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Integration of a plasma protein binding factor to the Chemical-Specific Adjustment Factor (CSAF) for facilitating the estimation of uncertainties in interspecies extrapolations when deriving health-based exposure limits for active pharmaceutical ingredients: Investigation of recent drug datasets

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ABSTRACT

The objective was to challenge cross-species extrapolation factors with which to scale animal doses to human by any route for non-carcinogenic endpoints. The conventional hypothesis of the toxicokinetics (TK)-toxicodynamics (TD) relationship was equal toxicity at equal plasma level of the total drug moiety in each species, but this should also follow the free drug assumption, which states that only the unbound drug moiety in plasma may elicit a TD effect in tissue. Therefore, a protein binding factor (PBF) was combined with the Chemical-Specific Adjustment Factor (CSAF) (i.e., CSAF x PBF). The value of PBF of each drug was set equal to the ratio between human and animals of the unbound fraction in plasma (fu_p). Recent drug datasets were investigated. Our results indicate that any CSAF value would be increased or decreased while PBF deviates to the unity, and this required more attention. Accordingly, further testing indicated that the CSAF values set equal to basic allometric uncertainty factors according to the conventional hypothesis (dog ~ 2, monkey ~ 3.1, rat ~ 7, mouse ~ 12) would increase by including PBF for 30% of the drugs tested that showed a superior fu_p value in human compared to animals. However, default uncertainty factors in the range of 10–100 were less frequently exceeded. Overall, PBF could be combined with any other uncertainty factor to get reliable estimate of CSAF for each bound drug in deriving health-based exposure limits.

1. Introduction

1.1. Theoretical background

Toxicological studies are designed to investigate the relationship between the toxicokinetics (TK) and toxicodynamics (TD) that describe adverse effects occurring below or above therapeutic doses, and carry the connotation of harm rather than therapeutic benefit in clinical studies. Therefore, the notion of TK-TD relationship represents the corresponding dose-response relationship for toxicity. The characterization of these relationships for any chemical or drug can be made either from *in vitro* or *in vivo* preclinical data before entering into human (Toutain and Lees, 2004; Wetmore et al., 2014; Weng et al., 2015; Zou et al., 2012). Moreover, models that describe these data well would depend of several extrapolation procedures, namely, the *in vitro*-to-*in vivo*, high dose-to-low dose, interspecies and/or interindividuals. For example, relying on any animal toxicological data (e.g., LOAEL or NOAEL) to estimate the safe dose in human of an active pharmaceutical ingredient (i.e., a drug) under occupational exposure would imply to understand particularly the uncertainty factors covering the interspecies differences and other variabilities in risk assessment. The Chemical-Specific Adjustment Factor (CSAF) is still the most commonly used traditional approach to adjust the toxicological data previously determined in animals (EU, 2001; Meek et al., 2002; IPCS, 2005; Naumann, 2005; Dourson and Parker, 2007; EPA, 2014; Dankovic et al., 2015).

The procedure used to calculate CSAFs allows the replacement of part of the usual default uncertainty factor of 10 or 100 used for risk assessment for the general population with quantitative chemical-specific data relating to either TK or TD. The replacement of a default subfactor for either TK or TD with quantitative chemical-specific data will result in a CSAF for that particular aspect for which data was available,

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thereby reducing the overall uncertainty. The CSAF approach may take into account for many uncertainty factors for which appropriate data were available on TK and TD differences, variability factor (V), and any other adjustment factor (AF).

$$CSAF = TK \times TD \times AF \times V \quad (1)$$

In practice, there is no consensus on the need for an additional sub-factor in the CSAF approach. However, any additional sub-factor of uncertainty must be taken into consideration using a CSAF approach when novel chemical-specific data become available (Rhomberg and Lewandowski, 2004; Feng et al., 2012; Reichard et al., 2016). Accordingly, the decision to add an additional adjustment/uncertainty factor must be based on a critical effect for which we understand the mode of action, the metric for TK or the measure of effect for TD in relation to the delivery of a chemical to the target organ, and the available data must relate to a measure of the active form of the chemical.

In this case, Silverman et al. (1999), Naumann et al. (2001), and Naumann (2005) already have established specific data-derived adjustment factors from published clinical trial data. These data were analyzed for human variability in young versus adult poor metabolizers, and these authors reported the mean and standard deviation values for two key parameters (i.e., area under the curve; AUC, and maximal plasma concentration; C_{max}), whereas Price et al. (2008) concluded that the inter-chemical variation in the toxic doses was important. Whether these observations could be explained by specific chemical or species data is not known because the knowledges were lumped into single statistical values of the mean and standard deviation. Alternatively, one may also consider deriving additional adjustment factors from more specific chemical and/or species data that may describe any other generic and critical mechanism of variability and/or toxicity.

1.2. Deriving additional adjustment factors for the effect of plasma protein binding

The conventional hypothesis of the TK-TD relationship was equal toxicity at equal plasma level by referring to the total drug moiety in each species, but this should also follow the free drug assumption, which states that only the unbound drug moiety presents in plasma may elicit a TD effect in tissue. Hence, it is generally assumed that only the unbound fraction of a chemical or a drug in plasma is toxicologically or pharmacologically active in the target organ (Trainor, 2007; Heuberger et al., 2013; Mariappan et al., 2013). Furthermore, species differences in plasma protein binding contributed to species differences and variabilities in TK and/or TD parameters of several drugs (e.g., Berry et al., 2011; Grime and Paine, 2013; Mariappan et al., 2013; Poulin, 2015a,b). Moreover, other studies also demonstrated the importance of binding to serum proteins that would alter the availability in tissue of free concentration, and, hence, the concentration bound to the receptors for potency of endocrine active compounds (e.g., Teeguarden and Barton, 2004). These analyses have identified important binding data gaps for implementing quantitative approaches for good interspecies extrapolations, and demonstrated that the binding affinity to serum proteins is a critical step that leads to the TD effects. Consequently, these observations support the notion that species differences in plasma protein binding, and, hence, in the fraction of unbound drug moiety in plasma (fu_p), should also be considered in the CSAF approach.

In the previous equation (1) describing CSAF, however, the suggested sub-factors of uncertainty for TK-TD and AF still not consider the impact of species differences in plasma protein binding. In order words, the bound and unbound drug moieties were not quantified separately in each species. The main explanation is because these sub-factors could be based on empirical factors (e.g., 10 or 100) that should estimate any expected species differences in TK and TD (e.g., by combining empirical factors of TK and TD; 3.3 × 3.3). However, with the empirical approach, the same uncertainty factor is used for any animal-to-human dose extrapolation and for each drug. This way any significant species difference in fu_p that would elicit a species difference in TD exceeding the empirical factors cannot be taken into account. Basic allometric scaling factors were also derived based on the body surface area ($weight^{0.67}$) or basal metabolic rate ($weight^{0.75}$). However, it is well known from several drug examples in the literature that the critical TK parameters of exposure determined *in vivo* (e.g., AUC in each species) would provide a different allometric relationship with the body weight whether the input AUCs are corrected or not with significant species differences in plasma protein binding (e.g., AUC or AUC x fu_p versus body weight of each species). Hence, the resulting regression analyses will provide a different exponent for each bound drug that would deviate to the generic exponent of 0.67–0.75. In other words, for example, the expected species differences in the basal metabolic rate ($weight^{0.75}$) would follow an exponent of 0.75 only while fu_p is considered similar in each species because it is generally assumed that only the unbound drug fraction can be cleared by an eliminating organ. And the motivation for using the surface area relationship compared to the basal metabolic rate to estimate the basic allometric uncertainty factors for human risk assessment is solely related to safety concern, since this provides a lower dose estimate, and, therefore, a larger uncertainty factor (i.e., dog-to-human ~ 2, monkey-to-human ~ 3.1, rat-to-human ~ 7, and mouse-to-human ~ 12 by using standard body weights) (Gaylor et al., 1999; Pelekis and Krishnan, 2004; Dorne and Renwick, 2005; Risk-MaPP, 2010; EMA, 2014; Dankovic et al., 2015; Faria et al., 2016; Reichard et al., 2016; Sussman et al., 2016).

In this contex, knowing that the existing basic sub-factors used to cover diverse uncertainties generally not separated the bound and unbound drug moieties in the presence of relevant species differences in plasma protein binding, these factors may need to be corrected for additional species differences in fu_p. Such a binding correction is still not routinely considered probably apart from isolated case examples, and is still not recommended by any guidance documents to facilitate the derivation of common health-based exposure limits (e.g., the acceptable and permitted daily exposure as well as the occupational exposure limit) for the active pharmaceutical ingredients present in occupational health (European commission, 2001; EMA, 2014; Risk-Mapp, 2010; EPA, 2014; IPCS, 2005). A reason why the species differences in plasma protein binding has not routinely been considered in risk assessment is probably because it is generally accepted that most of the chemicals and pollutants in occupational and environmental health are not highly bound to the plasma proteins; conversely, most of the active pharmaceutical ingredients (drugs) are bound in plasma as demonstrated in the recently published datasets (Gleeson, 2007; Berry et al., 2011; Poulin et al., 2011; Colclough et al., 2014). More importantly, the recently published datasets indicate that several drugs are less bound in human plasmas compared to animal plasmas, and, hence, this may result in potentially more unbound and active drug in human compared to animals, which could be of toxicological relevance by using a CSAF approach that is not correcting for the plasma protein binding effect. Consequently, a protein binding factor (PBF) can be combined with the concept of CSAF, which may override the old paradigm of the empirical and basic allometric uncertainty factors that are generally minimizing the species differences in plasma protein binding.

1.3. Incorporation of PBF in the concept of CSAF

One thing is for sure is that larger are the interspecies differences in fu_p, larger would be the interspecies differences in the unbound kinetic parameters, and, hence, larger would be the interspecies differences in the target tissue dose for the active unbound drug moiety. As said, the AUC is routinely determined to estimate the internal exposure of a drug in toxicological studies when the effect its time related. Therefore, the uncertainty factor for interspecies differences in TK x TD would depend