as the daily intake level posing a 10^{-5} lifetime risk of cancer. We performed a dermal exposure risk assessment to better understand the potential cancer risk associated with exposure to formaldehyde from personal use of hair relaxing products. Results from published bulk sampling studies reported formaldehyde concentrations in hair relaxing products ranging from below the limit of detection of 0.017 ppm up to 115,000 ppm. A systemic exposure dose (SED) was calculated for dermal application of hair relaxer using the formaldehyde concentrations, published exposure parameters for scalp surface area, skin adherence, hair relaxer retention factor, and percent dermal absorption of formaldehyde. The estimated SEDs ranged from 6.4 to 368 µg/day for formaldehyde concentrations reported in the literature. However, daily exposure to hair relaxers is not expected as the maximum recommended frequency of use is every two months as advised by the American Academy of Dermatology. Thus, to model a realistic use pattern, a less-than-lifetime (LTL) adjustment was applied to estimate exposure to formaldehyde from lifetime typical use of hair relaxing products. Using Haber's law (concentration × time = constant), which relates time and dose assuming that there is a linear relationship between time and toxicity, one can determine the appropriate cumulative dose. Assuming hair relaxer use up to six times per year for 70 years, the cumulative systemic lifetime exposure ranged from 2,688-154,560 µg of formaldehyde which is less than the cumulative lifetime NSRL of 1,022,000 µg. Our calculated MOS values were all greater than 1 (6.61-380), indicating that a significant risk of cancer from dermal exposure to formaldehyde from consumer use of hair relaxers following typical use is not expected. Our model includes some conservatisms, including the assumption that hair relaxer is used six times per year continuously for 70 years, and the inclusion of the highest reported formaldehyde concentration, which is not representative of most commercially available hair relaxers. The exposure assessment approach utilized in this study can be used to estimate the risk of other chemicals or endpoints of interest, including potentially adverse effects of other chemicals present in hair relaxers or in other products. One limitation of the model we present here is that only dermal formaldehyde exposure is being modelled, and inhalation exposure is also expected to occur through consumer use of hair relaxers. Our work modeling the dermal exposure is an important component of a comprehensive risk assessment.

4483 Evaluating the Reproductive Toxicological Potential from Dermal Exposure to Butylphenyl Methylpropional, a Popular Fragrant Chemical

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Butylphenyl methylpropional, more commonly known as Lilial®, is a synthetic aromatic compound that has historically been used as a fragrance additive in a variety of consumer products including household cleaners, detergents, and hair styling products. As of March 2022, Lilial® was banned for use in products on the European Union (EU) market due to the compound's classification as a 1B carcinogenic, mutagenic or reprotoxic (CMR) substance based on repeated dose oral toxicity studies conducted in rats. Specifically, Lilial® is presumed to be a reproductive toxicant because of adverse effects observed in the testes of male rats following oral exposure to Lilial®. While the EU has banned Lilial®, there is currently no ban on the use of the compound in products sold on other markets around the world; thus, there is a need to better characterize the potential toxicity of Lilial® to humans. In order to understand the possible reproductive toxicity risk associated with exposure to Lilial® from personal use of hair styling products, a quantitative dermal risk assessment was performed. Margin of safety (MOS) values were calculated to compare estimated human exposure levels, expressed as systemic exposure doses (SEDs), to an established derived no effect level (DNEL). MOS values greater than 1 indicate that there is not an increased risk of a health endpoint (e.g., reproductive toxicity) based on the exposure scenarios used in the calculation. The SEDs in this analysis were estimated to reflect typical and worst-case exposure scenarios to Lilial® from the dermal application of hair styling products over a 70-year life. In order to calculate the typical and worst-case SEDs, the concentration of Lilial® found in a popular hair styling product, an estimated hair styling product retention factor, and assumptions regarding the amount and frequency of hair styling product used by an individual (i.e., the average amount of product used weekly for a typical exposure scenario and the 95th percentile amount of product used daily for a worst-case exposure scenario) were considered. The estimated SEDs ranged from 0.267 mg/kg/day to 4.43 mg/kg/day. The lower- and upper-bound SEDs were then benchmarked against a DNEL of 0.89 mg/kg/day for Lilial®, which has been reported as a systemic, long-term DNEL derived to conservatively protect against reproductive toxicity, and MOS values were calculated for both exposure scenarios. The resulting MOS values ranged between 200- and 3500-fold greater than 1, indicating that dermal exposure to Lilial® through the lifetime use of Lilial®-containing hair styling products is not expected to contribute to reproductive toxicity. Adjustments to the exposure assessment approach utilized in this study can be made in order to estimate the risk of other chemicals or endpoints of interest.

4484 NAM-Related Robustness Analysis of Commercial hiPSC-Cardiomyocytes in the Light of Preclinical Cardiac Risk Assessment

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The use of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) in combination with new approach methodologies (NAMs) continues to increase in preclinical cardiac risk assessment. Especially commercial hiPSC-CMs play an important role as a stable source of biological material. Nevertheless, lot-to-lot robustness and the possibility to assess drug responses without the presence of serum is needed to address potential hazardous side effects reliably. Here we analyzed the lot-to-lot consistency of commercial human iPSC-CMs (iCell Cardiomyocytes[2], FCDI) as well as the effects of a defined serum-free medium on these cells. Contractile properties served as functional readout and were assessed with the FLEXcyte 96 technology using gold standard compounds nifedipine, sotalol, erlotinib and doxorubicin. For the robustness analysis, commercial hiPSC-CMs from 10 different cell lots were cultured on flexible membrane substrates for 6 days before compound treatment. Pre-compound conditions were analyzed regarding two parameters, contraction amplitude and beat rate. Cells were then treated acutely with two different concentrations of nifedipine and sotalol. Changes in amplitude and duration were analyzed and compared among the cell lots. To test the effect of serum-depletion on the dynamic mechanical activity of hiPSC-CMs, the cells were cultured for 6 days in either serum-free or serum-containing medium. Subsequently, their contractile properties were analyzed. Finally, the pharmacological response to chronic treatment (5 days) with erlotinib and doxorubicin was recorded. The pharmacological comparison of ten lots of hiPSC-CMs with sotalol and nifedipine showed robust results with non-significant fluctuations. Similar results were obtained in the serum-free study with comparable reactions of hiPSC-CMs cultured in either serum-containing or serum-free medium. Both studies demonstrate the stable performance of commercial hiPSC-CMs in combination with the FLEXcyte 96 technology, thus prove this combination to be a robust approach for human-relevant preclinical cardiac risk assessment.

4485 A Preliminary Quantitative Risk Assessment of Inhalation Exposure to Diethanolamine and Respiratory Effects

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Diethanolamine (DEA; MW=105.14 g/mol) is used in various industrial chemical processes. This work describes a preliminary quantitative risk assessment of DEA inhalation exposure and respiratory effects to extrapolate to the occupational context. The best available data identified were from a low dose inhalation exposure study (Gamer et al. 2008) using a head-nose apparatus to dose groups of 13 Wistar rats (strain CrlG1xBr1Han:WI) of each sex. Animals were exposed to 0, 1.5, 3, or 8 mg/m^3 of aerosolized DEA for 6 hours/day, 5 days/week, for a total of 30 hours/week, with exposures on 65 of 99 days (90-day study). The endpoint laryngeal epithelial squamous metaplasia in male rats had sufficient non-zero dose group counts of 0, 0, 3, and 9 with increasing dose and a significant Cochran-Armitage one-sided exact trend test ($p<0.0001$). This endpoint was deemed appropriate for dose-response modeling. Frequentist and model average (MA) approaches used the U.S. Environmental Protection Agency (EPA) Benchmark Dose Software version 3.2.0.1, with a 10% benchmark response, estimated background, extra risk, and 95% confidence interval. To extrapolate to a 40-hour work week, the point of departure (PoD) was multiplied by a factor of 30/40, or 0.75. Since DEA is an aerosol, the PoD was also multiplied by a dose adjustment factor equal to a regional dose deposition ratio of 0.08. Uncertainty factors (UFs) were used to account for interspecies, interindividual, and subchronic to chronic uncertainty and variability, following Dankovic et al. 2015. It was assumed that laryngeal epithelial squamous metaplasia is a site of contact effect, and as such is assumed to have similar toxicokinetic effects across species. The toxicokinetic component of the interspecies and interindividual uncertainty factors were set to 1, with the toxicodynamic component values of 2.5 for interspecies and 3.2 for interindividual UFs providing the basis of each total UF. The sub-chronic to chronic uncertainty factor was set to 3. The overall UF=24, calculated by multiplying individual UFs. The MA benchmark concentration (BMC) and benchmark concentration lower bound (BMCL) values for the endpoint of laryngeal epithelial squamous metaplasia in male rats were 2.3 mg/m^3 and 1 mg/m^3, respectively. The viable, recommended model, based on standard criteria from the U.S. EPA for the frequentist suite, was the multistage degree 3. This model had the lowest Akaike Information Criterion value of all frequentist models (37.1). The BMC and BMCL values for this model were 1 mg/m^3 and 0.7 mg/m^3, respectively. Although these values are lower, the MA values consider information available from all individual models contributing to the MA. The MA approach thus considers a broader set of dose-response relationship information than that considered by an individual model. The MA results were used to determine a human equivalent concentration (HEC). This gave an 8-hour time weighted average HEC, using the MA BMCL value, of [(1 mg/m^3) * 0.75 * 0.08]/24=0.0025 mg/m^3

(0.58 ppb). Similar calculation using the BMC=2.3 mg/m^3 results in a HEC of 0.006 mg/m^3 (1.4 ppb). The resulting 8-hour time weighted average value of 0.58 ppb has relevance for inhalation exposure to DEA in the occupational setting.

4486 Dissolution of Inorganic Lead (Pb) Compounds in Synthetic Sweat to Assess Risk of Dermal Exposure

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It is estimated that over 4.53x10^8 kg of inorganic lead (iPb) compounds were manufactured in the U.S. in 2020. Over 1.4 million U.S. workers have dermal exposures to iPb compounds in several industries with loading of iPb on hands varying widely (0.005-16.1 µg/cm^2). *In vitro* skin studies suggest that dermal exposures to iPb could increase blood lead levels (BLLs) by as much as 6.3 µg/dl. However, these studies did not evaluate the dissolution of iPb compounds in skin surface film liquids (SSFLs) (including both synthetic sweat and sebum) to determine the potential for Pb ion formation. Dissolution is a critical factor to determine dermal bioaccessibility and is different than solubility. Dissolution measures ion formation in SSFLs, does not necessarily reach equilibrium, and can be influenced by physiochemical interactions with the components in SSFLs. Dissolution data can be used to model bioavailability via dermal absorption using both the concentration of dissolved ions in sweat, and the permeation rate (Kp) of chemicals through the skin. As far as we know, the dissolution of iPb compounds under biologically relevant conditions has not been published. The study objectives were to 1) determine the pH-dependent static dissolution of four iPb compounds in SSFLs: Pb^{2+} nitrate (PbN), Pb^{2+} acetate (PbA), Pb^{2+} oxide (PbO), $Pb^{2+/4+}$ red oxide (PbRO); 2) evaluate iPb dissolution kinetics; and 3) provide screening estimates of the potential impact of these compounds on BLLs (assuming exposure to hands only). Statistical analysis using SAS® to fit negative exponential functions to data and calculate dissolution parameters were completed. Using the output from these data analyses, along with dermal loading estimates of Pb compounds in workplace settings, provides a starting estimate for the concentration of Pb ions potentially available in the sweat layer on skin. Estimated concentration of Pb ions available on the skin was used along with available permeability coefficients (Kp) to provide more robust understanding for the potential for dermal bioavailability of these compounds. The iPb compounds are bioaccessible in SSFLs; PbN and PbA have greater dissolution at 8 h (36.4-61.1%) compared to PbO and PbRO (0.01-2.5%). pH has a statistically significant effect on bioaccessibility for all four compounds tested. Screening estimates suggest that BLLs may be increased by 0.7-8 µg/dL for these iPb compounds. The screening level estimates based on this model suggest that the impact on BLLs warrants a more comprehensive assessment. In occupational settings where other routes of exposure to iPb may be relevant, dermal exposure estimates may represent a significant relative source contribution to overall body burden of Pb exposure. Examination of the impact of dermal exposures on BLLs could be incorporated into physiologically-based pharmacokinetic models (PBPK) to provide a more robust understanding of n the impact on BLLs. Given the potential for Pb ion availability to enable dermal absorption of Pb as demonstrated in this study and previously in the literature, reducing Pb exposure on skin may be important for reducing overall worker exposure to iPb. More research is needed including dissolution of iPb particles from industrial settings and the impact of particle size on dissolution.

4487 Avian Risk Assessment for 1,1,2-Trichloroethane in Surface Water

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1,1,2-Trichloroethane is an anthropogenic chemical primarily used as an intermediate in the production of 1,1-dichloroethene and 1,2-dichloroethane. In 2019, 1,1,2-trichloroethane was designated as a high priority substance for risk evaluation following the process required by section 6(b) of the Toxic Substances Control Act (TSCA). The U.S. Environmental Protection Agency (EPA) determined that this chemical's potential toxicity in birds is a data gap that needs to be filled. Thus, the current study conducted an avian risk assessment for 1,1,2-trichloroethane in surface water using existing data by considering (i) environmental concentrations of 1,1,2-trichloroethane and (ii) toxicity benchmarks derived from studies on 1,1,2-trichloroethane analogues as well as modeling data obtained for 1,1,2-trichloroethane from U.S. EPA's Web-based Interspecies Correlation (Web-ICE) tool. We calculated the average, median, and 95th percentile concentrations of 1,1,2-trichloroethane measured in approximately 40,000 surface water samples available from the Water Quality Portal (WQP), a public database that contains water-quality records from more than 400 federal, state, and local agencies. We found that the detection frequency of 1,1,2-trichloroethane in environmental samples is very low (e.g., <1% in surface water). Using the 95th percentile of the measured 1,1,2-trichloroethane concentrations from surface water, we predicted daily doses of 1,1,2-trichloroethane in bobwhite quails, mallard ducks, and Canadian geese, representing a range of potential avian sensitivities to chemical toxicities. The estimated exposure doses in birds due to ingestion of water containing 1,1,2-trichloroethane were lower than the toxicity benchmarks identified for 1,1,2-trichloroethane analogues as well as the estimated hazardous dose (HD_5) for 1,1,2-trichloroethane of 22 mg/kg, which would be protective of 95% of avian and mammalian species. The hazard quotients for daily exposure ranged from 3.34x10^{-5} to 8.35x10^{-5}; even if birds consumed surface water at the 95th percentile of measured 1,1,2-trichloroethane concentration for an entire lifetime, their cumulative 1,1,2-trichloroethane dose would remain well below the HD_5. Based on these analyses, we conclude that 1,1,2-trichloroethane is not anticipated to be a risk to birds that may be exposed to this chemical via ingestion of contaminated surface water.

4488 Making Safety Decisions for a Sunscreen Active Ingredient Using Next-Generation Risk Assessment: Benzophenone-4 Case Study

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Performing safety assessments for systemic toxicity without using any animal data is a significant challenge. Although an increasing number of examples are becoming available, there are few examples of next generation risk assessment (NGRA) being used to address the systemic safety of an ingredient of regulatory interest, such as a UV filter. The purpose of this work was therefore to see if new approach methodologies (NAMs) could be used to evaluate the systemic safety of such an ingredient. Benzophenone-4 is used at an inclusion level of up to 5% in sunscreen products and other formulations to prevent damage caused by the sun. An exposure-led and hypothesis-driven safety assessment was conducted, based on the International Cooperation on Cosmetics Regulation principles of Next Generation Risk Assessment and the Safety Evaluation Ultimately Replacing Animal Testing (SEURAT-1) *ab initio* safety assessment workflow. The overall hypothesis was that if biological activity measured using a broad suite of human-relevant test systems is not observed at concentrations experienced systemically by sunscreen users, there can be no adverse effects associated with product use. To test this hypothesis, experiments and computational modelling were conducted to i) provide a predicted consumer systemic exposure concentration of benzophenone-4, to compare with ii) point(s) of departure obtained using human-relevant NAMs which provide information on bioactivity of benzophenone-4. Bioactivities assessed included perturbation of cell stress pathways, *in vitro* pharmacological profiling, and high throughput transcriptomics in four different cell types. Because physiologically-based kinetic modelling indicated that concentrations of benzophenone-4 would be higher in the kidney than in any other organ, this included a primary human renal proximal tubular cell model. The safety decision relied on a calculation of a range of Bioactivity:Exposure Ratios (BERs) for different types of bioactivities. The median plasma level of benzophenone-4 was predicted to be 1.3 µM, with a 95th percentile of 9.8 µM. Benzophenone-4 showed very little biological activity, including in primary renal cells. A lowest point of departure of 4.2 µM was obtained from the transcriptomics assay in HepG2 cells, as at this concentration a single gene was differentially expressed. Because changes in single genes may or may not have toxicological significance, it is also important to consider whether gene changes could be meaningful by only calculating PODs where more than one gene present in a pathway is differentially expressed. This was done by benchmark dose pathway modelling using BMDExpress2, and the HepG2 BMDL was calculated to be 240 µM. This provided assurance that the single gene change seen at 4.2 µM is of limited toxicological significance. The cells stress panel, *in vitro* pharmacological profiling and BMD analysis of transcriptomics data provided median BERs between 110 and 510. Therefore, based on this toolbox, no significant bioactivity would be expected in the human body at relevant exposures. In summary, this case study demonstrated that NGRA is a protective and useful approach for the safety evaluation of this UV filter.

4489 Derivation of an Acceptable Daily Intake for Cannabidiol (CBD)

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The aim of this work was to derive an oral acceptable daily intake (ADI) for cannabidiol (CBD) when present in hemp-based dietary supplement products, as a detectable impurity or as a naturally occurring constituent at less than 70% of the hemp extract. At the time this research was conducted, the UK Committee on Toxicology of Chemicals in Food, Consumer Products and the Environment (COT) was the only authoritative body to propose an ADI (4 mg/day) for CBD intended for general consumption. A comprehensive literature search was conducted and all studies relevant to potential toxicological effects of oral CBD consumption in animals and humans were reviewed. The key studies selected for the derivation of a point of departure (POD) for this assessment included three randomized, controlled trials in human subjects being treated with the CBD drug Epidiolex® for epilepsy-related conditions. These studies ranged from three weeks to 14 weeks in duration and tested doses up to 20 mg/kg-day CBD. By pooling data on liver enzyme activities from these studies, it was determined that patients treated with 20 mg/kg-day CBD had elevated alanine aminotransferase (ALT) serum concentrations greater than 5-fold higher than the upper limit of normal (ULN). This observation occurred in

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