focused on particulate matter (PM). Recent studies suggest that certain biodiesel blends contain less PM and may be less toxic. Hence, a recent soy biodiesel study is discussed with respect to chemical composition and component analysis, and toxicological effects, including cardiovascular, pulmonary and carcinogenic endpoints, in several rodent models.

W 1608 Fracking, Coal, and Nuclear Energy: Impacts of Contemporary Methods of Power Generation on Air Quality and Remediation Efforts.

J. D. McDonald. *Toxicology, Lovelace Respiratory Institute, Albuquerque, NM.*

The complexity of the worlds power production needs requires that a number of approaches be used to generate and distribute power. Natural gas, coal, nuclear, and other sources are all in play. Each of these energy sources are subject of intense regulation targeted at mitigating potential air and other contamination, recently including mitigation of carbon dioxide. The increase in demand for natural gas has led to new methods for harvesting and obtaining it, including the controversial techniques such as fracking. Carbon capture and sequestration offers a number of engineering challenges, and methods for capturing include potential approaches that may initiate additional environmental concerns. Of course nuclear energy, especially considering the recent events in Fukushima, has its own environmental concerns. This presentation focuses on emerging considerations related to the impact of power generation on air quality. The emphasis will be on coal emissions (modern vs traditional), carbon capture and sequestration (CCS), and natural gas (including fracking). Some mention of nuclear concerns will be considered. The presentation includes recent toxicology data on the health effects of inhaled amines and their degradation products used in CCS, and data on emissions from coal after they are atmospherically transformed in the environment and on air contaminants associated with fracking.

W 1609 Predicting the Future: Getting Ahead of Problems—A Presentation and Discussion.

D. L. Costa. *Office of Research & Development, US EPA, Research Triangle Park, NC.*

Despite dramatic reductions in air pollution since 1970, the impact of pollutants on health and the environment remains a concern to both regulators and the general public. Studies have not been able to show thresholds of effect for prominent "criteria" pollutants like particulate matter (PM) and ozone (O3) and much uncertainty remains with air toxic air pollutants that vary across sources. Millions of people are exposed to the criteria pollutants, but there are subpopulations which are at risk due to unusual exposure circumstances or underlying biologic susceptibility or increasing age. Science continues to chip away at these concerns through human population studies, and human and animal toxicological studies. But as we look to the future with increasing national demand for energy and global population and industrial growth, there is increasing pressure on resources and the atmospheric reservoir for pollutants. Climate change with its impacts on air pollution chemistry as well as regional weather is widely thought to be undermining the gains we've seen in reducing the national air pollution burden through challenging environmental complexities. New technologies, fuels, and ambient pollutant profiles require systematic assessments and innovative tools if we are to dissect these many interlaced issues to ensure optimal strategies to protect human and environmental health. This presentation attempts to draw on what we know and speculate on what we need to know from our science to forecast both emerging issues and solutions – preferably preventative – that have been discussed in this workshop. The audience will be engaged to embellish and enhance this discourse.

W 1610 Breaking the Routine: Is There Room for Modern Techniques of Neuropathology Assessment in Routine Preclinical Safety Studies?

C. D. Toscano[1] and J. P. O'Callaghan[2]. *[1]FDA/CDER/OND/DNP, Silver Spring, MD; [2]CDC/NIOSH/Neurotoxicology Laboratory, Morgantown, WV.*

Neurotoxicity in routine preclinical safety studies is traditionally assessed with three H&E-stained brain sections; an approach that is not optimal, considering the brain's complex neuroanatomy. The need to increase the sensitivity of this approach is supported by the finding that routine neuropathology assessments would fail to detect MPTP, ethanol and carbonyl sulfide induced-CNS lesions. Increasing the number of brain sections sampled and inclusion of additional histology stains have been recommended but there is no expert consensus on the feasibility of incorporating modern methods of assessment into routine preclinical safety studies. We will explore and comment on the adequacy of the traditional approach to neuropathology assessment in routine preclinical safety studies. We will also examine the current regulatory guidance on neurotoxicity assessment in routine preclinical safety studies and discuss the feasibility of changing the current approach. Examples of emerging methods, such as MRI-directed histology and detection of circulating biomarkers of CNS damage, along with strategies for incorporating these techniques into standard preclinical safety studies will also be discussed. Finally, we will attempt to build consensus on appropriate approaches for improving the sensitivity of neurotoxicity assessment in routine preclinical safety studies by fostering a discussion between the audience and panel members. This discussion will focus on the feasibility of employing the proposed new markers, endpoints, and approaches and potential issues with interpretation of results of these studies. In conclusion, we believe that by examining the adequacy of current approaches of neuropathology assessment, discussing possible improvements to regulatory guidance and presenting emerging approaches of neurotoxicity assessment that this workshop will allow for a much needed dialogue on the need and feasibility of improving the current methods of neuropathology assessment in routine preclinical safety studies.

W 1611 Routine Neuropathology Analysis for Nonclinical General Toxicology Studies.

B. Bolon. *Veterinary Biosciences, Ohio State University, Columbus, OH.*

Microscopic neuropathological evaluation in Good Laboratory Practice (GLP)-type nonclinical general toxicology studies is one component of a battery of assays performed to assess potential nervous system toxicity of new chemical entities. Strategies for neuropathological assessment in such studies vary by species and among different industries and regulatory bodies. A Society of Toxicologic Pathology (STP) Working Group has recommended the following neuropathological strategy as suitable for all GLP-type nonclinical general toxicology studies. Selected brain areas should be examined routinely: caudate / putamen; cerebellum; cerebral cortex; hippocampus; hypothalamus; medulla oblongata; midbrain; olfactory bulb (in rodents only); pons; and thalamus. In rodents, these regions can be assessed in 6-7 full coronal sections on 2 standard-size slides; in non-rodents, they may be evaluated unilaterally in 6-7 standard slides each bearing 1 coronal hemisection. Spinal cord (cervical, thoracic, and lumbar regions) and peripheral nerve (sciatic and/or tibial) should be viewed in longitudinal / oblique and transverse sections. Current neurohistology practices—immersion fixation in 10% formalin, embedding in paraffin, and initial analysis only of H&E-stained sections—is acceptable for nonclinical general toxicology studies. These recommendations slightly expand current practice (i.e., analysis of 3-4 transverse brain sections in rodents) to improve sampling consistency using available technology. These recommendations affirm the importance of consistent routine neuropathological evaluation in GLP-type nonclinical general toxicology studies while acknowledging that histopathology is only one component of neural safety testing in such studies. Therefore, institutions should retain flexibility in devising the neuropathology portion of GLP-type nonclinical general toxicology studies as long as major nervous system regions are evaluated systematically.

W 1612 A Regulatory Perspective on the Current State of Neuropathological Assessments in Drug Development.

R. Mellon. *FDA/CDER/OND/DAAAP, Silver Spring, MD.* Sponsor: C. Toscano.

Neurotoxicological assessment of drug products is currently accomplished in preclinical studies by evaluation of central nervous system (CNS) safety pharmacology studies and general toxicology studies, which include simple behavioral observations and histopathological evaluation of the brain. Histopathological assessments in routine toxicology studies have identified adverse findings not detected by behavioral observation and therefore generate critical safety data. The scientific community has raised concern that histopathology in routine toxicology studies lacks adequate granularity for such a complex organ as the brain and therefore may not be appropriate for initial evaluations nor do they adequately identify when detailed "second tier" neurotoxicology studies are necessary. For example, the standard sampling and staining approach used in general toxicology studies may not be sufficient to detect certain CNS lesions (e.g. "Olney" lesions associated with NMDA receptor antagonists). Adopting an expanded sampling routine, such as the recently proposed Society of Toxicologic Pathology recommendations for the sampling and assessment of the brain in routine safety into Tier 1 testing, would increase the sensitivity of these studies. As there is currently no official CDER guidance on the assessment of the neurotoxicity of drug candidates, many approaches have been taken to addressing and reviewing the neurotoxicity of drug candidates; examples of these approaches and the level of success of such approaches will be provided. A regulatory perspective of the limitations of the current standard approach and feasibility of including modern methods of neuropathology assessment will be discussed. Overall, incorporation of modern methods of neuropathology assessment and improving the documentation of procedures used into the final study reports would provide greater confidence in the quality of the assessment. Such changes have the

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