of the total population (currently, 20- to 30-year-old medical students at four German universities), they are definitely not representative for the total population. They can, however, give indication of changes in exposure conditions and body burdens over time.

For many xenobiotic substances, food is the main route of intake. Local soil and dust pollution might cause contamination of home-grown vegetables or fruit and by this might be an exposure source for domestic animals (e.g., chickens in the exposure chain soil/eggs). Locally and home grown foods mostly play only a minor role in total nutrition. Most groups of products are obtained from supra-regional suppliers. Exposure via food from major marketing and distribution chains can be assumed not to differ significantly over regions. Provided the sample is large enough, provisional reference values might be derived from regional data. If the main exposure sources and exposure behaviour is similar over regions it is unlikely that the exposure level and the body burden will differ significantly from reference values generated “lege artis”. Provisional reference values might be derived under these restrictions, but it will remain necessary to take into account systematic age-, gender-, regional-, and subgroup-specific differences.

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3 Minimum requirements concerning sample size

Data used to derive reference values "…must be based on a sample sufficient in size from a statistical perspective…" [1]. Information as to what sample size should be regarded as "sufficient" differs from author to author. Referring to Reed et al. [3], the National Committee on Clinical Laboratory Standards (NCCLS) [2] mentions a minimum sample size of 120 observations. Given some stratification (for example, separate values for women and men or values stratified by age) this minimal requirement would also hold for each individual sub-group. The Xprob project group [4] decided to derive no exposure factors with 95% quantiles if less than 72 measurement results were available for the sub-group to be characterised. From this it follows that the necessary total sample size increases with the number of sub-groups of interest. Non-parametric derivation of 95% reference values and their confidence intervals is recommended whenever (a) a large proportion of values is below detection limit or (b) if the values from the sample to be characterised stem from inhomogeneous populations. If data from different laboratories are used for the derivation of reference values, the comparability of the analytical methods as well as the limits of detection must be taken into account, respectively.

For the derivation of reference values, the upper tail of the distribution will be of primary interest. If measurement results greater than the level of detection are available for at least 10% of specimens and the size of the sample is sufficient, a reference value can be formally derived. Whether the application of such a reference value is recommended must be evaluated on a case-by-case basis.

As a standard reporting format for reference values, the HBM Commission recommended to give information about the sample size, the proportion of measurement results above the detection limit (LOD), the concentration range (minimum value – maximum value), the median, the 95^{th} percentile and – if available – the confidence interval of the 95^{th} percentile.

4 Distribution of exposure within the population

Differences in environmental exposure burden contribute to differences in human body burdens. Human exposure due to the contamination of environmental media occurs through contact and uptake of the relevant pollutant by ingestion, inhalation or through the skin. Exposure is influenced by factors that show inter-individual variability, depending for example on age, sex, social status and behaviour. Exposure results in a measurable increase in the concentration of substance or metabolite (metabolites might be in body tissues or fluids). Exposure can be identified in HBM analyses and described via concentration levels in suitable matrices (blood, urine, etc.).

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If the upper tail of the distribution scatters widely, it may be assumed, taking analytical uncertainty into account, that the 95th percentile and hence the indicated reference value will be uncertain. If measured levels are very low overall, such a distribution would not, however, suggest that persons with levels above the 95th percentile experienced a specific exposure situation. If, on the other hand, individual high values are found in the upper area of the distribution, it may be suspected that the exposure is distributed unevenly among the population. In that case, exceedance of the 95th percentile could be an important indication of the presence of a particular exposure situation, for example specific exposure conditions for sub-groups of the population. It could also indicate the emergence of a new exposure, for example due to the use of a new substance or product by a subgroup. In situations with the majority of measurements below the level of detection (LOD), the occurrence of a group of measurement values greater than the LOD might give indication of specific exposure conditions. As with reference values in general, it would not be possible to draw any conclusions about the health-relevance of such an indication of exposure.

Whenever less than 50 percent of measurement results are above the detection limit, the Commission will, from a pragmatic viewpoint, decide on a case-by-case basis whether the derivation of a reference value is appropriate. For some substances, reference values cannot be derived because concentrations in specimens are mostly below the detection limit. If there is reliable and confirmed evidence for a given population sample that measured concentrations of a substance in blood and urine are above detection limit, this will suggest that some population subgroup(s) experience a specific, above-background exposure. Where HBM analyses produce systematic evidence of the presence of specific exposure groups, it will – where possible and appropriate – propose preventive measures to reduce that exposure (e.g. recommendations for behaviour and consumption, advisory information to reduce pollution of specific environmental media).

5 Assessment by the Commission

The Commission continues to see a great need for up-to-date HBM reference values for substances that are relevant to environmental medicine and evaluation. It sees at the same time an emerging lack of representative survey data that are suitable for deriving and updating reference values with sufficient representativeness for the German population. It has concluded that if the derivation of reference values is to be continued, an inevitable consequence will be a lack of representativity as well as up-to-dateness. Whether the well-established term “reference value” should be retained in these circumstances is under consideration. Since assessment on the basis of reference values has proved its value, the

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Commission recommends that the term “reference value” should be retained for future values only if the data on which they are based on give reason to expect that they can be applied in practice in the same way like reference values.

The Commission underlines its call on the Federal Environment Agency as well as on national and international research bodies to continue, to initiate and to implement suitable surveys. Only these data sets, applying appropriate laboratory measurements, give indication of population exposure to substances that are relevant to environmental health evaluation.

6 Need for action when reference value is exceeded

Reference values are statistically derived values, which have no toxicological and therefore no direct health evaluation background [1]. HBM values, on the other hand, are toxicology-based. Hence, only if HBM values are exceeded action will be warranted under toxicological aspects. No action will be necessary from a toxicological perspective if concentrations are below the HBM I value.

In practice, reference values are taken into account in the exposure and risk assessment. This holds especially in situations where the measured value is higher than the reference value but does not exceed the HBM I value. The same situation is given if HBM I values are not derived since the substances are considered as carcinogenic or no-threshold for effect is known.

In the opinion of the Commission, the following aspects should be considered in such a situation:
On the one hand, there will be no urgent need for action from a toxicological perspective if the HBM I value is not exceeded.
On the other hand, exceedance of the reference value indicates that an internal exposure is higher than “usual”, the measured value in that sense “stands out”. If the measurement value refers to a toxic substance exposure, the obvious response from the perspective of environmental hygiene and preventive medicine will be to consider whether this exposure can be reduced as far as reasonably possible. It should be clarified whether a conspicuous source exists and if it can be avoided. Otherwise other explanations for this “unusually high” value should be checked.

The persons concerned must be informed about the “outlying” character of the measured value and its evaluation. Some thoughts should be given to whether and what measures

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could be taken to clarify the source of exposure and how to avoid it. The intensity of these efforts will depend on how strong the test person's subjective concern is and on whether this concern might affect adversely his or her well-being. Despite the absence of a toxicological risk, measures may need to be taken in individual cases. Reasons of environmental hygiene and prevention, but also health aspects, following a broad interpretation of the concept of "health" as put forward by the WHO [5] might justify this procedure.

The above-mentioned aspects apply primarily to individual findings. In the case of exceeding values for groups of persons, an additional aspect must be considered. It should be checked (a) if samples stem from a certain area, (b) if they occurred after certain exposure events or (c) if an increase of exposure started at a specific time. This might provide an indication of a potential general problem even if the HBM I value is not or rarely exceeded.

What applies to both individual and group-based findings when reference values are exceeded but HBM values are not, is that no urgent need exists to take immediate measures. In such a situation, the persons or population groups affected should be properly informed as soon as possible in such a way that no excessive concern arises. When considering possible exposure abatement measures, the costs for such measures should be weighed up against the expected benefits and potential consequent risks.

For many substances, reference values can be identified. This does not hold for HBM values because the available toxicological data are not (yet) sufficient or because the existing dose-effect relationship does not allow the identification of an exposure level that is safe in the long term. In such cases, as in general, unnecessary exposures should be avoided for precautionary reasons. This rule should apply even when the present or expected exposure is within a reference range at which adverse health effects are not known or are not expected from a toxicological perspective.

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4 UBA, Umweltbundesamt: Xprob project: www.umweltbundesamt.de/gesundheit/methoden/xprob.htm

5 WHO, World Health Organization: www.who.int/governance/eb/who_constitution_en.pdf