A dataset of over 200 compounds covering experimental data in a number of relevant screens (measuring individual complex activity, cellular ATP levels, reactive oxygen species (ROS) generation, oxygen consumption, mitochondrial membrane potential and cytotoxicity) was constructed. Seven model compounds were identified as having sufficient data and plausible mechanistic evidence to construct AOPs. The compounds used were: Rotenone, Thenoyltrifluoroacetone, 3-Nitropropionic acid, Antimycin A, Myothiazol, and Cyanide for mapping the ETC pathway, and Oligomycin A for ATP synthase. Using these representative model compounds an AOP was mapped for each complex from the molecular initiating event (MIE) to effects at the cellular level. The AOPs for inhibition of complexes of the ETC were then combined to create a single pathway.
We report the construction of AOPs for oxidative phosphorylation in mitochondria and their speculative extrapolation to in vivo endpoints such as cardiotoxicity, neurotoxicity and hepatotoxicity. The AOP maps are described in terms of the normal physiological pathway processes and potential intervention points, with reference to experimental in vitro assays which were used to support the elucidated steps. Not all compounds with mitochondrial effects may go on to display in vivo toxicology. An AOP view of such pathways is an useful construct in providing information in a form suitable for assessing outcomes relevant to risk assessment.

PL 1624 Interactive Data Mining of Toxicogenomics and *In Vivo* Toxicity Databases Using Chemotypes to Improve Chemical-Disease Prediction Inferences and Mode-of-Action QSAR Models.

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The Comparative Toxicogenomics Database (CTD, http://ctdbase.org) aims to shed light on the connection between chemical exposures and human health outcomes by inferring relationships via integration of curated chemical-gene, gene-disease and chemical-disease data from the scientific literature. Independent of CTD, structural knowledge via chemotypes, features linking chemicals to phenotypes, has been developed based on in vivo studies from toxicity databases, including regulatory sources at the US EPA and the US FDA. A chemotype is defined as a chemical substructure annotated with atom/bond properties that carry biological activity information. We explored whether the chemical-disease links in CTD could contribute to the further development of chemotypes, and whether mode-of-action Quantitatve Structure Activity Relationship (QSAR) models for toxicity endpoints built around chemotypes could be used to validate CTD disease inferences or further delineate phenotypic effects. We applied a set of previously developed MOA models and chemotypes, e.g., for cleft palate, to the data found in CTD. Many of the same chemotypes (representing attributes of glucocorticoids, retinoids, conazoles, dioxanes, and phthalic esters) were found to be associated with cleft palate in CTD, either by direct curation or inferred via common interacting genes. The structural feature space enriched with cleft palate chemotypes was highly populated by the chemicals deemed associated with this condition in CTD. This work demonstrated how interactive data mining between CTD and in vivo toxicity databases with chemotype probes can improve the predictive power of gene-disease and chemical-disease associations, as well as the MOA models; also described is how these associations can be tested experimentally. This abstract does not reflect EPA policy.

PL 1625 Cheminformatics Analysis of Compound-Cytochrome P450 Interaction Profiles.

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Only five isoforms (1A2, 2C9, 2C19, 2D6, and 3A4) of Cytochrome P450 (CYP) enzymes are responsible for the metabolism of the vast majority of drugs. Beyond knowing what drugs are metabolized by a specific isoform and the subsequent metabolites, it is of critical importance to evaluate the CYP inhibition potency of a compound for predicting its most likely CYP-related adverse effects. In this study, our objective was to integrate, analyze, and model the growing compendium of publicly-available CYP-related datasets for these five isoforms using cheminformatics approaches: INSTEM (4,676 compounds) was obtained as assertional metadata generated from MEDLINE abstracts; SUPERCYP (678 compounds) extracted from the online webportal; NCGC (16,142 compounds) is a compilation of qHTS screening results released by the NIH Center for Translational Technologies. After chemical curation and duplicates' analysis, we have analyzed these datasets using cheminformatics approaches and addressed questions pertaining to: (i) the chemical concordance between the different isoforms illustrating the singularity of 1A2 and the tight 2C9:2C19 coupling, (ii) the identification of compounds being simultaneously potent and selective for a particular CYP isoform; compounds with selective CYP profiles found in the INSTEM database were experimentally confirmed in the NCGC screening, and (iii) the detection of erroneous database entries by performing neighborhood analysis using chemical similarity calculations. We have aimed to achieve and test robust predictors of CYP interaction profiles by building Quantitative Structure-Activity Relationships (QSAR) models for each isoform. To further benchmark our QSAR models (solely based on two-dimensional structures of chemicals), we docked our integrated CYP database into the CYP binding pockets using their crystal structures. We show how QSAR models and docking approaches can be used in synergy to predict CYP interaction profiles of drug candidates.

PL 1626 Mechanistic Analysis of Welding Aerosol Toxicity Using Ingenuity Pathway Analysis (IPA).

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Welding involves occupational exposure to an aerosol containing gases and metal-rich particulates that induce adverse physiological effects including inflammation, immunosuppression, and cardiovascular dysfunction. To develop a deeper mechanistic understanding of these adverse effects, mice were exposed by inhalation to gas metal arc-stainless steel (GMA-SS) welding fume at 40 mg/m3 for 3 hr/d for 5 d a week for 2 weeks followed by gene expression analysis of whole blood cells, aorta, and lung at 4 hr and 28 d post-exposure. New features in Ingenuity Pathway Analysis (IPA) were used to analyze the expression data. The analysis results establish the importance of interferons and the IRF-family of transcription factors, predicting that they are activated at 4 hours and maintained through 28 days in both blood and lung. The IPA Upstream Regulator Analysis also predicted involvement of several toxicants, such as nickel and ozone, which have been detected in welding aerosol thereby highlighting the utility of Upstream Regulator Analysis for toxicogenomics applications. In addition, as an important drug discovery tool, IPA predicted several compounds that might be useful to ameliorate the inflammatory phenotype. One such compound was LY294002, a PI3K inhibitor that has already been shown to be efficacious in a mouse model of asthma. The new Mechanistic Network Analysis in IPA was used to computationally construct a plausible hypothesis that TRIM24 inactivation may lead to activation of IRF7 and STAT1 and other upstream regulators to drive the gene expression profile after the first exposure. Finally, Downstream Effects Analysis in IPA predicted large increases in proliferation, chemotaxis, and trafficking of immune cells in the lung after 4 hours. In summary, IPA has a unique new set of capabilities to enhance the mechanistic understanding of toxicological datasets and to provide support for new hypotheses that can be tested in the lab.

PL 1627 Insights into the TBX2 Role in Cellular Senescence in COPD: A Bayesian Structure Learning Approach.

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COPD ranks among the top leading causes of death worldwide. The transcriptional factor T box 2 (TBX2) plays an important role in the COPD molecular etiology. A senescence hypothesis for the etiology of COPD has emerged. TBX2 and related genes have anti-senescence activity. Their expressions are suppressed in COPD, but elevated in many cancers. The purpose of this study was to identify the directionality of regulatory relationships between TBX2 and other genes involved in cellular senescence. From a compendium of lung epithelium cell microarrays generated using the Robust Multi-Array Average procedure, a subset of genes of interest was used for structure learning. The Bayesian Network Structure Learning approach was then used to learn the regulatory relationships. The Bayesian Network Inference with Java Objects toolkit (Banjo) was used, in each instance, to generate the single best-scoring direct acyclic network, given the gene expression data. In order to focus the large search space, an initial network of genes that TBX2 interacts with including ANF, NKX2-5, NDRG1, CDNK1A, PML, E2F, CDKN2A, and CDKN2B was identified. Simulated Annealing and Greedy Search were the network search algorithms used. The results predicted that TBX2 regulates both COL4A3 and PML. Reports in the literature confirm that TBX2 interacts with both COL4A3 and PML. Subsequently, the original known network was updated with these two interactions, and a new iteration of the learning procedure initiated.

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