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Letter to the Editor

Response to Farahmand and Maibach's Corrigenda

Farahmand and Maibach (2009b) originally attracted our attention because it claims to find 1000–10,000-fold discrepancies between dermal flux predictions based on data derived from in vivo versus in vitro experimentation. This finding is dramatically at variance with a large body of literature and hence struck us as almost certainly the result of erroneous analysis. Upon further inspection we found obvious errors regarding specification of aqueous solubilities and pointed those out in our prior letter (Kissel and Bunge, 2010). We further noted that the conceptual basis for Farahmand and Maibach's (2009a) predictive model was questionable, that the units of the normalized C_{max} at the center of their approach were incorrectly specified, that their model's coefficients are very likely incorrect, and that both papers contain numerous overt calculation errors and results not reproducible using stated assumptions. We hoped that this critique would spur serious reexamination of their work on the part of Farahmand and Maibach. Instead, Farahmand and Maibach (in an unpublished letter that accompanied their corrigenda) characterize the issues at hand as primarily involving typographical errors and inherent uncertainties in physicochemical properties. They further maintain that the originally published regression is valid although some of the data used to create that regression have changed. We take issue with Farahmand and Maibach's response on multiple grounds.

1. Normalization of C_{max}

In their corrigendum to 2009a and 2009b, Farahmand and Maibach (2010a, 2010b) state that the correct units of normalized C_{max} are ml^{-1}. However, neither the original papers nor the corrigenda reveal how C_{max} actually was normalized. In their unpublished letter accompanying the two corrigenda, Farahmand and Maibach explain that the normalized C_{max} (which for clarity, we indicate as $C_{max,norm}$) was calculated by dividing the observed C_{max} ($C_{max,obs}$) by the cumulative dose:

$$C_{max,norm} = \frac{C_{max,obs}}{[J \cdot A]_{label} \cdot t} \quad (1)$$

where the product of flux (J) and delivery area (A) is the delivery rate, and t is the application time. Farahmand and Maibach (2010a) also provide a new Table 4 that includes changes to most of the normalized C_{max} values provided previously, but their unpublished letter insists that these changes are merely cosmetic and do not affect subsequent work, in particular their regression (Eq. (4) in 2009a and Eq. (1) in 2009b), which was fit using the originally published values of $C_{max,norm}$.

Despite the attention the errors in the original papers have attracted, Farahmand and Maibach have not thoroughly checked the new results reported in their two corrigenda (2010a, 2010b). A particularly egregious example involves Transiderm-Nitro for which they report a normalized C_{max} of $6.43 \times 10^{-05}\ ml^{-1}$ in the modified Table 4 (2010a). This value is dramatically different than the values reported for all other nitroglycerin products in Table 4 despite very similar dosing regimens and reported values of observed C_{max} and so should have been detected with even minimal proofreading. Using the values from the two trials reported in Farahmand and Maibach's (2009a) Table 2.6, we calculate an average $C_{max,norm}$ for Transiderm-Nitro of about $7 \times 10^{-8}\ ml^{-1}$, a value nearly 3 orders of magnitude smaller than the value in the "corrected" Table 4. (This has implications for the regression as discussed under Issue 2 below.) We also find roughly one order of magnitude errors in six other entries in the "corrected" Table 4. (Of course this finding reflects our assumption that values compiled in Tables 2.1–2.12 in 2009a are faithful representations of the relevant data. We have not checked those tables and, mindful of the many other errors in these papers, have little confidence that this is true.)

2. The regression

Farahmand and Maibach have regressed normalized C_{max} against log octanol–water partition coefficient and numbers of hydrogen bond donor and acceptor groups on the molecule. They report the following result:

$$C_{max} = 8.265 \times 10^{-7} \cdot HA + 8.231 \times 10^{-7} \log K_{oct} - 1.22 \times 10^{-6} \cdot HD - 2.58 \times 10^{-6}$$

where, as noted above, C_{max} is actually dose-normalized C_{max}. We find at least four problems here.

First, we have attempted to generate this regression using data from both the original (2009a) Table 4 and the version in the corrigendum to 2009a (2010a) and have failed. Because Table 4 contains 40 sets of eligible dose-normalized C_{max}, $\log K_{oct}$, HD and HA values, rather than 10, there may be some unstated data selection/averaging step that differs between Farahmand and Maibach's approach and ours. Whatever the explanation, the coefficients in the result above are not reproducible given information available in 2009a or 2010a.

Second, given that the C_{max} values being subjected to regression vary over several orders of magnitude, a linear rather than logarithmic regression is a poor choice. On a linear scale, many of the values will be clustered near the origin, and the largest values will be disproportionately influential. This can lead to a misleadingly high r value. We find that the mistakenly large value of $C_{max,norm}$ for Transiderm-Nitro noted above is very influential even if averaged with the other nitroglycerin data. Correction of that value changes the regression substantially and one consequence is a much lower r value. Linear regression actually gives a poor fit to the data that Farahmand and Maibach address.

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Third, when we substitute in values of $\log K_{oct}$, HD and HA from Table 4, we frequently find a predicted $C_{max,norm}$ that is not close to the observed values listed Table 4. For example, entering the molecular parameters of estrogen into the stated regression leads to a prediction of 5.6×10^{-9} ml^{-1}. This result is 10–1000 times smaller than the observed values for the estrogen products. For the nitroglycerine products, the predicted result of 6.5×10^{-6} ml^{-1} is typically 2 orders of magnitude larger than the observed values. This finding is not at all surprising given the inappropriate use of linear regression, although additional errors could also be at play.

Our final, and perhaps primary, objection to the regression is that it is ill conceived from the start. Farahmand and Maibach have regressed a dose-normalized C_{max} that, as shown in Eq. (1), includes both clearance rate (i.e., the ratio of the delivery rate to the observed C_{max}) and the dose duration against molecular properties. Prediction of clearance rate from molecular properties alone is dubious given the various biochemical processes that contribute to elimination of different drugs. Prediction of dose duration is absurd. There is no reason that recommended treatment regimen duration should be predictable from molecular properties, so cumulative dose-normalized C_{max} is a poor candidate for prediction from those properties. Farahmand and Maibach would be on better footing had they regressed observed flux (label delivery rates divided by patch area) directly against molecular properties. However, even then comparison with estimates of maximum flux (defined as steady-state flux from saturated solution in the absence of skin barrier alteration) is not generally appropriate, as noted in our prior letter (Kissel and Bunge, 2010), since transdermal devices can be designed to deliver at higher or lower rates than the maximum flux (e.g., through the use of enhancers or rate-controlling membranes).

3. The in vivo model

In the first step of their in vivo model (2009b, p. 42), a clearance rate (CL) is estimated from label delivery rates (equal to the product of J and A) and reported (observed) C_{max} as specified by Eq. (2) (written with the units included):

$$\mathrm{CL}\quad \left[\frac{\mathrm{ml}}{\mathrm{h}}\right] = \frac{\left[J\ \ [\mathrm{ng/cm^2\ h}]\cdot A\ [\mathrm{cm^2}]\right]_{\mathrm{label}}}{C_{\mathrm{max,obs}}\ \ [\mathrm{ng/ml}]} \tag{2}$$

Farahmand and Maibach then claim to predict flux using the clearance rate calculated above, dose-normalized C_{max} from their regression, $(C_{max,norm})_{regr}$, and the delivery area of the patch. This process, summarized in Eq. (3) provides a result with units that are not the units of flux (i.e., mass per area per time):

$$J_{\mathrm{pred}}\ \ [\mathrm{units?}] = \frac{\mathrm{CL[ml/h]}(C_{\mathrm{max,norm}})_{\mathrm{regr}}[\mathrm{ml^{-1}}]}{A\ \ [\mathrm{cm^2}]} \equiv \left[\frac{1}{\mathrm{cm^2\ h}}\right] \tag{3}$$

In addition, when we follow the enumerated steps our results are 10^4 to 10^8 times smaller than the in vivo model results reported in either version of Table 4. However, Farahmand and Maibach do claim to produce results that are generally quite similar to observed flux (label delivery rates divided by patch area). Therefore, they must be taking an additional, undisclosed step to get results similar to observations. This, once again, makes their approach mathematically irreproducible. We suspect that they are "re-normalizing" using dosing data specific to each product since the range noted above is generally consistent with cumulative dose in ng, but even using this approach (i.e., multiplying J_{pred} by the ratio of $C_{max,obs}$ to $C_{max,norm}$ from the regression) we can match their result in only some cases listed in Table 2 (2010b). Even ifexecuted correctly, this process is simply a circular manipulation and cannot be viewed as genuinely predictive modeling. Farahmand and Maibach do not predict results for any compound not used to calibrate their regression. They do, however, suggest that their approach is general even though they (without explanation) exclude fentanyl and clonidine. In contrast the in vitro models that Farahmand and Maibach criticize do not require reinsertion of compound-specific experimental data other than molecular properties, and are applied to compounds not included in the databases from which they are derived.

Both the in vivo and in vitro-based predictions are ultimately compared to the "observed" in vivo values (label delivery rates divided by patch area). Unfortunately the latter are often miscalculated. In the worst case the stated value for Nicotine-alza is 7.27×10^3 ng cm^{-2} h^{-1} when it should be 7.29×10^4 ng cm^{-2} h^{-1}. Many of the other values of observed flux in the "corrected" Table 3 (2010b) are also inconsistent with the delivery rate and patch area values listed in the "corrected" Table 2.

4. Responsiveness

Farahmand and Maibach have withdrawn (in their unpublished letter) their claims regarding remarkably large in vivo–in vitro discrepancies for nicotine, nitroglycerin and oxybutynin, which they state were based on erroneous specification of water solubility for two of the compounds in their Table 2 (2009b). This change is also reflected in their modified abstract (2010b). Erroneous values for solubility explain the discrepancy for nicotine and oxybutynin. In the case of nitroglycerin their unpublished letter asserts that mistakenly specified solubility did not account for the discrepancy, but does not mention that the implausible result for nitroglycerin was due to incorrect computation using Models 11 and 12 instead. Significantly, all values for Model 12 and 6 of 18 values for Model 11 have changed in the corrigendum to 2009b (2010b), many by at least 3 orders of magnitude. With respect to the revised solubility of oxybutynin, the relevant concentration is the solubility of the non-ionized form, which is most easily determined at high pH, not physiological pH.

Many additional mistakes remain despite production of the corrigenda. For example, the value of $\log K_{oct}$ for Daytrana stated in the "corrected" Table 2 (2010b) disagrees with the value in the "corrected" Table 4 (2010a). We have not checked many of the values presented in the two papers and associated corrigenda. Failure on our part to find fault with any specific numerical quantity in either paper or the corrigenda should not be taken as endorsement of the value presented.

In summary, we find the response of Farahmand and Maibach to be inadequate. The shortcomings of these papers are significant both conceptually and in terms of implementation. The corrigenda fail to adequately address our concerns regarding the original papers and contain additional overt errors.

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