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P-629 INFLUENCE OF MATRIX FORMULATION ON DERMAL PERCUTANEOUS ABSORPTION OF TRIAZOLE FUNGICIDES USING QSAR AND PBPK/PD MODELS

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The successful use of the Exposure Related Dose Estimating Model (ERDEM) for assessment of human exposure to the triazole fungicides requires the accurate determination of representative and comparable input parameters. In the specific case of dermal exposure, the formulation matrix plays an important role in the absorption and distribution of specific chemicals. Addition of the matrix formulation (vehicle and additives) into a comprehensive physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model is crucial to understanding the effects of triazole fungicides for human risk assessment. Quantitative structure activity relationships (QSAR) were developed and used to obtain k_p values (cm/h) for percutaneous dermal absorption, skin/water and tissue/blood partition coefficients, and metabolic parameter values (V_{max} and K_m) for several triazole fungicides (diniconazole, hexaconazole, cyproconazole, propiconazole, fenbuconazole, uniconazole and triadimefon). Recently, Riviere and Brooks (2005) have developed a hybrid linear free energy relationship (LFER) method to describe the dermal absorption rate, k_p, in the presence of complex chemical mixtures utilizing the following baseline model,

$$\log k_p = c + m\mathrm{MF} + a\sum\alpha_2^H + b\beta_2^H + s\pi_2^H + rR_2 + vV_X,$$

where MF is a mixture factor that accounts for the properties of the formulation matrix; $\sum\alpha_2^H$, $\sum\beta_2^H$ and π_2^H are the usual solvatochromatic parameters describing hydrogen bonding acidity, basicity and dipolarity/polarizability; R_2 represents the excess molar refractivity; and V_x is the standard McGowan volume of the chemical penetrants. The linear regression coefficients *c*, *m*, *a*, *b*, *s*, *r*, and *v* couple these descriptors to k_p. Utilizing the above equation, we have included additional matrix formulation information via a hybrid LFER method to describe the effects of complex mixtures in the prediction of k_p within the framework of a PBPK/PD model.
Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.

P-630 ESTIMATION OF HISTORICAL AIRBORNE RADIONUCLIDE RELEASES BASED ON CONCENTRATIONS MEASURED IN OFF-SITE SOIL

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Introduction
In 1943, a large scientific laboratory was established and quickly became a lead facility for development of atomic weapon components. The environmental impacts of these operations have not been fully characterized. Few airborne effluent measurements were made before 1948, and monitoring was of low quality until the mid-1950s. This study demonstrates a method to estimate cumulative airborne releases of plutonium from the laboratory based on soil measurements collected after 1970.
Methods
Results of analyses of 679 soil samples from 34 locations were evaluated. Of these, 106 samples from 24 locations were considered associated with laboratory activities based on plutonium to cesium ratios that distinguished samples impacted by laboratory activities from those impacted only by worldwide fallout. Of this subset, only those with calculated total uncertainties less than 25% were further evaluated. The final data set included 37 samples from 34 locations within 5.5 kilometers of one of two areas of the laboratory responsible for plutonium processing (Site A and Site B). Net plutonium concentrations were calculated for these 37 samples, as was the range and bearing from each processing area. Dispersion and deposition modeling using the Radiological Safety Analysis Computer program was used to calculate the cumulative release required to produce the net plutonium soil concentration for each of the 37 data points.
Results
Two release scenarios were evaluated. The first attributed all plutonium released to Site A within the laboratory, and the second assumed the release was entirely from Site B. All results were log-normally distributed. Estimates of plutonium release were higher if it was assumed that Site A was responsible for all plutonium releases. Furthermore, the uncertainty associated with the Site A scenario was lower than the Site B scenario, suggesting that significant and previously undocumented releases from Site A occurred.
Discussion and Conclusions
This study provides an independent estimate of laboratory plutonium releases using soil samples collected after 1970. Although these results are preliminary, and further research is needed, they appear to be inconsistent with previous laboratory estimates. The methods described here can be used to reduce uncertainty in dose reconstructions and could be extended to other contaminants for which monitoring data are not available, such as beryllium.

P-631 USE OF A WATER DISTRIBUTION SYSTEM MODEL TO ASSESS EXPOSURE TO TETRACHLOROETHYLENE-CONTAMINATED DRINKING WATER

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Residents of eight towns in the Cape Cod region of Massachusetts were exposed to the solvent tetrachloroethylene (PCE, perchloroethylene) when it leached from the lining of asbestos-cement vinyl-lined (ACVL) water distribution pipes installed from the late 1960s to the early 1980s. Two population-based case control studies were conducted in the 1990s to evaluate the association between breast cancer and exposure to the volatile organic chemical in the drinking water. These studies determined exposure using a leaching and transport algorithm to calculate a relative delivered dose based on residential history and characteristics of the water distribution system. This approach was lacking the computational ability to solve large, complicated piping configurations and limited the models to simplified geometric representations of real networks. We were able to improve the estimation of water flow direction by inserting the leaching algorithm into a water distribution system modeling software program called EPANET, a public domain package developed by the U.S. Environmental Protection Agency. Using GIS maps of subject residences and a town's entire water distribution system, we created a schematic in EPANET of water source locations, pipes (indicating length, diameter, composition) and nodes, or points along the pipe where water consumption occurs. Given available data and several assumptions on water usage and historical operations, the program simulates the flow of water through the thousands of pipe segments in each network. The difference in the PCE estimation methods will be evaluated by comparing several hundred estimates generated in prior studies to new estimates calculated with the added EPANET simulation component. Preliminary analysis of approximately 50 locations show the PCE estimates are well correlated by a Spearman rank coefficient (0.79, $p<0.0001$) and a simple regression analysis showed similar results between loge transformed estimates (slope=0.87, intercept=-2.09, $p<0.0001$). Correlation was higher among the locations with simple pipe configurations (Spearman rank coefficient=0.96), while it was lower for those with complex geometry (Spearman rank coefficient=0.67). These results suggest that for straightforward geometries the original method was adequate, but that it did not adequately capture the estimates for more complex situations. To evaluate agreement, the Bland-Altman approach was used to compare the the difference between the estimates versus their average at each location. That approach suggests that there is little discrepancy between lower exposure levels, and that the discrepancy increases as the exposure level increases. This is relevant to the epidemiological investigation of PCE since small to moderate elevations in breast cancer risk were seen among women with the highest PCE exposure level.

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