The understanding of the processes of induction of human drug-metabolizing enzymes has advanced considerably over the past decade. If we concentrate on CYP3A4, the most abundant form of cytochrome P450 and the one most involved in the clearance of the majority of pharmacuticals, a clear pharmacological pathway emerges. We have receptors [VDR (1,25-(OH)(2)-vitamin D(3) receptor), PXR, constitutive androstane receptor], with some degree of selectivity and considerable diversity, that are part of a superfamily of transcription factors (Reschly and Krasowski, 2006). These receptors regulate the gene that produces the CYP3A4 protein, and their activity is controlled by small-molecule ligands. What separates many studies on induction from mainstream pharmacology is a dated and nonspecific use of terminology that does not reflect these understandings. Many times, whether in publications or talks, the phrase weak or potent inducer is used to describe an effect which is solely measured by the size of the response, without reference to the dose or concentration used to elicit that response. Now that we have a much greater understanding of the pharmacology underlying induction, perhaps our description of events leading to the effect and the effect itself should reflect this. The key descriptors of the events and effect are the affinity of the ligand for the receptor(s) and the character of the interaction: whether the compound is an agonist, partial agonist, inverse agonist, or antagonist (Chang and Waxman, 2006). The affinity of the ligand and the character of the interaction will determine the concentration-response curve.

According to Ross and Kenakin (2001), in Goodman and Gilman’s *The Pharmacological Basis of Therapeutics*, “drugs have two observable properties in biological systems: potency and magnitude of effect.” The authors draw attention to classifying drugs according to the magnitude of their two molecular properties: affinity for the receptor and efficacy once bound, and that comparison between drugs is best made by potency (comparison of EC50 values) and maximal asymptotes (Emax). An analogy can be made to enzyme kinetics and the necessity of using both Km (a measure of affinity) and Vmax (a measure of maximal velocity) to appropriately assess overall catalytic efficiency for turnover of a given substrate. By analogy, both EC50 and Emax values are needed to describe the overall induction efficiency of an inducer. [An additional complexity in describing receptor-mediated processes is that comparing only Emax and EC50 values does not distinguish the mechanism for different maximal responses which may be due to different receptor recruitment or the actual characteristics of the agonism or antagonism. Therefore, a third descriptor that could be incorporated is one that describes the character of the interaction: whether the compound is an agonist, partial agonist, inverse agonist, or antagonist (Chang and Waxman, 2006).]

The dated terminology often used to describe induction (potency defined purely by the size of response) as outlined at the beginning is at best a simplification but at worst is at odds with the definitions used in pharmacology. Why does this matter? Well, first, it seems strange to be part of the overall pharmacology discipline and then have a terminology counter to one of the most widely read text books on the subject. Moreover, often induction and its implications are considered by a large body of people far removed from those working on P450 induction, and the term potent will imply an activity at low concentrations. To a medicinal chemist, for instance, the terms potency and concentration are tightly linked. Describing a compound as a “potent” inducer when its high maximal response occurs at 10 μM is generally erroneous and an oxymoron to a medicinal chemist. Almost all inducers have relatively weak affinity (micromolar range) for PXR and constitutive androstane receptor when judged against affinity values for most pharmacological targets. This is why compounds with weak affinity for their pharmacological target, such as phenytoin (approximately 50 μM against the Na+ channel), given in high doses to achieve high plasma concentrations that match the pharmacological potency, can act as clinical inducers. This contrasts with compounds that are potent against their pharmacological target, such as nifedipine (approximately 4 nM against the Ca2+ channel); therefore, given in low doses to achieve low concentrations to match the pharmacological potency, they do not act as clinical inducers. Both drugs would give the same maximal response for induction, as pure agonists, if the appropriate concentrations could be achieved. It is sound science (and correct pharmacology terminology) to describe induction in terms of receptor affinity and response. As in the above example, the correct use of the terminology allows immediate understanding of clinical outcomes. For instance, Sahi et al. (2003), in examining the comparative effects of thiazolidinediones on P450 induction (in vitro) describes troglitazone as the most potent of the three, but achieving the lowest maximal effect. The potency or affinity for CYP3A4 induction allows comparison with the potency against the pharmacological target (peroxisome proliferator-activated receptor γ), the major factor in their widely different clinical doses, and a clear understanding as to why troglitazone is the only clinically significant inducer (Smith, 2000). If comparison between inducers is needed (comparison to target pharmacological potency for a compound may be of much higher value), maybe the “gold standard” inducer rifampicin should be used (EC50 0.7 μM, maximal response 7 times resting levels) (Chang and Waxman, 2006). A partial agonist of PXR (or perhaps a different interplay with the receptor system) could then be described as more potent than rifampicin (say 0.2 μM) but with lower maximal response (3 times). Not all elements of the science are complete. We have not
yet characterized the size of the response sufficiently for enough compounds to understand exactly the mechanism for the range of maximal responses, but we are close, and technically, it is achievable. Putting our language in place now seems very appropriate. The fact that appropriate pharmacology terminology and concepts apply to P450 induction studies is demonstrated in a recent publication. Ripp et al. (2006) related in vitro induction data ($E_{\text{max}}$ and $EC_{50}$ values) of 24 drugs, obtained in induction studies using Fa2N-4 cells, with their efficacious free plasma concentrations and calculated a relative induction score. This score correlated highly ($r^2$ values $>0.92$) with decreases in area under the plasma concentration versus time curve values for coadministered CYP3A4 object drugs (midazolam or ethinylestradiol) from previously published clinical drug-drug interaction studies. Similarly, Sinz et al. (2006) have recently correlated the concentration-response values for transactivation of human pregnane X receptor, with clinical concentrations and induction response. In addition, a recent comprehensive review of P450 induction discusses the importance of using $EC_{50}$ and $E_{\text{max}}$ values to interpret in vitro induction data (Lin, 2006). These recent publications demonstrate that induction indeed follows established pharmacological and pharmacodynamic principles, and we should acknowledge this in the words we use to describe the response. We advocate that “potent or weak inducer” no longer be used to describe the clinical significance of induction, and that the term should be reserved for the affinity of the compound against the receptor either measured or inferred. Where possible, dose or concentration response should be defined to elicit maximal response to give sound pharmacodynamic understanding of the event. To follow our present ad hoc usage of terminology belittles the progress that the science has made. We would welcome dialogue on the topic.

**References**


**Address correspondence to:** Dennis A. Smith, Sandwich Laboratories, Kent, UK, CT13 9NJ. E-mail: dennis.a.smith@pfizer.com