1.12 µg/day for a $1x10^{-5}$ increased lifetime risk of cancer of the small intestine (*i.e.,* duodenum, jejunum, and ileum). The Unregulated Contaminant Monitoring Rule (UCMR) contains the results of analytical testing for 1,995 public water systems in California, with 9,966 samples, 869 of which were below the minimum reporting level of 0.03 µg/L. Based on the UCMR data, average (2.1 µg/L) and maximum (47 µg/L) concentrations of Cr^{6+} were determined in CA drinking water, which correspond to exposures of 4.2 and 94 µg/day (assuming 2 L/day), respectively. Leather-bound consumer products are frequently targeted for Proposition 65 compliance, as Cr^{6+} is commonly used in the tanning process of leather. Exposure to leather gloves, purses, and couches were considered the most relevant avenues for Cr^{6+} exposure. Based on published analytical data for leather products, exposure estimates were calculated using exposure scenarios based on typical use patterns. Assuming that the concentration of Cr^{6+} in leather is 0.15 mg/kg, the lowest non-zero concentration identified in the literature, the sum of oral and dermal exposure to Cr^{6+} from leather gloves, purses, and couches were calculated to be 0.00323, 0.00206, and 0.0115 µg/day, respectively. The sum of oral and dermal exposure from leather gloves, purses, and couches, assuming a worst-case concentration of 26.1 mg Cr^{6+}/kg, were calculated to be 0.562, 0.359, and 2.01 µg/day, respectively. It should be noted that comparing the sum of oral and dermal exposure to a NSRL derived for oral exposures to Cr^{6+} is considered conservative based on the low extent of dermal absorption of Cr^{6+} relative to the gastrointestinal absorption of ingested Cr^{6+}. **Conclusions:** Based on this work, mean and maximal exposures to Cr^{6+} from drinking water would exceed the derived oral NSRL, highlighting the need to continue monitoring efforts of chromium in public water supplies. Furthermore, the exposure assessment conducted for leather gloves, purses, and couches highlight the significant variability of Cr^{6+} in natural leather products such that low levels of exposure are unlikely to exceed the derived NSRL. Exposures to the highest identified levels of Cr^{6+} in leather products did not exceed the derived NSRL for leather gloves or purses, however, the exposure scenario for leather couches did slightly exceed the derived NSRL. Nonetheless, the estimated exposure from drinking water exceeded that from each of the consumer products considered herein. As such, Cr^{6+} in public drinking water may represent a target for future efforts to reduce Cr^{6+} exposure to average Californians.

PS 3634 Using next generation risk assessment to make safety decisions for cosmetic ingredients under regulatory scrutiny

S. V. Cable, M. Baltazar, and M. Dent. Unilever, Bedford, United Kingdom. Sponsor: *P. Carmichael*

Background and Purpose: In 2019, the European Commission established a list of chemicals that were thought to have endocrine activity and therefore required further safety assessment by the Scientific Committee on Consumer Safety (SCCS). A priority list A and list B were compiled consisting of 28 materials in total, including UV filters and preservatives used in cosmetics. Cosmetics Europe's Long Range Science Strategy (LRSS) initiated a series of systemic toxicity case studies to practically implement, test and refine non-animal-based workflows in applied safety assessments using these priority list chemicals as examples of the application of Next-Generation Risk Assessment. Next Generation Risk Assessments (NGRA) should be exposure-led, hypothesis driven and designed to prevent harm. Published ab initio systemic toxicity case studies such as phenoxyethanol (ENV/CBC/MONO(2021)35) and coumarin (Baltazar et al, 2020) followed these principles in comparing estimates of internal exposure to *in vitro* measures of bioactivity to determine bioactivity:exposure ratios (BERs) to understand the likelihood of systemic bioactivity occurring at consumer relevant concentrations. **Methods:** Use case scenarios were identified for each case study chemical (Octocrylene, Butylated hydroxytoluene, Climbazole and Ocytlmethoxycinnamate) based on regulatory limits, alongside benchmark comparators (Prochloraz, 4-MBC, Aminoglutethimide and Diethylstilbestrol) known to have endocrine activity. Data were generated in a suite of assays including; *in vitro* ADME experiments for parameterising physiologically-based kinetic (PBK) models, *in vitro* pharmacological profiling of protein interactions, cellular stress assays, and high throughput transcriptomics in 3 cell lines (HepaRG, HepG2, MCF7). Points of departure (PoDs) were determined where appropriate from each assay using custom Bayesian statistical models to analyse the dose response data or IC50s were derived from the pharmacological profiling data. These PoDs were then compared with plasma C_{max} estimates from the PBK models to calculate BERs for each chemical exposure scenario identified. **Results:** Low risk use scenarios were defined for the case study chemicals based on SCCS opinions and regulatory limits, and plasma C_{max} estimates were calculated for each ranging from 0.0034 µM (0.2% climbazole in a face cream) to 0.08 µM (10% OMC in a sunscreen). For each case study the leading PoD from the *in vitro* assays came from either the transcriptomics data or the pharmacological profiling IC50s. Following incorporation of uncertainty analysis in the exposure estimates, BER values were calculated for each chemical-use scenario ranging from 0.4 (10% OMC in a sunscreen) to 21 (0.2% Climbazole in a face cream). Similar data were also generated for the comparators where high risk exposure scenarios were identified resulting in BERs ranging from 0.00002 (Ingestion of 2.5 mg Prochloraz) to 0.08 (4% 4-MBC in a sunscreen). **Conclusions:** The results from the application of a non-animal-based workflow and early tier tools demonstrated that these methods can differentiate between high and low risk chemical exposure scenarios as there was no overlap in the BERs determined for high and low risk benchmarks.

PS 3635 Characterizing the narcotic effects of acute nonpolar solvent exposure by quantitative comparison of reaction time data to alcohol-intoxicated subjects in human studies

E. A. Frank, and R. J. Smith. NIOSH, Cincinnati, OH.

Background and Purpose: NIOSH develops Immediately Dangerous to Life or Health (IDLH) values to protect workers from serious injury or death in the event of unforeseen exposures to high concentrations of chemical gases such as during an accidental release or spill. IDLH values are used in combination with direct monitoring and are designed to enable workers to evacuate a workplace without experiencing irreversible or potentially lethal health effects, including incapacitating effects that could impair a worker's ability to escape further exposure. Experimental data from studies in human volunteers can be used to measure the narcotic effects of exposure to nonpolar solvents such as toluene, but there are no well-accepted definitions or standards for what constitutes an incapacitating effect level for the purposes of determining an IDLH value or any other kind of short-term toxicity estimate. **Methods:** This work evaluated the feasibility of characterizing changes in simple reaction time (SRT) test performances in human volunteers acutely exposed to toluene by way of quantitative comparison to the effect magnitudes observed in human subjects administered similar SRT tests under the influence of alcohol as measured by blood alcohol content (BAC). Datasets were identified from literature that reported SRT performance in both toluene-exposed and alcohol-administered subjects in sufficient detail to compare the effect sizes across datasets. These data were used to quantitatively estimate the concentration of toluene in acute exposures causing a degradation on SRT performance equivalent to a known BAC. Two key studies exposed groups of 12 adults to 100, 300, 500, or 700 ppm toluene for 20-minute periods, while 40 adults were tested at measured BACs of 0.02, 0.035, 0.05, or 0.08%. The relative impact of intoxication on SRT performance was expressed in terms of the ratio of group mean change in SRT in the intoxicated subjects compared to SRT performance of unexposed controls. Ordinary least squares were used to fit linear dose-response functions to the group mean SRT ratios for intoxicated:control subjects and estimates of the toluene concentration associated with impaired SRT performance equivalent to a given BAC were derived by multiplying the BAC by the alcohol:toluene ratio of the fitted slopes. Precision of estimation of the toluene concentration was based on 95% confidence limits for the ratio of the slopes. **Results:** Group mean performance degradations in SRT tests in toluene- or alcohol-intoxicated groups were fitted to ordinary-least-squares functions, yielding central estimates of toluene concentrations corresponding to performance at a given BAC along with the confidence limits of the comparisons. The effects of 0.03, 0.05, or 0.08% BAC were functionally equivalent to exposure to 300, 500, and 810 ppm toluene with exposure durations of 20 minutes. The lower-bound 95% confidence limits were 170, 290, and 460 ppm, respectively. The risk of error from bias due to differences in representation of group means (arithmetic vs geometric averaging) ranged from 0.1 to 0.5%, appearing negligible. **Conclusions:** Data related to acute neurological impairment and narcosis in alcohol-intoxicated adult subjects may be used to characterize the effect of acute exposure to nonpolar solvents such as toluene. This provides a context for determining when changes in experimental endpoints signify a level of impairment that would affect a worker's ability to escape from a hazardous workplace during an emergency. This approach leverages the considerable body of quantitative data on the acute neurobehavioral effects of alcohol in adults to characterize the concentration-effect relationship of nonpolar solvent exposure in terms of risk policy and provides a recognizable standard for consideration of functional impacts in workers.

PS 3636 Hazard Identification and Risk Assessment of Non-Nicotine Ingredients in Oral Nicotine Pouches

M. E. Pitegoff, *V. E. Haase*, C. A. Anderson, and R. W. Morgan. Altria, Richmond, VA.

Background and Purpose: Oral tobacco-derived nicotine pouch products or nicotine pouches (NPs) are a relatively new tobacco product category that does not contain leaf tobacco but instead contain tobacco-derived nicotine and non-tobacco ingredients, principally food-grade flavors, and filler material such as cellulose-based fibers. Toxicants that are typically present in combustible and smokeless tobacco products are substantially lower in NPs and in most cases below method limits of quantitation. We evaluated individual ingredients for potential toxicological risks that may be associated with their use. In the absence of tobacco product-specific ingredient standards, most flavors used in NPs are generally recognized as safe (GRAS) for foods, and processes for determining the safety of food additives provide guidance for toxicological assessments. However, there are conflicting or incomplete safety data for some flavor compounds, and this raises uncertainty about health risks from long-term exposure. We present a case study of hazard identification and toxicological risk assessment for two flavor compounds, maltol and ethyl maltol, that concludes that they do not present a toxicological risk after a lifetime of exposure. **Methods:** Literature databases were searched to locate relevant preclinical and clinical data that characterize the toxicological effects of maltol and ethyl maltol. Curated safety and toxicity information underpinning the recommended daily intake levels or guidance values established by regulatory agencies and authoritative institutions were also identified. Study quality was considered with, for example, good laboratory practice (GLP) studies ranked higher

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