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# The importance of inclusion of kinetic information in the extrapolation of high-to-low concentrations for human limit setting

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ABSTRACT

Human health risk assessment of inhalation exposures generally includes a high-to-low concentration extrapolation. Although this is a common step in human risk assessment, it introduces various uncertainties. One of these uncertainties is related to the toxicokinetics. Many kinetic processes such as absorption, metabolism or excretion can be subject to saturation at high concentration levels. In the presence of saturable kinetic processes of the parent compound or metabolites, disproportionate increases in internal blood or tissue concentration relative to the external concentration administered may occur resulting in nonlinear kinetics.

The present paper critically reviews human health risk assessment of inhalation exposure. More specific, it emphasizes the importance of kinetic information for the determination of a safe exposure in human risk assessment of inhalation exposures assessed by conversion from a high animal exposure to a low exposure in humans. For two selected chemicals, *i.e.* methyl tert-butyl ether and 1,2-dichloroethane, PBTK-modelling was used, for illustrative purposes, to follow the extrapolation and conversion steps as performed in existing risk assessments for these chemicals.

Human health-based limit values based on an external dose metric without sufficient knowledge on kinetics might be too high to be sufficiently protective. Insight in the actual internal exposure, the toxic agent, the appropriate dose metric, and whether an effect is related to internal concentration or dose is important. Without this, application of assessment factors on an external dose metric and the conversion to continuous exposure results in an uncertain human health risk assessment of inhalation exposures.

## 1. Introduction

### 1.1. High-to-low concentration extrapolation

In inhalation toxicity studies, the applied concentrations are generally chosen such that the highest concentrations (combined with a specific exposure duration, in general 6 h/d for an inhalation study) induce toxicity. In practice, experimental animals are usually exposed to concentration levels which vary over one order of magnitude. In addition, the experimental animal concentration levels are in most cases significantly higher than the human exposure levels. This illustrates the need to apply a high-to-low concentration extrapolation in human risk assessment. In order to derive a human health-based limit value, *i.e.* the human concentration level, related to a specific exposure duration, likely to be without adverse effects, extrapolation is performed in general over two orders of magnitude by application of one or more assessment factors. In this way a high animal concentration related to the most relevant toxicological endpoint in the animal toxicity study (being a NOAEC (No-Observed-Adverse-Effect-Concentration) or a BMCL (lower 95% confidence limit of the benchmark concentration)) is converted into a substantial lower human concentration level likely to be without adverse effects.

Although high-to-low concentration extrapolation is a common step in human risk assessment, it introduces various uncertainties. One of these uncertainties is related to the toxicokinetics of the specific chemical. Many kinetic processes such as absorption, metabolism or excretion can be subject to saturation at high exposure levels, while the threshold for saturation may be species-dependent. In the presence of saturable kinetic processes, disproportionate increases in internal blood or tissue concentration relative to the external concentration may occur resulting in nonlinear kinetics. For example Åstrand et al. illustrated that high inhalation exposure to trichloroethylene during rest and

*Abbreviations:* ADME, absorption, distribution, metabolism and excretion; AUC, area under the blood/plasma concentration time curve; BMDL, lower 95% confidence limit of the benchmark dose; $C_{max}$, maximum blood/plasma concentration; NOAEL, no-observed-adverse-effect-level; PBTK, physiologically based toxicokinetic; POD, point of departure; TK, toxicokinetics

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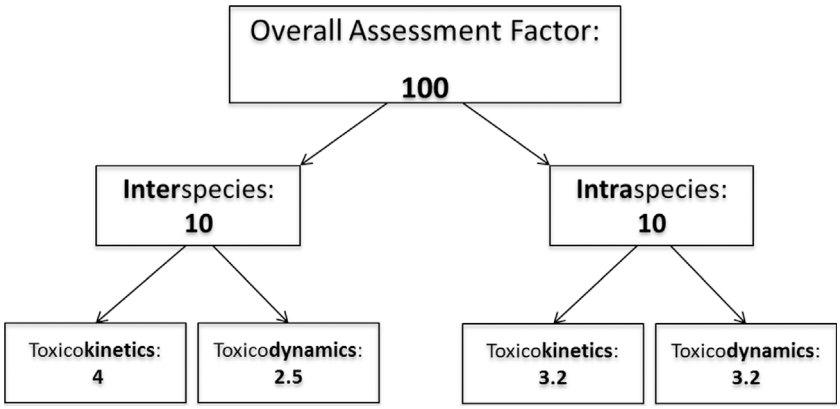


**Fig. 1.** Build-up of the total default assessment factor compensating for inter-and intra-species differences in toxicokinetics and toxicodynamics (WHO, 2005).

exercise on bicycle ergometers resulted in venous blood concentrations approaching the arterial blood concentrations, probably resulting from saturation of uptake in tissues. Consequently, this may lead to exhalation of a near equal amount as is inhaled resulting in a declined pulmonary uptake in specific individual subjects (Astrand and Ovrum, 1976). Further, saturation of metabolism will affect the internal time profile of the parent compound vs. metabolites. An important issue which then comes in is whether the saturable pathway results in bioactivation or detoxification of the chemical. In other words, is the toxic agent the parent compound or one of its metabolites? For example, in setting acute exposure guideline levels (AEGLs) for methylene chloride, saturation of metabolism (*i.e.*, formation of carboxy hemoglobin) was previously taken into account using PBTK modelling (Bos et al., 2006).

### 1.2. Risk assessment of inhalation exposure

In addition to high-to-low concentration extrapolation the inhalation risk assessment contains several additional issues, some of which are unique for inhalation. These issues will be briefly described in this section.

Toxicity following inhalation exposure is the result of the exposure concentration in combination with the exposure duration. Although in risk assessment of inhalation exposure, the focus is generally on the total exposure, *i.e.*, the product of concentration and time: $C \times t$, it is the specific combination of exposure duration and concentration that often determines the outcome of health effects. For instance, it is assumed that a 1-h exposure to 800 ppm will result in similar toxicity as an 8-h exposure to 100 ppm; an assumption also known as Haber's Law (Haber, 1924). Haber's Law states that the product of concentration and time determines the toxicity outcome, i.e., $C \times t$ for a given chemical always results in similar toxicity. However, this assumption does not apply to many chemicals and or endpoints of toxicity. A better description is that the toxicity is determined by $C^n \times t$, in which n may range from 1 to 3 (ten Berge et al., 1986). For some endpoints, exposure duration is of limited importance and the toxicity outcome is predominantly determined by the concentration. This is acknowledged within the framework of AEGL derivation (See for more information: https://www.epa.gov/sites/production/files/2015-09/documents/sop_final_standing_operating_procedures_2001.pdf (AEGL, 2001)). The rate at which a chemical enters the systemic circulation is therefore an important aspect to be taken into account in the risk assessment.

A specific issue for risk assessment of inhalation exposures for the general population is straightforward conversion from intermittent to continuous exposure. For example, for the general population an exposure of 6 h/d, 5d/wk as applied in general in an animal experiment is linearly extrapolated to a 24 h/d, 7d/wk exposure, which is also based on application of Haber's Law. The question then is how this approach influences the internal exposure, *i.e.* whether a change on an external level reflects the same change on an internal level. In this manuscript, the term *total exposure* refers to the product of exposure concentration and exposure duration on a week-basis. A second point in this step is that conversion to continuous exposure also implies that potential recovery during periods without exposure have disappeared. A standard animal inhalation study exposure of 6 h/d, 5d/wk includes daily 18 h recovery periods during weekdays and a full two-day recovery period during the weekend. Converting this intermittent animal exposure to a continuous human exposure (*i.e.* 24 h/d; 7d/wk) will exclude potential recovery in the human exposure situation.

Although kinetics is implicitly included in a toxicity study (*i.e.* as the kinetics contributes to the toxic response), potential interspecies differences in kinetics (i.e. between experimental animal and man) are important to consider in human risk assessment, thus also when extrapolating from high-to-low concentrations or when converting from intermittent to continuous exposure and should preferably be taken into account. Information on toxicokinetics is therefore considered essential for a reliable risk assessment.

### 1.3. Assessment factors and dose metrics in risk assessment

Human risk assessments include the application of default assessment factors for interspecies and intraspecies differences in toxicokinetics and toxicodynamics on an external dose metric (WHO, 2005). These interspecies and intraspecies extrapolation steps are thought to account for differences in systemic exposure and susceptibility between the test animal and the average human and between the average human and the most sensitive human, respectively. Fig. 1 presents the WHO default approach towards the general build-up of these assessment factors (WHO, 2005). Considering that the internal exposure is the critical measure for the ultimate systemic adverse health effects, applying assessment factors on an appropriate internal dose metric would be the preferred approach, but in general not applicable. Without insight in the kinetics it is unknown whether the application of assessment factors on the external dose metric (*e.g.*, an overall factor of 100, consisting of default factors of 4 and 3.2 for interspecies and intraspecies differences in toxicokinetic, respectively; see Fig. 1) has a quantitatively similar effect on the internal dose metric.

A first step in assessing internal dose levels would be obtaining information on the extent of absorption (*i.e.*, absorption fractions), and using these fractions in order to correct the critical external dose levels (NOAEL or BMDL) for the relative availability. Next, the most preferred internal dose metric remains to be determined. The question is whether the critical toxicity endpoint is related to an internal dose metric such as the AUC (area under the blood/plasma concentration time (C,t) curve) or $C_{max}$ (maximal blood/plasma concentration), or a combination of both. Hereto, data on the mode of action would be considered most valuable though in most cases not available.