Vision System Function and Neurotoxin-Induced Illness.
On line vision test Building Forensics

Visual system function is a sensitive indicator of toxic effects due to factors involving exposure, measurement ability, susceptibility to toxins, and associations of visual deficits with symptomology, biochemical alterations, objective indicators of human illness and clinically recognized diseases.

Photoreceptors transduce light to neural signals that are processed by a variety of neuronal types in multiple layers of the retina prior to transmission via the optic nerve to brain stem nuclei for further processing. Anatomically and physiologically distinct pathways relay visual signals to the visual cortex and beyond for integration and discrimination that results in perception.

The visual system is unique among Central Nervous System (CNS) systems in several ways. First, although the retina is a component of the CNS, it is spatially segregated from the rest of the CNS, and separated from the environment only by thin layers of dermally derived tissue. The close proximity of the retina to the external environment provides the opportunity for direct ocular absorption of some environmental pollutants, resulting in toxic exposure of the retina without the necessity of systemic exposure. The retina, which is also susceptible to exposure from systemically circulating toxins, may receive higher doses of some toxins than other CNS areas.

Second, the retina is a highly complex tissue containing many of the neuronal and non-neuronal cell types and biochemicals that are found throughout the brain. Components of this "microcosm" of the brain are known to be susceptible to disruption by a variety of toxins. More proximal portions of the visual system provide further potential targets for toxic insults that can interfere with visual perception.

Third, unlike the vast number of functionally significant outputs of the cognitive system, the visual system has relatively few functionally outputs which can be readily measured. The primary functional outputs of the visual system are the perceptions of pattern and motion that are defined by variations in luminance contrast and/or color over space and time. Specialized processes produce achromatic perception under dim or scotopic viewing conditions, and chromatic perceptions under bright or photopic viewing conditions. Visual resolution diminishes rapidly from fovial or central vision to the less highly compact macular and peripheral portions of the retina. Methods are available to quantify detection abilities for pattern, motion, achromatic, chromatic, central and peripheral perception. Behavioral methods are preferred in humans due to high accuracy, but can be supplemented by electrophysiologic methods.

Electrophysiologic techniques are less accurate at quantifying absolute detection and discrimination thresholds due to low signal-to-noise ratios, but can in some cases assist in identifying the locus of effect, as can some brain-imaging techniques. Electrophysiologic techniques are particularly useful for addressing issues of interspecies extrapolation, such as similarities and differences between human and rodent visual system function and susceptibilities to toxic exposures.

Visual system function has been a highly sensitive indicator of toxic effects. Color discrimination measurements have shown organic solvent-induced effects after shorter exposure periods and at lower exposure levels than measures of cognitive function in perc, styrene and mixed-solvent exposed populations. For example, relative to matched-control subjects, workers exposed to perc levels around 3 ppm showed color discrimination deficits that developed within 2 years. Attention deficits have been reported only after exposures to perc at levels above 12 ppm for more than 11 years, and memory deficits were reported only after more that 20 years of exposure to more that 40 ppm of perc. Our paper recently accepted for publication in the NIH/NIEHS journal, Environmental Health Perspectives, (17) on populations environmentally exposed to perc is the first to report results from a measurement of visual pattern detection ability, visual contrast sensitivity (VCS). VCS deficits were observed in two populations exposed to environmental perc concentrations of 0.1-0.3 ppm for 4-6 years, a dose at which significant group differences were not observed on a sensitive test of color discrimination. VCS has been a sensitive indicator of neurotoxicity induced by other organic solvents. Persistent or permanent VCS deficits in the presence of normal visual acuity have been observed in styrene and mixed-solvent exposed workers in the absence of detectable optical, retinal or optic nerve head pathology. Higher-level exposures to a variety of solvents have been associated with multiple-system symptoms, illnesses such as hepatitis and encephalopathy and carcinogenicity. This suggests that a diverse set of organic solvents may share a common mode(s) of action that first induces subclinical deficits in visual function, followed by multiple system symptoms and neurobehavioral deficits and, with continued exposure, clinically relevant cancer and non-cancer health outcomes. Further research is needed to elucidate mode(s) of action and biochemical alterations triggered throughout the course of solvent exposure. The association of early subclinical vision effects and later stage clinical conditions with a common set of modes of action could form the scientific basis for a harmonized approach to risk assessments of a wide variety of volatile organic compounds.

VCS, a non-specific indicator of sub-clinical visual impairment, also revealed neurologic deficits associated with exposure to toxic Pfiesteria sp.-inhabited estuaries. Pfiesteria sp. are fish killing dinoflagellates first discovered in NC during around 1989 and subsequently associated with human illness in laboratory and environmental settings. As with other aquatic, toxin-forming organisms, world wide proliferation has been associated, at least tentatively, with habitat alterations from environmental pollutants. Our recent publications reported significant VCS deficits in a population of watermen who had not been exposed to Pfiesteria sp.-related fish kills for approximately 1 year, and for whom no deficits were observed in a large battery of neuropsychological, clinical and analytical chemistry tests (5,6). Association of the VCS deficit with exposure to toxic Pfiesteria sp.-inhabited estuaries was verified by an independent research group. Our subsequent articles showed strong associations between exposure to Pfiesteria sp.-related events, development of the VCS deficit concurrent with a multiple-system symptom complex, with prompt symptom resolution and VCS recovery following a novel therapy to bind and eliminate biotoxins (7,8). Researchers from a NOAA laboratory recently reported partial isolation of a Pfiesteria sp. toxin with high affinity for an ATP P2X7 receptor found on retinal and central microglia and peripheral macrophages. Activation of the receptor has been reported to trigger a cascade of events that trigger release of the proinflammatory cytokine, interleukin 1 beta (IL1ß). Clinical measures in cases exposed to Pfiesteria sp.-inhabited estuaries show elevated serum IL1ß levels and reduced blood flow in retinal microvasculature of the lamina cribrosa and around the optic nerve head. Cytokine-induced inflammation could potentially account for the VCS deficit, as well as for the multiple-system symptom complex reported by cases. A toxin was recently isolated from the bacterial spirochete, Borrelia burgdorferi, which caused Lyme disease. Data from cases of chronic Lyme disease suggest a multiple-system symptom complex, elevated level of another proinflammatory cytokine, tumor necrosis factor alpha (TNFa), a VCS deficit and respond to toxin-binding therapy. Whereas toxin-binding with cholestyramine (CSM) provides a permanent cure, temporary relief is provided by drugs in the thiazolidinedione family, such as piaglitazone (Actos). Actos induces peroxisome proliferator activated receptor gamma (PPARgamma) which downregulates TNFa and other proinflammatory cytokines. TNFa is also associated with human carcinoma through potent induction of vascular endothelial growth factor (VEGF) mRNA. The literature suggests that toxicity from another dinoflagellate, Ciguatera sp., indoor air fungi, and cyanobacteria may involve visual system dysfunction, a multiple-system symptom complex, and proinflammatory cytokine induction. For example, microcystin LR, a toxin from the cyanobacteria, Microcystis sp., has classically been associated with inflammation-induced hepatotoxicity and hepatic carcinogenicity, also through VEGF mRNA upregulation. Recent use of microcystin LR-contaminated water at kidney dialysis centers in Brazil resulted in rapid blindness, followed by disorientation, nausea, headache, abdominal pain (N=100/131) and death due to liver failure (N=76/131). The marine dinoflagellate, Prorocentrum sp., produces okadaic acid, best known as an inhibitor of protein phosphatases 1 and 2A and for causing diarrhetic shellfish poisoning(DSP), considered to be the most serious and globally widespread phytoplankton-related seafood illness. The first occurrence of DSP in North America occurred in 1990, and other events have ensued. Interestingly, okadaic acid is also associated with neurologic symptoms (although vision has not been tested) and human carcinoma. The carcinoma is associated with induction of VEGF through mRNA upregulation, mimicking the action of TNFa and microcystin LR. Further research is needed on the potential for relationships between VCS deficits induced by low levels of biotoxins, multiple-system symptom induction, proinflammatory cytokine upregulation and long-term health outcomes to form the scientific basis for a harmonized approach to risk assessments of cancer and non-cancer outcomes.

It is suspected that many clinical diseases involve both genetic and environmental risk factors, and many are known to involve deficits in visual perception, although little research has sought to relate toxic exposures to modes of action which may produce measurable alterations in visual function prior to progression of disease to a diagnostic level. VCS deficits are present at diagnosis in diseases better known for effects on other body systems, such as Type 1 diabetes mellitus (deficiency in insulin release), in which there is little or no observable retinopathy. Multiple sclerosis patients display VCS deficits which are orientation specific, suggesting cortical rather than retinal or optic nerve damage. A primarily low spatial-frequency VCS deficit is present in Alzheimer's disease, a classical "cognitive" illness, and in Parkinson's disease, a classical "motor" illness. A number of recent papers present evidence that VCS and other vision impairment in Alzheimer's disease may be responsible for behavioral and functional outcomes previously attributed to cognitive impairment. The report that the extent of cognitive impairment in Alzheimer's disease can be predicted by VCS scores supports the hypothesis of a common mode of action for the cognitive and visual dysfunction. If Alzheimer disease etiology in at least some patients involves toxic exposure, and if visual disturbances are present well in advance of diagnosis, measures of visual function in prospective studies of exposed populations could help link exposure to risk for Alzheimer's disease. Recent research on exposure to airborne manganese and risk for a Parkinson-like disease provided support for this approach. Only measures of VCS significantly predicted the risk for development of Parkinsonism 5 years later in a study of workers at a ferro-manganese alloy plant. In studies of oncologic conditions associated with toxic exposures, no studies have been found which sought to identify early, neurobehavioral indicators of risk for tumor development. This is somewhat surprising since many studies on volatile organic compounds, for example, have reported symptom complexes and neurobehavioral deficits in exposed populations, while other studies have reported an increased incidence of carcinoma in similarly exposed populations. Whether or not a common mode of action underlies the earlier developing non-cancer, and later developing cancer, outcomes of exposure is unknown. The mode(s) of action of solvent-induced deficits and illness undoubtedly differs from that of biotoxins, as evidenced by reports that biotoxin-induced VCS deficits are reversible(7,8), whereas solvent-induced VCS deficits are irreversible (12-14). Yet the potential for common modes of action in visual dysfunction, multi-system symptoms and cancer is shown by the relationships between these endpoint and the proinflammatory cytokine, TNFa, in biotoxicity. Prospective or follow-up study designs which include biochemical measures and clinical outcomes are needed to characterize and link together early, sub-clinical effects, modes of action and clinical outcomes resulting from environmental exposures to toxins.