PS 2227 An Inhalation Risk Assessment for Measured Ambient Air Concentrations of 6: 2 Fluorotelomer Alcohol.

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6:2 Fluorotelomer Alcohol (CAS# 647-42-7, 1-Octanol-3,3,4,4,5,5,6,6,7,7,8,8,8 tridecafluoro-, 6:2 FTOH) is a raw material used for manufacturing surfactant and polymeric products. 6:2 FTOH vapor phase inhalation is a potential exposure route. The aim of the current investigation was to 1) compare the oral and inhalation repeated-exposure toxicity data to confirm systemic toxicity, target organs, and lack of an exposure route effect, 2) confirm similar metabolic and toxicokinetic profiles via both exposure routes, and 3) conduct an inhalation risk assessment for reported ambient air concentrations. In an inhalation range-finder (5-days) and a 28-day inhalation toxicity study, the profile of 6:2 FTOH and its metabolites in plasma under controlled inhalation exposure was investigated as well as the systemic toxicity and target organs. These studies provided a basis for toxicity comparison, plasma metabolites, and dosimetry between inhalation and oral dosing. Similar toxicity, metabolic and toxicokinetic profiles via both exposure routes was confirmed. Benchmark Dose Analysis (BMD) was conducted on the subchronic toxicity endpoints to determine the most sensitive effect and the corresponding BMD associated with this effect. Based on this analysis, the corresponding human equivalent dose (HED) was calculated to be 1.4 mg/kg bw/day. An additional assessment factor of 2 was applied to extrapolate from the subchronic exposure to a chronic exposure and resulted in a final HED of 0.7 mg/kg bw/day. An equivalent air concentration was determined using an allometric scaling factor to arrive at a human equivalent concentration (HEC) of 2.5 mg/m3. This HEC was then divided by the reported indoor and outdoor air concentrations to arrive at a margin of exposure (MOE). MOEs calculated for inhalation exposure to indoor or outdoor air ranged from 1.1E+05 to 2.5E+07. This assessment indicates there is no human health risk expected even at the highest ambient air concentrations of 6:2 FTOH reported.

PS 2228 Derivation of an Occupational Exposure Limit for Inorganic Borates Using a Weight of Evidence Approach.

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Inorganic borates are encountered in many settings worldwide, spurring international efforts to develop exposure guidance (U.S. EPA 2004; WHO 2009; ATSDR 2010) and occupational exposure limits (OEL) (ACGIH 2005, MAK 2011). We derived an updated OEL to reflect new data and current international risk assessment frameworks. We assessed toxicity and epidemiology data on inorganic borates to identify relevant adverse effects. International risk assessment frameworks (IPCS 2005; IPCS 2007) were used to evaluate endpoint candidates: reproductive toxicity, developmental toxicity, and sensory irritation. For each endpoint, a preliminary OEL was derived and adjusted based on consideration of toxicokinetics, toxicodynamics, and other uncertainties. Dose-response modeling supported selection of the point of departure for each endpoint. Developmental toxicity was the most sensitive systemic effect. An OEL of 1.6 mg B/m3 was estimated for this effect based on a point of departure (POD) of 63 mg B/m3 with an uncertainty factor (UF) of 40. Sensory irritation was considered to be the most sensitive effect for the portal of entry. An OEL of 1.4 mg B/m3 was estimated for this effect based on the identified POD and an UF of 1. Reproductive effects are not the most sensitive basis for OEL derivation. An OEL of 1.4 mg B/m3 was derived as an 8-hour TWA based on sensory irritation potential. The OEL is expected to protect from systemic toxicity endpoints.

PS 2229 US EPA Decabromodiphenyl Ether Alternatives Hazard Assessment Results.

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The U.S. Environmental Protection Agency (US EPA) Design for Environment (DfE) Program undertook a chemical alternatives assessment for decabromodiphenyl ether (decaBDE) as part of the Action Plan for Polybrominated Diphenyl Ethers (PBDEs) published in December 2009. DfE convened a multi-stakeholder partnership to explore the human health and environmental profiles of functional and viable alternatives to decabromodiphenyl ether (decaBDE). The partnership identified ~ 30 functional alternatives to decaBDE. The hazard assessment for decaBDE and the alternatives used DfE hazard evaluation criteria to assign hazard designations for human health toxicity, ecological toxicity and environmental fate endpoints. The alternatives included a range of flame retardant chemistries including both halogenated and non-halogen organic substances, inorganic materials, polymeric and non-polymeric substances and novel, new to market substances. Some alternatives were well characterized for all endpoints, while others were lacking data. Analog data, predictive models, structural alerts and expert judgment were used to make hazard designations for endpoints with data gaps. Trends for human health, ecological toxicity and fate characteristics were indicated in a number of the alternatives and are described in the poster. In general, molecular size ranges, molecular structures, and/or functional groups were found to be most influential on the hazard designations. A novel component of this assessment was the evaluation of higher molecular weight polymers for their human health and ecological toxicity based on their low potential for bioavailability and variability in low molecular weight components. Effective hazard assessment approaches of hazard criteria coupled with decision-making protocols are practical tools for businesses to use early in materials selection processes and will contribute to more sustainable product development. The resulting hazard profiles should be of value to manufacturers making substitution decisions in preparation for the upcoming decaBDE phase out.

PS 2230 Predicting Bioavailability of Arsenic in Mining Soils.

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Arsenic (As) is a naturally occurring element in soil and a key chemical of concern at former mine sites in California. Risk assessment calculations typically utilize default oral toxicity values, which are based on ingestion of readily soluble forms of As such as sodium arsenate (NaAs). However, mining soils in California are relatively high in iron hydroxide phases that bind As strongly, resulting in reduced solubility/bioavailability. The juvenile swine model is an approved, but often cost prohibitive, method for determining the relative bioavailability (RBA) of As in soils compared to that of NaAs. RBAs can be used to adjust toxicity criteria, resulting in a more accurate site-specific risk assessment. In vitro methodologies have proven to be useful surrogates for in vivo feeding studies in predicting bioavailability for other metals but lack precision for arsenic, particularly in high iron content soils. Six soil samples collected from Empire Mine State Historic Park (total As 302-12,041 mg/kg) were analyzed in the juvenile swine model. RBA's ranged from 4 to 20%. Gastrointestinal modeling correlated but underestimated RBA (1-9%). Sequential chemical extraction procedures (SEP) were applied to fractionate the As in soils into (F1) non-specifically sorbed; (F2) specifically sorbed; (F3) amorphous and poorly-crystalline oxides of Fe and Al; (F4) well-crystallized oxides of Fe and Al and residual As phases. The results of these extractions demonstrated that the sum of non-specifically sorbed and specifically sorbed arsenic (F1+F2) was similar to the predicted in vitro bioaccessibility while F1+F2+F3 is a conservative estimate of the in vivo RBA (10-50%). SEP could prove to be a cost-effective and valuable screening tool for estimating in vivo RBA. In summary, the assumption of 100% bioavailability of As in mining soils grossly overestimates exposure and risk to human health. Adjustments for As bioavailability in these materials and similar mining wastes provides a more accurate assessment of human exposure.

PS 2231 A Quantitative Risk Assessment of 1-Bromopropane, Based on Tumor Data.

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The "green" movement has resulted in the introduction of several new "environmentally-friendly" substitutes into commerce, including 1-bromopropane (1-BP; CAS no. 106–94–5). Although use of 1-BP is intended to minimize ozone depletion, occupational exposure is of concern. Case studies, occupational exposure assessments, and epidemiological investigations have suggested that workplace exposure to 1-BP may be associated with neurological, reproductive, and hematological effects. Previous quantitative risk assessments of 1-BP have been based on toxicological studies of these and other non-cancer endpoints. This poster presents a quantitative risk assessment based on a NTP chronic bioassay, in which rats and mice were exposed to 125-500 or 62.5-250 ppm 1-BP, respectively, for up to 2 years. Inhalation of 1-BP produced alveolar/bronchiolar adenomas and carcinomas in female mice, adenomas of the large intestine in female rats, and keratoacanthoma/squamous cell carcinoma of the skin in male rats. Benchmark concentrations (BMC) and lower 95% confidence limits (BMCL) estimates at the 1 in 1000 response level (0.1%) were based on a previously published model average procedure. The BMC (BMCL) estimates were 0.85 (0.41) ppm for alveolar/bronchiolar adenoma + carcinoma; 13.5 (2.76) ppm for large intestine adenomas; and 3.73 (1.44) ppm for keratoacanthoma +squamous cell carcinoma of the skin. The BMC

(BMCL) estimates were extrapolated to humans on a (body weight)$^{0.75}$ basis, assuming a 45-year occupational exposure. Human-equivalent concentrations for a 1 in a 1000 lifetime added risk at the various tumor sites are 0.39 (0.19) ppm, for lung tumors; 6.17 (1.26) ppm for intestinal tumors; and 1.75 (0.68) ppm for skin tumors. These results suggest that even sub-ppm occupational exposures to 1-BP may pose an increased risk of cancer.
The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

PS 2232 Human Health Risk Assessment of Inhaled Acudyne™ Shine Polymer in Hair Care Products.

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ACUDYNE™ Shine is one of a family of acrylic polymers used in hair care product applications such as gels/mousses, and pump or aerosol sprays at concentrations up to 7 wt% to enhance the properties of the product. The pattern of use provides a potential for inhalation exposure to both consumers and salon workers. Sprague Dawley rats were exposed 6 h/day, 5 d/wk, for two- or 13-wks to ACUDYNE™ polymer concentrations of 0, 2, 11, and 100 mg/m^3 or 0, 1, 8, and 82 mg/m^3, respectively, to provide toxicologic data for human risk assessment. A simulated consumer/occupational exposure monitoring study was conducted to determine typical breathing zone aerosol concentrations during product use. In the 13-wk study, no treatment-related changes in daily clinical observations, functional tests, ophthalmology, urinalysis, hematology, clinical chemistry, or coagulation parameters were observed. Males and females exposed to 82 mg/m^3 ACUDYNE™ had increased mediastinal and tracheobronchial lymph nodes, higher absolute and relative lung weights, and chronic-active bronchiolar-alveolar inflammation after 13-wks of exposure. Females also had decreased feed consumption and body weight gains. The No Adverse Effect Concentration was 8 mg/m^3 for males and females. Assuming 100% deposition, the inhaled dose of ACUDYNE™ polymer at an aerosol concentration of 8 mg/m^3 was estimated to be 0.47 mg/gm lung/day in rats. Based on a rat-to-human inhalation dosimetry factor of 24-32, the human equivalent inhaled dose at the same aerosol concentration was estimated to be 11.3 to 15.1 mg/gm lung/day. Results of the exposure monitoring study indicated breathing zone concentrations of respirable aerosol particles of 0.38 and 0.11 mg/m^3 and daily polymer lung deposition of ≤ 0.19 and ≤ 0.44 μg/gm lung for consumer and occupational exposure senerios, respectively. Based on the calculated human equivalent margin of exposure of > 25,000 to 150,000 for all exposure scenarios, repeated daily inhalation exposure to ACUDYNE™ Shine polymer in hairspray formulations poses no significant human health risk.

PS 2233 Derivation of Acceptable Drinking Water Levels for Bromine and Bromide-Releasing Antimicrobial Agents.

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Elemental bromine is the active ingredient in brominating cartridges, and is registered for disinfection of drinking water aboard ships and oil drilling platforms. Since bromine disproportionates in water to bromide (stable) and hypobromite (unstable) ions, this assessment applies specifically to inorganic bromide, whereas health-based guideline values for bromate and organic bromine compounds have been developed elsewhere. Repeated oral exposure in various mammalian species is associated with central nervous system effects expressed as behavioral and EEG changes. Repeated oral dosing also causes a hypothyroid effect that is specific to rats and not observed clinically. In a rat three-generation study with NaBr administered via the diet, the NOAELs for reproductive and parental effects were 48 and 12 mg Br/kg-day, respectively. In oral developmental toxicity studies, the NOAELs for both parental and developmental effects were 77 and 196 mg Br/kg-day, in rats and rabbits, respectively. Chronic administration of KBr or methyl bromide via the diet of rats did not result in treatment-related adverse findings. There is extensive clinical experience with various bromide salts based on their historical use as sedative-hypnotics and in treatment of seizure disorders. When male and female volunteers were administered NaBr capsules for 12 weeks, there was a small effect on EEGs that was reproducible but within normal limits. Serum T4, T3, and related hormone levels remained within normal limits. The most sensitive effect was gastric irritation expressed as nausea that occurred shortly after the ingestion of the capsules, but no longer occurred when the capsules were taken with a meal. Based on the absence of sedation and EEG changes within normal limits, the human systemic NOAEL was 7 mg Br/kg-day. Using a 10x uncertainty factor to account for intraspecies variability, an RfD of 0.7 mg/kg-day was determined for bromide, which corresponds to a Total Allowable Concentration of 12 mg/L in drinking water and accounts for exposure of the general population to bromide from the diet.

PS 2234 Low-Level Arsenic in Drinking Water and Bladder Cancer Risk: Meta-Analysis Update and Risk Assessment Implications.

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A published meta-analysis of relevant case-control and cohort studies was updated with two recent studies to further examine the association between low-level arsenic exposure and bladder cancer risk, and whether meta relative risks (mRR) differed significantly from bladder cancer risks predicted in a 2001 report by the National Research Council (NRC). Cancer risk estimates from NRC (2001), which are based on data from southwestern Taiwan, form the basis of the U.S. Environmental Protection Agency's 2010 proposed cancer slope factor for assessing arsenic cancer risks. Our updated meta-analysis of nine studies improved the precision of the previous estimate (mRR = 1.11; 95% CI: 0.95–1.30), with no significant association observed between low-level arsenic exposure and bladder cancer (1.07; 0.95–1.26; p-heterogeneity = 0.54). RRs for never-smokers in the individual studies and the mRR were consistently below 1.0 (0.83; 0.65–1.06; p-heterogeneity = 0.89). Thus, exposure misclassification/regression to the null cannot explain the lack of a significant positive relationship for never-smokers. The mRR was modestly elevated for ever-smokers, but not significantly, with heterogeneity among studies (1.19; 0.95–1.45; p-heterogeneity = 0.04). To evaluate the independent effect of arsenic in comparison to NRC (2001) risk estimates for the U.S., the mRR for bladder cancer in never-smokers was compared to RRs predicted by NRC (2001) at various water concentrations within the low-level studies and for less than lifetime exposures. The collapsed category mRR for never smokers was 0.82 (0.62-1.10) (using cut-points in individual studies near 50 ppb) and was compared to RRs calculated for non-smokers in the U.S. based on NRC (2001). The 95% CI did not include NRC predicted RRs at 20 or 50 ppb, even for half lifetime exposures (RRs of 1.14 and 1.31, respectively). Results of low-level studies differed significantly from, and were inconsistent with, risks predicted by NRC (2001) for non-smokers including those with less than lifetime exposure.

PS 2235 A Chronic Oral Reference Dose for Hexavalent Chromium.

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Intestinal tumors have been observed in mice (but not rats) following chronic exposure to high concentrations of hexavalent chromium [Cr(VI)] in drinking water. Mice (but not rats) also exhibit histological lesions consistent with intestinal wounding, specifically villous blunting and crypt hyperplasia—collectively termed diffuse hyperplasia. Recent mode of action studies support that these tumors were indeed the result of chronic wounding and regenerative hyperplasia to repair the intestinal mucosa. Herein, we develop an oral reference dose (RfD) that is protective of the tumor precursor lesion (diffuse hyperplasia), and therefore is protective of intestinal cancer. A rodent physiologically based pharmacokinetic (PBPK) model was used to predict internal dose measures for chromium in the duodenum, jejunum, and ileum of mice under the conditions of the 2-year bioassay. These internal dose metrics together with corresponding incidences for diffuse hyperplasia in each intestinal segment were used to characterize the dose-response relationship for the small intestine in a single plot containing a robust dataset with as many as 24 data points. Points of departures (PODs) were derived using benchmark dose modeling and global nonlinear regression, with models providing acceptable fits differing <3-fold. Human equivalent lifetime average dose values were estimated for each POD using two different methods of extrapolation with the human PBPK model for chromium. Dividing the PODs by uncertainty factors (UFs) of 10-30 yields a range of 8 RfD values (2 modeling approaches × 2 human equivalent dose methods × 2 UF values). The resulting RfD range is protective against diffuse hyperplasia, and is therefore protective of both noncancer and cancer effects in the small intestine. This range of RfD values leads to acceptable Cr(VI) concentrations in drinking water that are greater than those typically found in drinking water sources (≤5 μg/L).

PS 2236 Mode-of-Action Evaluation for Hexavalent Chromium-Induced Lung Cancer.

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Inhalation of hexavalent chromium [Cr(VI)] has been associated with increased lung cancer risk among workers of certain industries, but no well recognized or published mode of action (MOA) exists. Although it has been suggested that

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