Orthogonal approaches to empirically determine the inter-individual variability in human sensitivity to environmental mutagens

Abstract: Genotoxicity testing plays an important role in hazard assessment of new and existing chemicals. Calculation of Health-Based Guidance Values, below which the risk of adverse human health effects can be deemed negligible, requires use of an uncertainty factor (UF) to account for inter-individual variability in human sensitivity. Our work describes two orthogonal approaches to empirically assessing the human inter-individual uncertainty factors relevant to mutagens. In Part I, Dr. Lauren Gallant employed quantitative analyses of *in vitro* concentration-response data to assess the effect of compensatory pathway knock-out (KO) or knock-down (KD) on cellular sensitivity to genotoxic substances. This work involved collection of *in vitro* concentration-response data from peer-reviewed scientific literature, more specifically, matched data documenting the effects of genotoxicants on animal and human wild-type and genotypically compromised cells (i.e., DNA repair KO or KD). Results to date reveal that an inter-individual UF value of 10 may be sufficiently protective; indeed, in many instances the results indicate that it might be considered conservative for genotoxic agents. Further analyses will investigate the effect of factors such as species, cell type, and mode of action on the relative genotoxicant sensitivity. In Part II, Dr. Madison Bell performed a systematic review of *ex vivo* experimental studies that quantified human DNA repair capacity (DRC). Fold-changes between maximum and minimum DRC were calculated on a per-study basis. The distribution of fold-changes in DRC across all studies were then used to estimate the 5^{th} and 95^{th} percentiles of inter-individual variations. Furthermore, the 95^{th} percentile of the fold-change distribution was used to evaluate the adequacy of the default inter-individual UF of 10. To date, 8856 studies were extracted from our database query, of which only 1568 were deemed relevant after duplicate removal and abstract screening, and only 315 studies contained enough relevant data for extraction. Thus far results indicate the mean inter-individual variation of DRC is 2.30 with a 95^{th} percentile of 30.19. Calculations are ongoing, but these preliminary results suggest that the default inter-individual UF (i.e., 10) may be sufficiently conservative. Nevertheless, the analyses do not account for inter-individual variability in metabolic capacity, i.e., toxicokinetic variability.