(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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