been recorded in dogs, the relation between waves and the visual pathway is not well known. We analyzed the flash VEPs in dogs using a topographic method. On the topographic mapping, a negative response area indicated that evoked potentials were observed in the frontal region of the brain in the stimulated site followed by the shifting of the area to the contralateral frontal region and occipital region, during the first 100 msec. The negative response area in the frontal region in the stimulated site, contralateral frontal and/or temporal region, and occipital region were observed at latencies of N1, P2 and N2 of the flash VEP, respectively. On the ERG, the latencies of a- and b-waves were 12 and 30 msec, respectively. The latencies of a- and b-waves on the ERG were coincident with the latencies of P1 and N1 on the flash VEP. In the dogs with experimentally impaired right lateral geniculate bodies, the latency of P2 was prolonged and the N2 and P3 components of the flash VEPs disappeared after stimulation in the left eye. Only the early negative response area was detected at the stimulated site of the frontal region on the topographic mapping. Therefore, it is concluded that P1 and N1 are referred to ERG, P2 is referred to the potentials from the retina to the brainstem and N2 is referred to those from the brainstem to the visual cortex, respectively.

## 851 MORPHOMETRIC MEASUREMENT VALIDATION STUDY COMPARING DAY 9 AND DAY 11 SPRAGUE-DAWLEY RATS.

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This study validates an approach to the morphometric component for the US EPA OPPTS 870.6300 Developmental Neurotoxicity Study. Rather than subjecting pregnant rats to a variety of neurotoxic agents, the decision was made to initially perform the morphometric measurements on Day 9 and 11 Sprague Dawley (Crl:CD®BR VAF/Plus®) rat pups. Days 9 and 11 were chosen to demonstrate that the measurement data from the selected neuroanatomic areas would reveal age-related developmental difference and might, therefore, be predictive of either an *in utero* neurotoxic effect or a delay in brain development. Nine gross and microscopic morphometric measurements were made on the five brains/sex/timepoint: anterior-posterior length of the cerebrum and cerebellum; thickness of the frontal and parietal cortex, corpus callosum, hippocampal gyrus and external granular layer (cerebellum); width of the caudate/putamen; and height of the cerebellar cortex. As expected, the mean values for all of the neuroanatomic measurements were greater for the 11 day-old rat pups than for the 9 day-old pups, but there was overlap between the Day 9 and Day 11 rat pup data with the greatest measurement for at least one 9 day-old pup being greater than the lowest measurement for one of the 11 day-old pups. However, in spite of moderate data overlap between the two age groups and the presence of moderate intra-age group variability in the measurements for each neuroanatomic location, statistically significant increases were found for the following brain regions: anterior-posterior length of the cerebrum and cerebellum, thickness of the frontal cortex, width of the caudate/putamen, and height of the cerebellar cortex. Control morphometric data from six Developmental Neurotoxicology Studies will also be presented.

## 852 NEUROBEHAVIORAL EVALUATION OF RESIDUAL EFFECTS OF ACUTE CHLORINE INGESTION.

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**Rationale:** Chlorine exposure can lead to respiratory dysfunction resulting in brain cell hypoxia, injury and neurobehavioral disorders. **Assessment Approach:** Comprehensive neurobehavioral toxicity evaluations were performed on 2 cases, including WAIS, Neurotoxicity Screening Survey, Trailmaking (TT), and memory tests including Benton Visual Retention test (BVRT), Expanded Paired Associates Tests (EPAT), a logical memory test (LM), Selective Reminding Test (SRT), and tests for malingering and distortion. **Summary of Findings:** Case 1, 59 year old Ph.D., pre-exposure IQ 95th %, was served water contaminated with chlorine disinfectant, went into respiratory distress and treated at the local emergency room. He was examined 3 years post-exposure, and found to have vocal cord dysfunction and sleep apnea, central-type. BVRT showed 9 errors (strong indication of brain impairment); EPAT was at 34th and 17th %; *Neurotoxicity Screening Survey* was elevated at 236; SRT was at the 8th %; TT was at the 50th and 31st %; and LM < 1st %. Case 2, 40 year old male nurse, pre-exposure IQ at the 63rd%, was examined 1.5 years post-exposure to iced tea contaminated with chlorine. He developed reactive airway disease. Current IQ was at the 32nd %, with specific deficits in immediate memory, visual logic and psychomotor speed, all at the 16th %. BVRT showed 14 errors; EPAT was at 5th and 1st%; *Neurotoxicity Screening Survey* was elevated at 332; SRT was at 2nd %; TT was at 2nd and 24th %; LM < 1st. Follow-up interviews at 1 and 2 years post-exam indicated continued symptoms. In both cases, all test results of malingering were negative, and medical record review found no other explanations for the declines. **Conclusion:** Chlorine ingestion neurotoxicity was found which lasted many years after exposure.

## 853 USE OF TWO AROCLOR® LOTS TO EVALUATE TEQ AND OXIDATIVE STRESS PREDICTORS.

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In order to characterize risk associated with exposure to polyhalogenated aromatic hydrocarbons (PHAHs), the toxic equivalency factor (TEF) approach was created. Mixtures of polychlorinated biphenyls (PCBs) can thus be compared against dioxin. Two commercial mixtures of Aroclor 1254, Lot 6024 and Lot 124-191, were analyzed and Lot 6024 has approximately ten times the dioxin toxic equivalents (TEQ) of Lot 124-191. The purpose of this study was to determine if the TEQ for the two lots is predictive of any oxidative responses seen on a weight basis. Previous studies in our laboratory indicate that the TEQ is not predictive of all induced enzyme levels in lots with high non-dioxin like congeners. The TEQ works for EROD and MROD, not for PROD or T4 tests. Cytochrome c reduction, a measure of superoxide anion production, was in evidence only at the highest dose of Lot 124-191. Ascorbic acid, an antioxidant, was elevated at the highest doses for both lots. Uric acid, an antioxidant, showed a significant decrease over control at the highest dose for Lot 124-191. This suggests that multiple mechanisms that can lead to higher than expected levels of oxidative stress. In the present study, it is apparent that TEQs for mixtures can explain the variances in dioxin-like effects, but non-dioxin like congeners cause other responses that are not associated with the Ah receptor. The TEQ approach works well when only dioxin-like PHAHs are present. However, when non dioxin-like PCBs are present, application of the TEF approach must be used with caution. This is due to both synergistic and antagonistic interactions that have been observed with PCB mixtures. For antagonism, the TEF approach would overestimate the toxicity of a PCB mixture. For synergism, the TEF approach could significantly underestimate the toxicity of a mixture. For protection of human health and the environment, current regulations rely on the toxicity of individual congeners and do not take into account possible interactions. (This abstract does not necessarily represent EPA policy. DEB supported by EPA CT902908.)

## 854 HUMAN INTERINDIVIDUAL VARIABILITY IN THE EXPRESSION OF CYTOCHROME P450 FORMS CRITICAL TO XENOBIOTIC METABOLISM.

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Estimates of human interindividual differences in susceptibility to toxic insult may have their basis in pharmacokinetic (PK) and/or pharmacodynamic (PD) variations. Although the US EPA does consider separating uncertainty factors into PK and PD components, as done for perchlorate, there are no guidelines to inform such a process, and critical data are often absent. However, other agencies have separated the animal to human uncertainty factor ($UF_A$) into PK and PD components. To quantify human interindividual differences and produce results which might be used to support data-derived uncertainty factors for human interindividual variability ($UF_H$) with respect to the PK component, we have quantified and determined the distribution of several cytochrome P-450 (CYP) forms in a group of 141 human hepatic microsome samples. Mean and SD values (pmol CYP/mg microsomal protein) of CYP1A, CYP2E1 and CYP3A forms were 33.6±28.1, 59.4±18.2, and 141.9±104.5, respectively. Further, activity (pmol/min/pmol microsomal protein) towards substrates characteristic for a total of 7 CYP forms demonstrated standard deviations of 46 to 111% of mean values and normal distributions.Immunologically-detected CYP1A, CYP2E1 and CYP3A forms were also normally distributed. When data on enzyme selectivity for a given chemical exist, the specific activity of that enzyme can be combined with data describing the varaibility of enzyme expression to determine the extent of human interindividual variability in the intrinsic metabolism of the chemcial. Variations in intrinsic metabolism can be included in physiologically based PK models as has been done for trichloroethylene (*Toxicol Appl Pharmacol* 152:376-387, 1998). This improves estimates of human PK variability by including physiologic constraints such as solubility in blood and delivery to the liver.

# The Toxicologist

*An Official Publication of the Society of Toxicology*

*and*

*Abstract Issue of*

# TOXICOLOGICAL SCIENCES

*An Official Journal of the Society of Toxicology*

*Published by Oxford University Press, Inc.*

***Abstracts of the***
***39th Annual Meeting***
***Volume 54, Number 1***
***March 2000***