= 1.06) and Cu (slope = 1.77). In most cases, b-XRF results were slightly more similar to reproducing ICP-OES results. The results and methods will be used in future studies including the measurement of metals in welding fumes via personal air sampling and the understanding of how the different metals in toenails reflect chronic exposure to various welding types. *This study is supported by NIEHS R01 ES032478 and the International Manganese Institute.*

3823 How the 70-kg Man Impacts NIOSH-Recommended Exposure Limits

C. Whittaker[1], and L. Lucas[2]. [1]*NIOSH, Cincinnati, OH; and* [2]*Harvard T.*H. Chan School of Public Health, *Boston, MA.*

This study examines the impact of assuming a single human body weight value when developing occupational exposure limits. NIOSH uses quantitative risk assessment to evaluate the risks of chemical exposures in the workplace and as a basis of its occupational exposure limits, Recommended Exposure Limits (RELs). Simplifying assumptions are a necessary part of quantitative risk assessment and there are several key assumptions that go into occupational risk assessments - one, of note, is the assumption that the typical human body weight is 70 kg (typically also assumed to be male). In this investigation, the public draft proposed NIOSH REL for 1-bromopropane (1-BP) was used as a case study to explore the impact of this assumption. In the public draft risk assessment, NIOSH used data from a National Toxicology Program mouse 2-year bioassay to estimate the risk of cancer in workers exposed to 1-BP over a working lifetime. The risks were calculated using Bayesian model averaging of Benchmark Dose estimates of the mouse dose-response data. The BMDL (lower limit on the Benchmark Dose estimate) was extrapolated to humans, assuming dose equivalence in units of mg/kg-day scaled according to body weight to the 0.75 power to find the human equivalent BMDL at 70 kg. This value was then converted to ppm and adjusted to account for an 8-hour workday 5 days per week to derive the proposed REL of 0.3 ppm. At the draft REL, the risk of cancer was estimated to be 1 excess case per 1000 workers exposed to 1-BP every workday over a working lifetime of 45 years. In this study, the NHANES data for body weights by gender in the United States were used to create a distribution of weights for both adult male and adult female populations. From data collected in 2021, the mean body weight in the female population was 77.5 kg $\pm$ 21.2. In the male population, mean body weight was 90.6 kg $\pm$ 20.85. A simulation was run on a randomly selected body weight from the distribution of body weights and the risk of 1-BP was recalculated based on this selection. This experiment was repeated 10,000 times, each time using different randomly selected body weights. The results show how risks vary depending on body weight. Instead of a risk of 1/1000, for example, an 80 kg person exposed to 0.3 ppm 1-BP would have a risk of 0.91/1000 - a nearly 10% difference. Conversely, a lighter individual would have a higher risk when exposed to the same concentration of 1-BP. Since the mean body weights for males and females were higher than the assumption of 70 kg, the mean female risk was 0.99/1000 and the mean male risk was 0.87/1000. However, for more than 38% of the female population and 17% of the male population, the estimated risks were higher than the 1/1000 target risk level in the NIOSH public draft document. These results demonstrate the importance of understanding and explaining the impact of the assumptions used in quantitative risk assessment. The unbalanced impact of the assumption depending on gender also points out hidden potential gender bias in occupational risk assessment. Clearly identifying and discussing the assumptions used in a quantitative risk assessment is an important aspect of ensuring that the occupational exposure limit is appropriately used in the workplace. *The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.*

3824 Developing the Internal Threshold for Toxicological Concern (iTTC): Generating *In Vitro* Caco-2 Permeability and Hepatocyte Metabolism Datasets Needed for PBPK Modeling

D. Selechnik[1], K. Joshi[1], A. Api[1], R. A. Becker[2], N. Hewitt[3], and C. Ellison[4]. [1]*Research Institute for Fragrance Materials, Woodcliff Lake, NJ;* [2]*American Chemistry Council, Washington, DC;* [3]*Cosmetics Europe, Brussels, Belgium; and* [4]*Procter & Gamble, Cincinnati, OH.*

The Threshold for Toxicological Concern (TTC) is a health-based guidance value used for risk-based screening and prioritization. If an exposure is below the TTC value, the probability of adverse health effects is low. Current TTC thresholds establish limits for external exposures. This project aims to derive internal TTC (iTTC) values for comparisons to *in vitro* assay responses or for risk assessments based on internal exposures (e.g., plasma concentrations). Physiologically based pharmacokinetic (PBPK) modeling is being used to convert the external No Observable Adverse Effect Levels (NOAELs) of chemicals in the existing TTC database to estimates of internal exposure. PBPK modeling requires chemical-specific input parameters for absorption, distribution, metabolism, and excretion. Accordingly, *in vitro* Caco-2 permeability and hepatocyte metabolism studies were conducted for ~200 chemicals in a collaboration between the Research Institute for Fragrance Materials (RIFM), Cosmetics Europe (CosEU), and the American Chemistry Council (ACC). Caco-2 assays measured bidirectional cell permeability, with pHs of 6.5 and 7.4 in the apical (A) and basolateral (B) compartments, respectively, to mimic intestinal pH. Metabolism assays used cryopreserved hepatocytes (from the species from which NOAELs were derived) to measure *in vitro* intrinsic clearance using the substrate (0.1 and 1 µM) depletion approach. The apparent A to B permeability of 189 chemicals measured in Caco-2 cells ranged from 0.03 to 100.6×10^{-6}cm/sec. Due to low recovery in plastic, 44 chemicals were incubated with 0.5% or 4% BSA in the Caco-2 buffers. Metabolism data for ~16% of the assays were unsuitable for clearance determination due to interference in the analytical method (these were endogenous in cells or media), chemical instability, or rapid loss of test chemical under the assay conditions. Clearance of >5µL/min/10^6 cells was observed for ~60% of the assays as indicated by a depletion slope that was significantly different (F-test) from zero, while 24% of the assays had no/very low clearance (< 5µL/min/10^6 cells). These *in vitro* values are currently being used in the PBPK modeling portion of the iTTC project and will help refine the interim iTTC value of 1 µM. Additionally, they will inform future research, e.g., high throughput toxicokinetic models or the design of new studies to address underrepresented chemistries.

3825 Developing the Internal Threshold of Toxicological Concern (iTTC): Evaluation of Bottom-Up PBPK Model Performance

A. Nong[1], T. Antonijevic[1], J. Fitzpatrick[1], M. Moreau[1], J. W. Fisher[1], A. Y. Efremenko[1], P. McMullin[1], N. J. Hewitt[2], A. Schepky[3], and C. A. Ellison[4]. [1]*ScitoVation, Durham, NC;* [2]*Cosmetics Europe, Brussels, Belgium;* [3]*Beiersdorf, Hamburg, Germany; and* [4]*Procter & Gamble, Cincinnati, OH.*

The threshold of toxicological concern (TTC) is a risk assessment tool developed to screen and prioritize low level exposures to chemicals with unknown toxicity. The TTC limits define exposure thresholds below which there is a low probability of adverse health effects. Current TTC thresholds establish limits for external exposures. A project is underway to derive internal TTC (iTTC) values (i.e., a TTC based on plasma concentration) to permit TTC assessments based on internal exposures. *In vivo* data was previously collected as a part of the systematic literature review for metabolism and pharmacokinetic data in rats on 1,251 chemicals. Physiologically based pharmacokinetic (PBPK) modeling is used to convert the chemical-specific external No Observable Adverse Effect Levels (NOAELs) to an estimate of systemic concentration. Bottom-up PBPK model (PLETHEM™) simulations were compared with corresponding *in vivo* time course data (oral and intravenous (iv)) for a subset of 56 chemicals. For each rat *in vivo* study, four PBPK simulations were performed by combining restricted (predicted plasma binding, Fu) and unrestricted (no binding, Fu = 1) clearance with *in vitro* rat hepatic clearance measurements at 0.1uM and 1uM. For each chemical, ratios between *in vivo* data and PBPK simulated plasma concentrations ($Ratio_C = C_{invivo}/C_{PBPK}$) and ratios between corresponding AUCs ($Ratio_{AUC} = AUC_{invivo}/AUC_{PBPK}$) were evaluated. For oral administrations, maximum plasma concentrations were compared with maximum *in vivo* concentrations. For iv administrations, plasma concentrations at the first blood draw were compared with corresponding simulated concentrations. Additionally, the reproducibility of the *in vivo* PK data was tested by dividing the areas-under-curve (AUC) for the same chemical, administration, dose, species, strain, and sex, but different experiments across 16/56 chemicals. The average fold difference in AUC between repeated *in vivo* PK studies was 1.76, with a standard deviation of 0.85. The PBPK modeling workflow resulted in a total of 782 simulations, and the best simulation conditions captured 75% plasma concentration and 85% AUC values within ±10 fold. In general, unrestricted clearance gave better agreement between *in vivo* experiments and PBPK model simulations. Principal Component Analysis (PCA) did not show visible differences between chemicals' physical-chemical properties ($logK_{ow}$, logD, vapor pressure, water solubility, molecular weight, and Henry's law constant) and goodness of fit by the PBPK model. These results provide the first evaluation of the bottom-up PBPK modeling approach that will be utilized in the development of the iTTC; further model evaluation will be approached in an iterative manner.

3826 Stochastic Simulation of Tumor Growth to Support Carcinogen Risk Assessment: Formaldehyde Case Study

R. Conolly, H. Clewell, and R. Gentry. *Ramboll U.*S. Consulting, *Inc., Monroe, LA.*

Clonal growth modeling in support of carcinogen risk assessment requires an estimate of the time needed for a single tumor cell to expand clonally into a clinically detectable tumor. We refer to this time interval as the delay (D). D cannot be measured directly, since the exact time at which a tumor cell arises by mutation of its precursor Is unknown. However, D can be estimated by formal optimization against tumor dose-response, time-course, and related mechanistic data (Conolly et al., Toxicol. Sci. 75, 432-447, 2003). Rodent bioassay tumors can be classified as incidental (identified at scheduled sacrifice) or fatal (identified in moribund rats). Conolly et al. (2003) assumed that the difference in D between incidental and fatal tumors was small enough to be ignored, thereby limiting the number of unknown parameters in their biologically based dose response (BBDR) model for formaldehyde. Subramaniam et al. (Risk Anal. 27, 1237-1254, 2007) altered the Conolly et al. (2003) model, using separate values of D for incidental and fatal tumors. The single value of D identified by Conolly et al. (2003) was 6,982 hr (290 days, 41 weeks) and the two values from Subramaniam et al. (2007) were 244.6 and

62nd Annual Meeting & ToxExpo
Nashville, TN • March 19–23, 2023

The Toxicologist

Supplement to *Toxicological Sciences*

SOT | Society of Toxicology

Toxicological Sciences

The Official Journal of the Society of Toxicology

OXFORD UNIVERSITY PRESS

ISSN 1096-6080 Volume 192, Issue S1 March 2023
www.academic.oup.com/toxsci

Publication Date: March 14, 2023