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Guidelines for application of chemical-specific adjustment factors in dose/concentration–response assessment

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Abstract

This manuscript addresses guidance in the use of kinetic and dynamic data to inform quantitatively extrapolations for interspecies differences and human variability in dose–response assessment developed in a project of the International Programme on Chemical Safety (IPCS) initiative on *Harmonisation of Approaches to the Assessment of Risk from Exposure to Chemicals*. The guidance has been developed and refined through a series of planning and technical meetings and larger workshops of a broad range of participants from academia, government agencies and the private sector. The guidance for adequacy of data for replacement of common defaults for interspecies differences and human variability is presented in the context of several generic categories including: determination of the active chemical species, choice of the appropriate metric (kinetic components) or endpoint (dynamic components) and nature of experimental data, the latter which includes reference to the relevance of population, route and dose and the adequacy of the number of subjects/samples. The principal objective of this guidance developed primarily as a resource for risk assessors, is to foster better understanding of the components of and criteria for adequacy of chemical-specific data to quantitate interspecies differences and human variability in kinetics and dynamics. It is anticipated that this guidance will also encourage the development of appropriate data and facilitate their incorporation in a consistent fashion in dose–response assessment for regulatory purposes (IPCS, 2001).

Keywords: Chemical-specific adjustment factors; Toxicokinetics; Toxicodynamics; Interspecies differences; Human variability; Uncertainty factor

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1. Introduction

This manuscript addresses the development of guidance for the consideration of kinetic and dynamic data as a basis for replacement of default values for interspecies differences and human variability in dose–response analyses through the application of chemical specific adjustment factors (CSAFs). CSAFs represent part of a broader continuum of approaches which incorporate increasing amounts of data to reduce uncertainty, ranging from default ('presumed protective') to more 'biologically-based predictive' (Meek, 2001).

This guidance is being developed in one of the projects of the initiative of the International Programme on Chemical Safety (IPCS) on *Harmonisation of Approaches to the Assessment of Risk from Exposure to Chemicals*. Principal objectives of the project include fostering of better understanding of the components of uncertainty relevant to assessment of interspecies differences and human variability and greater consistency in the evaluation of the adequacy of quantitative kinetic and dynamic data as a basis to replace default in these areas. A better common understanding of the appropriate nature of relevant data should also facilitate development and incorporation of such information in dose–response assessment for regulatory purposes.

The outcome of a small meeting of the authors convened in March, 1999, to formulate some thoughts as a basis for preliminary guidance (Meek et al., 1999) was refined in the context of a series of fictitious but realistic case studies on specific chemicals at a much larger IPCS workshop on *Human Variability and Uncertainty in Risk Assessment* held in Berlin, Germany, in May, 2000 and discussed further at a drafting meeting in Ottawa in August, 2000. Based on the outcome of this series of meetings, a more detailed guidance document including illustrative case examples was prepared and is now posted at the IPCS harmonization website (IPCS, 2001).

2. Framework for development of CSAFs

Tolerable intakes or concentrations are based on approximation of 'subthreshold' concentrations through division of a no-observed-(adverse)-effect level or benchmark dose/concentration (i.e. effects without measurable or small responses) for critical effects most often in animals by an uncertainty factor. The factor is generally the product principally of two 10-fold factors, one for interspecies differences (i.e. the variation in response between animals and a representative healthy human population) and one for inter-individual variability in humans (the variation in response between a representative healthy human population and sensitive subgroups) (IPCS, 1994).

Renwick (1993) proposed a framework to subdivide these factors to address kinetics and dynamics separately, which was subsequently modified by an international review group (IPCS, 1994). Quantitation of this subdivision is supported by data on kinetic parameters and pharmacokinetic–pharmacodynamic modeling for a range of pharmacological and therapeutic responses to pharmaceutical agents (Renwick, 1993; Renwick and Lazarus, 1998). This framework allows the incorporation of quantitative chemical-specific data, relating to either toxicokinetics or toxicodynamics, to replace part of the usual 100-fold uncertainty factor but collapses back to the usual 100-fold default in the absence of appropriate data (Fig. 1).

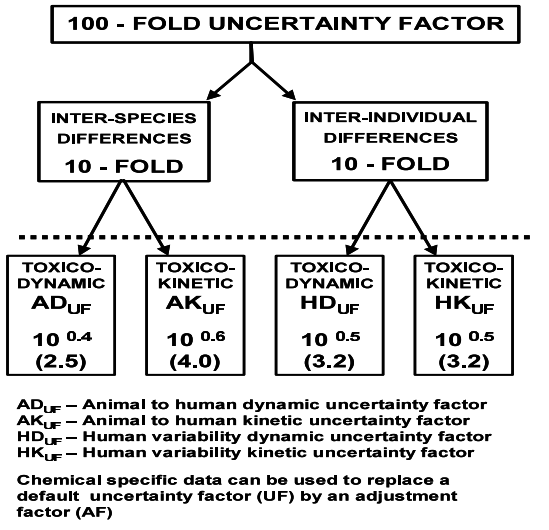

Fig. 1. The sub-division of the 100-fold fold uncertainty factor to allow chemical-specific data to replace part of the default factor.

In the context of the framework for development of CSAFs, 'toxicokinetics' relates to the movement of the chemical around the body (i.e. the absorption, distribution, metabolism and excretion of the compound). 'Toxicodynamics' relates specifically to the processes occurring in the target tissue(s). In the text which follows, application of the framework for development of CSAF is described in the context of the nature of data relevant to replace default for its four components and relevant guidance concerning adequacy.

3. Chemical-specific animal to human toxicokinetic adjustment factor—[AK_{AF}]

The chemical-specific adjustment factor for this component is a ratio in humans and animals of a measurable metric for internal exposure to the active compound such as area under the curve (AUC), C_{max} or clearance. This is generally determined on the basis of comparison of the results of in vivo kinetic studies with the active compound both in animals and a representative sample of the healthy human population.

4. Chemical-specific animal to human toxicodynamic adjustment factor—[AD_{AF}]

The chemical-specific adjustment factor for this component is a ratio of the dose which induces the critical toxic effect or a measurable related response of defined magnitude in animals and a representative sample of the healthy human population. Data that inform this adjustment factor are those that define relative target site sensitivity directly, without any toxicokinetic influences such as kinetic–dynamic link models. More often, they are based on comparative effects of the active compound in animal and human tissues in vitro. At its simplest, the replacement to the default factor for interspecies differences in dynamics is the ratio of the effective concentrations in animal versus human tissues (e.g. $EC_{10animal}/EC_{10human}$).

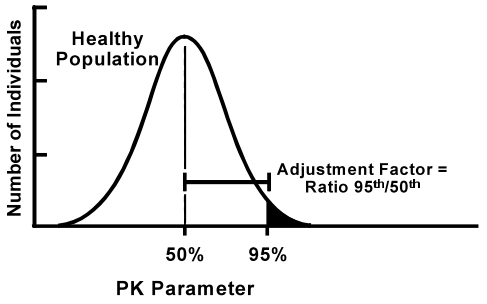

Fig. 2. Development of CSAF based on Population Distribution of Relevant Kinetic Parameter—Unimodal Population.

5. Chemical-specific human variability toxicokinetic adjustment factor—[HK_{AF}]

This adjustment factor could potentially be addressed on the basis of in vivo kinetic studies in a sufficiently broad range of subgroups of healthy and potentially susceptible populations to adequately define the population distribution. However, since this may not be practicable or even possible, more often, factors responsible for the clearance mechanisms are identified (renal clearance, CYP-specific metabolism, etc.) and a chemical-specific adjustment factor derived based on measured or PBPK modelled human variability in the relevant physiological and biochemical parameters. The population distribution for the relevant metric (e.g. AUC, C_{max}, renal clearance) for the active entity is analyzed and the CSAF (HK_{AF}) calculated as the difference between the central values for the main group and given percentiles (such as 95th, 97.5th and 99th) for the whole population (Fig. 2). These differences are

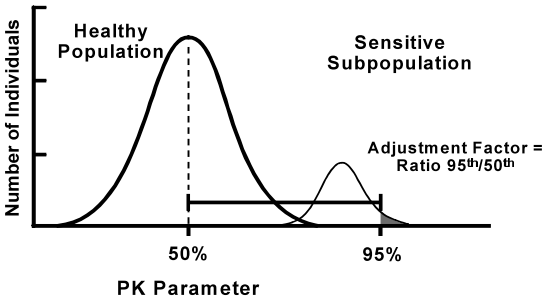

Fig. 3. Development of CSAF based on Population Distribution of Relevant Kinetic Parameter—Bimodal Population.

analyzed separately for any potentially susceptible sub-group (Fig. 3).

6. Chemical-specific human variability toxicodynamic adjustment factor—[HD_{AF}]

Where there are adequate in vivo data in healthy adult humans only, or where data on dose–response are available only from studies in animals, there is a need for adjustment to allow for potentially susceptible subpopulations. As for AD_{AF}, data that inform this adjustment factor (i.e. those that define relative target site sensitivity directly, without any toxicokinetic influences) include kinetic–dynamic link models but more often, are based on comparative (either the critical or related) effects of the active compound in human tissues from healthy versus sensitive subgroups in vitro. At its simplest, the replacement to the default factor based on in vitro data on response in healthy human and susceptible subpopulations is the ratio of the concentration which induces a specified measurable response in average versus sensitive humans (e.g. the $EC_{10\ average}/EC_{10\ sensitive}$).

7. Guidance for development of CSAF

Data for application in the four components of the framework must relate to the active form of the chemical. Information that is relevant in this regard include data on the mode of toxicity of structural analogues, the effects of metabolites administered directly, the influence of induction or inhibition of metabolism of the chemical on the critical effect and variations in patterns of toxicity with metabolic profiles across species, strains and sexes.

For the components of the framework addressing toxicokinetics [AK_{AF}], [HK_{AF}], *choice of the appropriate metric* is an essential first step. Observation of the effect only following administration of an intravenous bolus dose or administration by gavage compared with continuous administration in diet or drinking water may indicate the importance of dose rate (i.e. C_{max} being the appropriate metric). In the absence of such data, a reasonable assumption is that effects resulting from sub-chronic or chronic exposure are related to the AUC, especially for chemicals with long half-lives, while acute toxicity could be related to either the AUC or the C_{max}. Alternatively, the AUC is a reasonable default because there are likely to be greater species differences or human variability in AUC or 1/CL than in C_{max}.

Choice of the appropriate endpoint is critical for the components addressing toxicodynamics [AD_{AF}], [HD_{AF}]. The selected measured endpoint must either be the critical effect itself or intimately linked thereto (with similar concentration–response and temporal relationships) based on an understanding of mode of action.

In addition, the metric for toxicokinetics or the measure of effects to address toxicodynamics as a basis for CSAF needs careful consideration in relation to the delivery of the chemical to the target organ. Measures of various endpoints in vivo may represent purely toxicokinetics, or toxicokinetics and part or all of the toxicodynamic processes and necessitate consideration of their impact to replace the toxicokinetic and potentially a proportion or all of the toxicodynamic default for interspecies differences.

For data that serve as the basis for all components, *relevance of the population* must also be considered. For the subfactors in kinetics [AK_{AF}] [HK_{AF}], for which the data are normally derived in vivo, this entails that the human population investigated is sufficiently representative of the subpopulation at risk for the adverse effect detected in the animal studies (e.g. males if the critical effects are those on the testes, pregnant females if critical effects are developmental, relevant age group). If not, the impact of any discrepancy on the validity of the calculated ratio needs to be considered. For in vitro studies which inform primarily dynamic components [AD_{AF}] [HD_{AF}], the quality of the samples should be considered, and evidence provided that they are representative of the target population, e.g. viability, specific content or activity of marker enzymes.

Relevance of the route of exposure needs to be considered in relation primarily to in vivo kinetic studies in animals and humans. If not performed via the route of exposure for the study in animals on which the effect level or benchmark dose/concentration is based (which should also be the route by which humans are normally exposed), then the impact of route-to-route extrapolation will need to be critically assessed in relation to the development of a CSAF.

The relevance of dose/concentration needs also to be considered for all components. Ideally, CSAFs for toxicokinetics [AK_{AF}, HD_{AF}] are based on comparison of kinetic parameters in animals exposed to doses similar to the critical NOAEL, effect level or benchmark dose/concentration to those in human kinetic studies, where exposure is similar to the estimated or potential human exposure. Any discrepancies should be assessed for their potential impact on the dose metric and the validity of the resulting CSAF. For in vitro investigations which inform primarily CSAFs for toxicodynamic aspects [AD_{AF}] [HD_{AF}], relevant studies should include a suitable number of concentrations to adequately characterise the dose/concentration–response relationship. The guidance document provides additional detail on selection of relevant points for comparison, where the dose/concentration–response curves between animals and humans or in different human subgroups are not parallel (IPCS, 2001).

The adequacy of numbers of subjects/samples needs also to be considered in relation to all components of the framework. For interspecies comparisons in both kinetics and dynamics [AK_{AF}] [AD_{AF}], the numbers of animals and humans should be sufficient to ensure that the data allow a reliable estimate of the central tendency for each species. Guidance in this context is provided, from both a statistical and pragmatic perspective (IPCS, 2001). For considerations of factors related to within human variability (HK_{AF}, HD_{AF}), the numbers of humans should be sufficient to ensure that the data allow a reliable estimate of the central tendency and of the population distribution.

8. Composite factor for interspecies differences and human variability

The composite factor (CF) (described previously as a 'data-derived uncertainty factor') is the product of four different factors, each of which could be a chemical-specific adjustment factor or a default, as follows (UF = default uncertainty factor):

$$CF = [AK_{AF} \text{ or } AK_{UF}] \times [AD_{AF} \text{ or } AD_{UF}] \times [HK_{AF} \text{ or } HK_{UF}] \times [HD_{AF} \text{ or } HD_{UF}]$$

CFs should be developed for several effects which might be considered critical to ensure that resulting tolerable, acceptable or reference intakes/concentrations are sufficiently protective.

Depending on the nature of the data, the CF can be either greater than or less than default. If the CF for an effect considered potentially critical based on consideration of the entire database is similar to or exceeds the normal default (i.e. 100), then this concentration/dose–response assessment should be protective for most other toxic effects. If, however, the CF for a potentially critical effect is less than the normal default, a different toxic effect with a higher NOAEL/NOAEC combined with a default uncertainty factor could become the critical effect.

9. Conclusions

Consideration of relevant data in the context of a framework that addresses kinetic and dynamic aspects, explicitly, should result in greater understanding of contributing components and transparency in risk assessment. It is also hoped that consideration in this context will lead to clearer delineation and better common understanding of the nature of specific data required which would permit development of more informative measures of dose–response.

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