

means to access information from a large population. However, obtaining pesticide exposure history on the subjects of secondary data sources is difficult. The objective of this project was to develop a model for estimating cumulative pesticide exposure (CPE) of subjects in a secondary health database. A proxy of CPE for cases in a dataset derived from the Mississippi Cancer Registry was calculated by using the age and year at diagnosis, county of residence, and surface area and annual amounts of pesticides (based on harvested crop records) used in the county of residence. Data mining techniques including factor, correlation, and logistic regression analysis were used to measure the strength of association between CPE and the occurrence of specific types of cancer while accounting for gender, race, and age. Because pesticides are tested for lack of carcinogenicity prior to registration, no associations were expected. Among the possible 6,790 potential univariate models of association between CPE of individual pesticides and cancer type, statistically significant associations were found between 13 pesticides and the occurrence of three types of cancer. Odds ratios were generally close to 1.00 suggesting that the associations were weak. The relatively few significant associations that were determined, only 0.002%, suggest that the model is quite specific and is not likely to report many false positives. The model will be applied to other secondary health databases to determine its utility in measuring associations between pesticides and other health outcomes. (Supported by NIH P20 RR17661)

### 1536 ALKYL BENZENE SULFONATES RISK ASSESSMENT.

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The USEPA OPP conducted a human health risk assessment for the linear alkylbenzene sulfonates as part of pesticide tolerance reassessment required by the 1996 Food Quality Protection Act (FQPA). These antimicrobial pesticides are disinfectants and food-contact sanitizers in agricultural, food handling and commercial settings. They are also inert ingredients in pesticide formulations. The EPA selected an oral no-observable adverse effect level (NOAEL) of 50 mg/kg/day, and an inhalation NOAEL of 1 mg/m<sup>3</sup> for use in risk assessment. The Agency applied an uncertainty factor of 100 (10X for inter- and intra-species variability) to the NOAELs, and the FQPA safety factor was removed (1X). Chronic dietary exposure was evaluated for food-contact sanitizing solutions, fruit and vegetable washes, and for inert pesticide formulations applied to agricultural crops and animals. For the inert assessment, the Agency utilized the Dietary Exposure Evaluation Model (DEEM<sup>TM</sup>) that assumed 100% of all commodities and crops were treated. Residential exposures from the inert uses for turf treatment, hard surface cleaners, and pet flea products were evaluated using the EPA's Pesticide Inert Risk Assessment Tool (PiRat), and EPA's Residential Standard Operating Procedures (SOPs). Aggregate assessments were conducted following the USEPA OPP guidance. For children, the aggregate assessment includes average dietary exposure (food and drinking water) from both the active food contact sanitizer uses and the inert uses on agricultural commodities, in addition to estimated incidental oral exposures from hard surface cleaning products as an inert ingredient. For adults, the aggregate assessment includes food and drinking water exposure from both active and inert uses and residential inhalation exposures from wiping hard surface cleaning products. The aggregate oral and inhalation risks are not of concern for adults and children, and the EPA was able to make a safety finding for the existing pesticide tolerances.

### 1537 PROVISIONAL ADVISORY LEVELS (PALS) DEVELOPMENT FOR DICROTOPHOS.

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Provisional Advisory Levels (PALs) that are being developed for hazardous materials by the U.S. EPA represent general public emergency exposure limits. Initial PALs correspond to different effect severity levels (PALs 1, 2, and 3) and exposure durations (24 hours, 30 days, and 2 years). Application of PAL protocols has been performed for the organophosphate pesticide dicrotophos to estimate oral (in drinking water) and inhalation exposure limits, as experimental exposure data permit. The experimental data set for dicrotophos was marginally adequate, including only animal studies. Data gaps are identified. These estimates were evaluated and approved by an Expert Consultation Panel for Provisional Advisory Levels in June 2006.

PAL estimates for dicrotophos will be presented. Oral PAL values for a 24-hour exposure duration to dicrotophos are 0.58 mg/L (PAL 1), 5.8 mg/L (PAL 2), and 9.3 mg/L (PAL 3); for 30-day oral exposure duration, the value is 0.11 mg/L (PAL 1); and for 2-year oral exposure duration, the values are 0.12 mg/L (PAL 1) and 1.2 mg/L (PAL 2). Data were insufficient to derive oral PAL 2 or PAL 3 estimates for the 30-day exposure duration or a PAL 3 estimate for the 2-year exposure duration. Data were insufficient to derive inhalation PAL values for all exposure durations. Route-to-route extrapolation was suggested. The Panel identified a need to compare oral vs. inhalation data for a range of organophosphates, and then use relative

potency and available data to assess the feasibility of using route-to-route extrapolation for estimating inhalation PAL values. In the future, route-to-route extrapolation may be accepted as an approach for deriving PAL values if adequate pharmacokinetic or other data are available. (This abstract presents PAL values that are subject to change pending further review.)

### 1538 OPTIMAL EXPERIMENTAL DESIGNS FOR TESTING COMPLEX NONLINEAR HYPOTHESES: COMPARING THE DOSE THRESHOLDS AND ED30'S IN ADULT VS. JUVENILE RATS.

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The 1996 Food Quality Protection Act set stringent standards to protect children from pesticide risks. To enforce these standards, the United States Environmental Protection Agency requires studies on pesticides to investigate the neurotoxicity of these chemicals. An important design strategy is to compare the dose responsiveness of adult versus juvenile rats. Of concern is that juvenile rats may be more sensitive than adult rats; here, we characterize sensitivity through the dose-threshold and ED30's. Our objective is to describe use of optimal experimental design strategies to test complex nonlinear hypotheses. Here we find the optimal design that minimizes the variance of the test statistic over dose (x) and proportion (q) of the total sample size for simultaneously testing the coincidence of the dose-thresholds and ED30's for adult versus juvenile rats. For illustration purposes we considered a single pyrethroid, Lambda-cyhalothrin. Preliminary estimates of the ED30 and dose threshold for adult Long Evans rats varying in ages from 60-66 days were taken from Wolansky et. al (ToxSci, 2005). We conjecture a 50% decrease in the dose-threshold and/or approximately a 30% decrease in the ED30 for the juvenile rats. Constrained optimal designs were found such that at least 5% of the sample is allocated to each control group. Based on the experimental range used by Wolansky, another constraint was implemented such that the maximum dose does not exceed 15mg/kg. We conclude that the optimal design for testing the hypothesis of coincidence between adult versus juvenile rats depends on (1) the preliminary assumptions about the dose-threshold and the shape of the dose response curves and (2) that the sample proportions are not equal across the dose groups.

### 1539 HUMAN RISK ASSESSMENT FOR CHLORPYRIFOS UTILIZING A CYP-SPECIFIC PBPK/PD MODEL.

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Protecting humans from the toxicological effects of organophosphorus pesticides (OPs) is dependent in part upon accurate physiologically based pharmacokinetic / pharmacodynamic (PBPK/PD) models. OP toxicity is dependent upon the balance between the formation of oxons by cytochrome P450 (CYP) catalyzed desulfuration (activation), dearylation (detoxification) by CYPs and paraoxonase (PON1), and inhibition of B-esterases by oxons. Current PBPK/PD models, which utilize single kinetic constants (Km, Vmax) for a given metabolic pathway, using rat liver microsomes, do not accurately reflect the variability in content and activity of key enzymes (CYPs, PON1) which regulate OP metabolism in humans. Simulations with chlorpyrifos have demonstrated that CYP-specific PBPK/PD models can better estimate exposure, target tissue dose and effects of chlorpyrifos in human populations by incorporating 1) kinetic parameters (Km and Vmax) for OP metabolism by specific human CYPs, 2) hepatic content of specific CYPs, 3) PON1 activity and content, and 4) serum protein binding data for OPs and metabolites into the PBPK/PD model of Timchalk et al., (2002). CYP2B6 and CYP2C19 exhibit low Km and high Vmax values for the desulfuration and dearylation of chlorpyrifos, respectively, supporting their role as the primary enzymes that regulate metabolism at low-level human exposures to chlorpyrifos. Since the hepatic levels of specific CYPs exhibit marked variability across both population and age groups, the CYP-specific PBPK/PD models should prove to be more accurate and more easily modified to address factors such as age, CYP content and genetic polymorphisms in CYP2B6, CYP2C19 and PON1 (biomarkers of susceptibility). CYP-Specific PBPK/PK models for OP pesticides, that better estimate variability in exposure, target tissue dose and effect, will be valuable tools for risk assessment efforts for chlorpyrifos and other OPs in the general population, special exposure groups, and susceptible individuals, exhibiting polymorphisms in CYPs and /or PON1. Supported by US EPA STAR grant R-83068301

### 1540 ASSESSMENT OF HEALTH EFFECTS RESULTING FROM POSSIBLE EMISSIONS FROM A PESTICIDE FORMULATION FACILITY.

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The cyclodiene insecticides, aldrin, chlordane, and heptachlor, were widely used in the 1950s and 1960s for insect control due to their persistence in soil, resistance to degradation, retention of biological activity, and selective toxicity. Cyclodiene pesti-

cides were often prepared for sale at "formulation facilities," wherein bulk quantities of pesticides were received and repackaged into bags of various sizes. In the late 1980s, near one such facility in a rural Illinois town, it was suggested that historical cyclodiene emissions may be posing a health risk to local residents. We designed and implemented a "risk-based" sampling methodology to focus data collection on the needs of a health risk assessment. Samples of residential soils, garden vegetables, well water, and suspended particulates were collected and analyzed. A stratified sampling plan was used to permit distinction between cyclodienes associated with facility emissions vs. those associated with other sources (e.g., homeowner application and/or drift from nearby treated crops). Incremental health risks were then calculated for the "facility-related" cyclodiene concentrations in these media. Three exposure scenarios were developed ("typical", "maximum", and "minimum"), and the following exposure pathways were considered: garden vegetable and incidental soil ingestion, dermal contact with soil, and inhalation of suspended surface soil particles. The estimated incremental carcinogenic risks were  $4.72 \times 10^{-7}$ ,  $9.73 \times 10^{-6}$ , and  $3.75 \times 10^{-7}$  for typical, maximum, and minimum exposures, respectively. The greatest contributor to total carcinogenic risk from all sources combined was found to be the result of homeowner application of cyclodienes to lawns and gardens.

#### 1541 PROVISIONAL ADVISORY LEVELS (PALs) DEVELOPMENT FOR G-SERIES NERVE AGENTS.

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Provisional Advisory Levels (PALs) that are being developed for hazardous materials by the U.S. EPA represent general public emergency exposure limits for 24-hour, 30-day and 2-year durations. Application of PAL protocols has been performed for chemical warfare nerve agents GA, GB, GD, GE and GF to estimate oral and inhalation/ocular exposure limits, as experimental exposure data permit. The experimental data set for agent GB was robust and included controlled human and animal studies. The remaining G-series agents were less well characterized, necessitating PAL estimation on the basis of relative potency. These estimates were evaluated and approved by the Expert Consultation Panel for Provisional Advisory Levels in August 2006.

PAL estimates for all 5 G-agents will be presented. Oral PAL values for 24-hour exposure are 0.037 mg GB/L (PAL1), 0.11 mg GB/L (PAL2), and 0.57 mg GB/L (PAL3); for 30-day oral exposure duration, values are 0.0081 mg GB/L (PAL1), 0.012 mg GB/L (PAL2), and 0.25 mg GB/L (PAL3); for 2-year oral exposure duration, the PAL1 value is 0.0020 mg GB/L. Data were insufficient to derive oral PAL 2 or PAL 3 estimates for the 2-year exposure duration.

Inhalation/Ocular PAL values for 24 hour exposure are 0.00020 mg GB/m<sup>3</sup> (PAL1), 0.0010 mg GB/m<sup>3</sup> (PAL2), and 0.015 mg GB/ m<sup>3</sup> (PAL3); for 30 day inhalation/ocular exposure duration, values are 0.000018 mg GB/ m<sup>3</sup> (PAL1) and 0.00073 mg GB/ m<sup>3</sup> (PAL 2). Insufficient data are available to estimate a 30 day PAL3 value. For 2-year inhalation/ocular exposure duration, the PAL1 value is 0.000018 mg GB/ m<sup>3</sup> (equivalent to PAL1 for 30 days) and the PAL2 value is 0.00016 mg GB/m<sup>3</sup>. Data were insufficient to derive an inhalation/ocular PAL 3 estimate for the 2-year exposure duration. (This abstract presents PAL values that are subject to change pending further review.)

#### 1542 ALTERNATIVE APPROACHES FOR NONCANCER RISK ASSESSMENT OF PHOSGENE.

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Phosgene is primarily used in the polyurethane industry for production of polymeric isocyanates. The majority of phosgene for industrial applications is made on site by the reaction of carbon monoxide and chlorine gas using an activated carbon analyst. Inhalation is the primary route of exposure. The noncancer risk to humans from exposure via inhalation is assessed by deriving a chronic inhalation RfC. The RfC is an estimate of daily exposure to the human population that is likely to be without appreciable risk of deleterious effect during a lifetime. The RfC was based on two inhalation subchronic studies which measured immune response and pulmonary damage. These studies used the same strain of rats with similar exposure protocols. Support for the derivation of the RfC for phosgene came from the use of three different approaches: 1) the traditional NOAEL/LOAEL approach; 2) the benchmark dose (BMD) approach; and 3) the categorical regression (cat Reg) approach for the analysis of severity-graded pulmonary damage data using the recently developed USEPA cat Reg software. The BMD approach was used to determine the RfC for phosgene because it has several advantages compared to the NOAEL/LOAEL approach: 1) it is not restricted to be set of doses used in the experiments; 2) the result is not dependent on sample size; 3) it incorporates information on statistical uncertainty. The cat Reg approach allowed the incorporation

of data on the severity of the pathological lesions, and therefore it complemented the other approaches. Conclusions from the three approaches were consistent. The BMD approach could not be used for the immune response data because it was not possible to define an adverse effect level for bacterial resistance. Use of the NOAEL/LOAEL approach for that data was consistent with the RfC derived from the lung pathology data. This paper will summarize the three approaches used in derivation of the phosgene RfC. The derivation of the RfC uses uncertainty factors to account for variation between humans, extrapolation from animals to humans, and subchronic to chronic exposure duration.

#### 1543 PERCEIVED RISKS AND HAZARDS OF NANOTECHNOLOGY.

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Nanotechnology is the study or application of any matter at the 1-100 nanometer scale. The study objectives were to measure and evaluate differences between nanotechnologists/nanoscientists and environmental health scientists in behavior, knowledge, beliefs and attitudes relating to nano-development. This study surveyed University of Washington faculty associated with the Center for Nanotechnology and the Department of Environmental and Occupational Health Sciences. The hypotheses were that 1) environmental health scientists will perceive greater risk and greater need for nano-development regulation and public awareness than will nanotechnologists and that 2) nanotechnologists will perceive greater benefit to nano-development than will environmental health scientists. Variances in knowledge, communication, and attitudes including trust, regulation and perceived benefits and risks were examined to better understand cross-disciplinary differences. Results indicated that nanotechnologists and environmental health scientists 1) did not trust regulatory agencies to minimize risks of scientific development; 2) tended to not trust business leaders within the nanotechnology industry to minimize risks associated with nano-development; and 3) tended to think the precautionary principle is an appropriate strategy for reducing risks. The two groups tended to differ in that 4) environmental health scientists were statistically significantly more likely to believe that current regulations were insufficient, while nanotechnologists general agreed but the finding was not significant; and 5) nanotechnologists were significantly more likely to think the benefits of nano-development would outweigh the risks, while the majority of environmental health scientists only concurred. These results can be used to improve cross-disciplinary communication about nanotechnology's benefits and potential hazards, and identify appropriate levels of nano-regulation, and spark discussion about methods for nano-regulation.

#### 1544 DEPOSITION OF INHALED NANOPARTICLES IN THE HUMAN LUNG.

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Increased production of industrial devices based on nanostructured materials raises the possibility of environmental and occupational human exposure with consequent adverse health effects. Nanoparticles are suspected of having increased toxicity due to their internal structure and size characteristics that elicit unique carrier transport properties. For this reason, it is important to assess the dose and distribution of inhaled nanoparticles in the human lung. A model of nanoparticle transport and deposition in the human lung was developed based on the convective and diffusive properties of nanoparticles. Local, regional, and total lung deposition was calculated by performing a mass balance on particles moving through each airway of the lung during a breathing cycle. Particle losses due to diffusive transport were found to be insignificant in the upper airways of the lung because of high airflow convection. In the deep lung, particle transport by axial diffusion was significant and deposition tended to occur more distally compared to when axial diffusion was not included in the model. However, total deposition of nanoparticles in the lung was independent of axial diffusion because of high deposition efficiency (near 100%). The nanoparticle deposition model will yield more accurate predictions of site-specific and local deposition of particles and better correlations for dose-response relationships.

#### 1545 CARDIOVASCULAR MORTALITY AND LUNG CANCER RISK FROM DIESEL EXHAUST PARTICULATE IN CALIFORNIA.

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Diesel exhaust particulate (DEP) was identified as a Toxic Air Contaminant by the Air Resources Board in California in 1998 following a lengthy process that included a quantitative risk assessment based on lung cancer in occupational settings.