Development and Analysis of a Harmonized QSAR Database of Chemical Health Guidance Values

Authors: Eugene Demchuk[1], Jay L. Tunkel[2], Mike Fay[1], Dennis Jones[1], Julie Stickney[2], Larry Lockwood[2], Robert Garrett[3], Thomas Miller[3], Hugh Hansen[1]
[1]Centers for Disease Control and Prevention (CDC)/Agency for Toxic Substances and Disease Registry (ATSDR)/Division of Toxicology & Environmental Medicine, United States
[2]Syracuse Research Corporation/Environmental Science Center, United States
[3]Armed Forces Medical Intelligence Center, Washington DC

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The Agency for Toxic Substances and Disease Registry (ATSDR) develops minimal risk levels (MRLs) to be used as health guidance values (HGVs) for populations exposed to toxic chemicals at hazardous waste sites. An MRL is usually derived for non-cancer health effects by applying science-based uncertainty factors to a toxic endpoint (point of departure) observed in an animal bioassay or a human epidemiology study. The most commonly used points-of-departure are the LOAEL (lowest observed adverse effect level), the NOAEL (no observed adverse effect level), the BMD (benchmark dose) and the BMDL (benchmark dose level). Because the potential exists for exposure to chemicals for which there is no existing MRL or other HGV, we explored an alternative method for developing *provisional* health guidance values (pHGVs). Our approach was based on a systematic classification and restructuring of toxicological information in a standardized, internally consistent manner (harmonization of data), using a combination of formal guidelines, expert assessment, and quantitative structure-activity relationship (QSAR) analysis. HGV data from eight regulatory and advisory sources, including ATSDR and the U.S. Environmental Protection Agency are being evaluated. To date, pertinent data for 407 HGVs for the chronic oral exposure route of 314 organic chemicals have been collected, evaluated, and systematically entered in the Harmonized QSAR Database (HQDB). Information collected included the following for each HGV: LOAEL/NOAEL/BMD/BMDL (point-of-departure), individual and composite uncertainty factors (UFs), species, gender, critical effect, target organ, and various supporting information. Using these data, four proprietary QSAR models were tested for their ability to predict existing laboratory-derived LOAELs and HGVs. A separate analysis of UFs in the database was also carried out. By analyzing HQDB information, we derived an optimized LOAEL-to-NOAEL ratio for computationally-derived pHGVs. It was found that the use of a statistically-grounded UF, suitable for extrapolation of LOAELs to pHGVs, improved the overall predictive accuracy relative to the commonly used default value of 10. The influence of other UFs on pHGV estimates was also determined as a function of the point-of-departure. Results indicated that the uncertainty of pHGV values was comparable to uncertainty in the underlying LOAEL values, which suggests that this new approach improves the internal consistency of QSAR-based pHGV predictions.

Point of Contact:
Eugene Demchuk, Ph.D.
CDC/ATSDR/Division of Toxicology & Environmental Medicine
1600 Clifton Road, N.E. (MS F-32)
Atlanta, GA 30333
770-488-3327
edemchuk@cdc.gov