

Derivation of human biomonitoring (HBM) values based on tolerable intake doses.

Part II: Rationale and way of derivation

Opinion of the Human Biomonitoring Commission of the German Federal Environment Agency (Umweltbundesamt)

1 Introduction

Up to now, the Human Biomonitoring Commission of Germany's Federal Environment Agency (Umweltbundesamt) has established reference values (i.e. statistically derived values) for 23 chemical substances and human biomonitoring values (based on toxicological/epidemiological data) for four chemical substances [1].

Human biomonitoring (HBM) values are generally derived using published studies that investigate health-relevant effects of hazardous chemicals in humans as a starting point [2, 3]. For many substances, however, adequate data from studies in humans are lacking. Nevertheless, there is often an urgent need of toxicology-based criteria for assessing human biomonitoring data.

Supplementary to the methods currently used, the derivation of HBM values may be based on acceptable or tolerable doses published by broadly accepted expert groups or organisations. Such dose values could be, e.g., ADI (acceptable daily intake) or TDI (tolerable daily intake) values. The present report describes such a way of derivation and its application to di(2-ethylhexyl)phthalate (DEHP) [4].

2 Rationale

2.1 Starting point

ADI and TDI are defined as follows in a report on a WHO/IPCS project (WHO: World Health Organization; IPCS: International Programme on Chemical Safety) [5]:

Acceptable Daily Intake (ADI):

“Estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub)population may be exposed daily over their lifetimes without appreciable health risk .”

Tolerable Daily Intake (TDI):

“Analogous to Acceptable daily intake. The term ‘tolerable’ is used for agents that are not deliberately added, such as contaminants in food.”

As a related term¹, “reference dose” is used and defined as follows [5]:

Reference dose:

“An estimate of the daily exposure dose that is likely to be without deleterious effect even if continued exposure occurs over a lifetime.”

The approach based on daily intake comes from regulations on food. ADI and TDI values have been derived by the Joint FAO/WHO Expert Meeting on Pesticide Residues (JMPR) and the Joint FAO/WHO Expert Committee for Food Additives, Veterinary Drugs and Contaminants (JECFA) [6].

These derived values are generally based on results of animal investigations with oral exposure, i.e. exposure via the gastrointestinal tract. Following resorption, the substances under study are transported via the portal vein to the liver and then distributed in the body by blood circulation. This liver passage can induce the so-called first pass effect². This could - among other effects - alter the balance between non-metabolized and metabolized fractions of the substance under study. Human biomonitoring reflects all exposure pathways, thus the possibility of a first pass effect must be taken into account when considering whether or not an HBM value can be derived based on ADI/TDI values.

¹ “Related term” suggests that the wording *without appreciable risk* may be used by WHO/IPCS synonymously to *without deleterious effect* .

² The effects of oral and inhalative exposure may differ for substances whose toxicity is altered by metabolic processes in the liver which lead to increased or reduced toxicity. In the case of inhalative exposure, part of the resorbed substance is distributed via blood circulation without the metabolic changes in the liver which they would have been subject to in the case of oral exposure.

Toxicology-based values defined by other groups or organisations can also be used as a basis for deriving HBM values, provided that deriving procedures used and protection levels chosen are comparable with those mentioned above.

2.2 Exposure periods

Generally, separate HBM values for adults and children are specified. In principle, ADI and TDI values are by definition related to lifelong exposure. On the other hand, the definition of ADI also refers to “individuals in a (sub)population”. Acceptable / tolerable daily intake doses differing for various age groups are incompatible with the lifetime paradigm if it is applied rigorously. In order to avoid this problem, the term “tolerable intake” is used for shorter exposure periods and is defined as follows:

Tolerable intake (TI):

“Estimated maximum amount of an agent, expressed on a body mass basis, to which each individual in a (sub)population may be exposed over a specified period without appreciable risk.”

Hence in contrast to acceptable/tolerable daily intake, which refers to exposure over the course of an entire lifetime, tolerable intake (TI) may be applied to different exposure periods, too.

The use of tolerable intake as a starting point allows for the derivation of values for specific age groups and periods, thus expanding the scope of the method described in the present report.

2.3 Intended protection level

A Human Biomonitoring Commission report defines the HBM I value as follows [2, cf. 3]:

“The HBM-I-value corresponds to the concentration of a substance in human biological material below which – according to the Commission’s current assessment - adverse health effects are not expected. In this case, there is no need for action. At a concentration level higher than the HBM I (and lower than the HBM II value), the result should be verified by further measurements. If these measurements confirm

the initial result, potential sources of exposure should be found and minimised or eliminated where necessary and achievable with adequate and proportionate effort.”

It therefore follows that the protection levels intended by the tolerable intake values mentioned in sections 2.1 and 2.2 correspond to the protection level intended by the HBM I value, since under toxicological aspects no measures have to be taken if both tolerable intake values and HBM I values are not exceeded.

2.4 Prerequisites for the derivation and application of HBM values based on tolerable intake

In the view of the Human Biomonitoring Commission, HBM values can and should be derived on the basis of tolerable intake doses for a specific substance or its metabolites and applied if the following data and methodological requirements are met:

- A nationally and or internationally recognized tolerable intake value such as ADI, TDI or TI must be available for the target substance.
- Basic substance-/metabolite-specific human toxicokinetic data must be available for, e.g., resorption, metabolism, elimination rate, and the known intake-excretion ratio, including known intra- and interindividual differences (age and gender).
- A reliable and sufficiently sensitive assay method for the target substance or its metabolites must be available in a readily accessible human biological matrix (generally blood/serum/plasma³ or urine).

There is an essential prerequisite for the HBM value derivation way described here. The concentration of a target substance A measured in blood or urine⁴ must reflect reasonably accurately the amount of substance A which would result in the same concentration if regularly ingested, taking adequately into account the temporal concentration course. Likewise, if the concentrations of one or more metabolites of target substance A are measured, in lieu of the substance itself, such concentrations must likewise indicate the amount of the target substance A that was ingested.

³ In the remainder of the present text, the term *blood* refers to blood, serum or plasma.

⁴ Only these two media are discussed in the present report.

Generally, the derivation of HBM values is based on the assumption that an equilibrium between intake and concentration/excretion has been established in the body matrix at the time the sample to be analysed is taken.

3 Way of derivation

3.1 From a tolerable intake value to the HBM value

In human biomonitoring, the concentration of a substance or the metabolite(s) thereof in blood or urine is used and understood as a biomarker of exposure. Figure 1 illustrates the process involving intake, resorption, distribution, metabolism and elimination of a substance (shorter arrows), and indicates the retrograde calculation of the amount originally ingested on the basis of the concentration in the target body matrix (longer arrows).

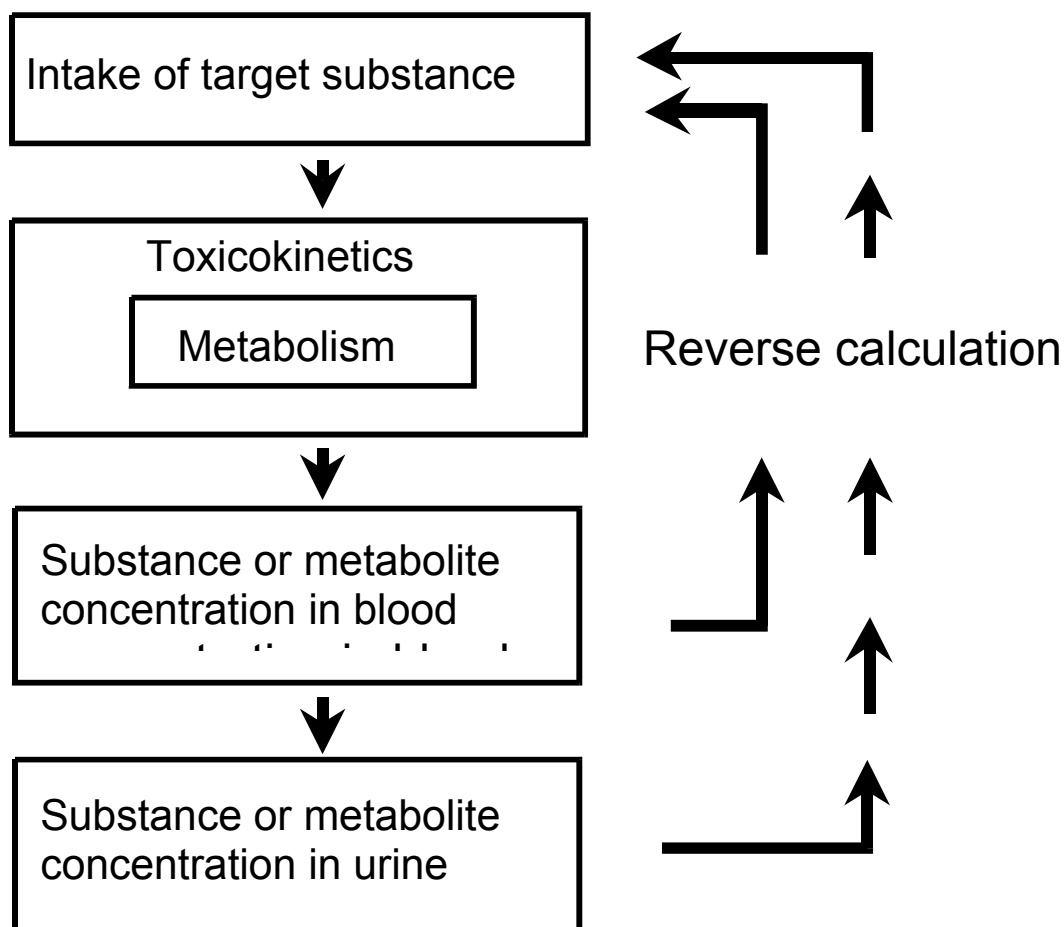


Figure 1: Relationship between substance intake and blood/urine concentration following distribution/metabolism and reverse intake calculation.

If the regularly ingested dose is equal to the tolerable intake value, following establishment of an equilibrium, a specific exposure biomarker concentration X will be found in the body matrix analysed (i.e. blood or urine) which corresponds to this specific tolerable exposure level.

3.2 Preconditions for the way of derivation of HBM values based on tolerable intake

The HBM value derivation that uses tolerable intake as a starting point is based on the reverse calculation from an exposure biomarker concentration (i.e. the concentration of a chemical substance itself or its metabolites in blood or urine) to the corresponding intake.

This approach is valid insofar as the following conditions are met:

- Proportionality: In steady state, there must be a correlation in the target concentration range between intake and exposure marker concentration (initial substance or its metabolites) in the blood or urine. This correlation would ideally be a linear one. At least, increased intake must result in a higher exposure marker concentration, and lower intake must result in a lower concentration. This correlation must hold true for all population groups to which the derived HBM values are meant to apply.
- Specificity: No circumstances should be present that could question the quantitative conclusions concerning substance intake that are based on the exposure biomarker concentrations. Such circumstances include the following:
 - Substantial changes in metabolism or excretion of the exposure marker caused by the intake of other unknown/non-measured substances
 - In cases where the target substance is not the only source of the measured exposure marker, i.e. the biomarker measured is also a metabolic product from by substances other than the target substance.

3.3 Reference to body weight

Regular intake of a specific substance results in an equilibrium between daily intake and blood concentration as follows:

Daily resorbed dose/clearance = equilibrated blood concentration.

If the clearance or elimination rate and the distribution volume for the target substance are constant and the equilibrium described above is maintained, the dose can be extrapolated directly. In such cases, the blood concentration of the substance is proportional to intake per kilogram of body weight.

However, urine volumes (unlike blood samples) can vary considerably. Thus, deriving HBM values based on 24-hour urine samples would be favourable and reasonable if daily intake is the starting point for the derivation. Unfortunately, 24-h sampling is rather impracticable. Hence allowance must be made for this variability in investigating substance concentrations in morning or spot urine samples. Although reference to the creatinine concentration in urine is widely used for normalizing, it does not fully compensate for variations in urine volume over time [7].

ADI, TDI and TI values are expressed as doses related to body weight⁵, and urine volume and body weight are correlated [8]. Therefore, derivation of HBM values can be simplified by referring to the urine volume per kg body weight. This approach does not require additional assumptions, and the derivation of HBM values for specific age or gender groups is relatively simple. For urine volume, the following values can be applied in such cases:

Children	30 ml/day/kg body weight
Adults	20 ml/day/kg body weight

Using the correlation between daily urine excretion and body weight obviates the need to define a specific child/adult or male/female body weight when deriving HBM values.

3.4 Extrapolation factors considered and additional ones to be considered

Derivations of tolerable intake consider interindividual and interspecies differences. Such determinations should also have taken into account male/female and child/adult toxicity differences. If this is not the case, the use of additional extrapolation factors

⁵ In this text the term body weight is used despite the fact that body mass is actually meant, according to the common usage.

might be considered. However, under normal circumstances no additional extrapolation factors are required.

4 Conclusions

If the aforementioned prerequisites are fulfilled, the procedure described here opens an additional way of HBM value derivation. According to the definition of HBM values [2], a value derived using this procedure is considered to be an HBM I value. However, HBM II values cannot be derived directly using this method.

Nevertheless, if sufficient data are available, HBM values should continue to be derived on the basis of empirical correlations between the concentration of a substance or its metabolites in blood/urine and adverse health effects.

5 References

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