

quality of the test data depends largely on the observer's ability to detect and describe changes in the animal's behavioral and neurologic function. To aid in the training of observers and to achieve consistency across laboratories, the U.S. Environmental Protection Agency and the American Industrial Health Council developed a Training Video and Manual for the FOB. This video will be available for viewing during the workshop session.

With the increasing concern over potential neurotoxicologic consequences of chemical exposure in the developing organism, there is growing interest in testing laboratory animals at very young ages. The FOB, with modifications of the individual test measures to make them age-appropriate, can be useful in detecting behavioral and neurological changes in young rats. We have evaluated pre- and postweaning rats to learn the range of behaviors at each age, develop appropriate scoring criteria, and collect control data to document the ontogeny of each of the 30 or so endpoints in the FOB. These findings will also be presented during the workshop session. This refined FOB protocol may be useful for assessing neurotoxicologic response due to acute chemical exposure, or following gestational/lactational exposures typical of developmental neurotoxicity studies.

HOT NEW TOPICS IN DEVELOPMENTAL NEUROTOXICOLOGY: NOVEL AND CHANGING PERSPECTIVES

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DEVELOPMENTAL NEUROTOXICOLOGY OF THERAPEUTICS: SURVEY OF NOVEL RECENT FINDINGS. William Slikker, Jr. *Division of Neurotoxicology, National Center for Toxicological Research/FDA, Jefferson, AR*

Therapeutic agents present special challenges to risk assessment because many may represent both risks and benefits to human health. Two agents fitting this description are the HIV therapeutic AZT and the vaccine preservative Thimerosal. Treatment of HIV infected pregnant women with AZT has decreased the vertical transmission of HIV infection to the infant from 25 to 8%. Safety assessments are incomplete, however, and data suggest that prenatal exposure in rodents may result in cancer or behavioral alterations in the offspring. Recent data in pregnant nonhuman primates and humans suggest that monkey fetal tissue and human cord blood contain AZT incorporated into DNA after maternal AZT treatment. Thimerosal is frequently used in life saving vaccinations including diphtheria-tetanus-pertussis (DTP) and influenza. Thimerosal (sodium ethylmercurithiosalicylate) crosses the blood-brain and placental barriers and results in appreciable mercury content in tissues including brain. Thimerosal contains 49.6% mercury by weight and is metabolized to ethyl mercury and thiosalicylate. Even though Thimerosal has been used as a preservative in biologics and vaccines since the 1930s, recent recommendations by the Food and Drug Administration, Public Health Service and the American Academy of Pediatrics that Thimerosal should be removed from vaccines has heightened concern over the potential for Thimerosal to induce developmental neurotoxicology. These two examples reinforce the need for further study of these important ingredients of therapeutic agents that have both benefits and potential associated risks.

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DEVELOPMENTAL NEUROTOXICITY OF ENDOCRINE DISRUPTORS: FOCUS ON ESTROGENS. BA Schwetz. *US Food and Drug Administration, Rockville, MD. *Until recently, Dr. Schwetz was the Director, National Center for Toxicological Research, Jefferson, AR, and the Senior Advisor for Science, FDA.*

Evidence that endocrine disruptors (EDs) in the environment cause adverse effects in wildlife species first appeared in the literature in the 1970s, with claims for effects in humans appearing more recently. Adverse effects on reproductive tissues have been the primary focus of attention, but effects on other organ systems and processes, such as carcinogenesis, have also been reported. Epidemiology studies have been suggestive but inconclusive in the

opinion of many investigators regarding potential adverse effects in humans.

Chemicals with estrogenic activity can affect the development and function of neural tissues through several different mechanisms, some receptor mediated and others not, such as effects on cell membrane properties.

Experimental approaches to detect neurotoxic effects of estrogenic chemicals include neurobehavioral, neuropathological and neurochemical endpoints such as a) measures of physical activity, b) social behaviors, c) taste preferences, d) sexually dimorphic brain structures, and e) neurotransmitter and steroid receptor regulation.

A series of studies is planned or in progress at the FDA's National Center for Toxicological Research on chemicals representing a range of hormonal potency as EDs. These studies are funded in large part by the National Institute of Environmental Health Sciences. Genistein, a naturally occurring estrogen mimic found in soy beans and soy products, and nonylphenol, a chemical intermediate with estrogenic properties used in the manufacture of latex coatings, adhesives, paper products, agricultural chemicals, cosmetics, medical devices, and drugs, are two chemicals on which multigenerational studies are in progress. Research on other chemicals will begin in the future. These studies will compare toxicity in neural, immune, and reproductive systems and in some cases will evaluate potential carcinogenicity. For initial studies, rats were given soy free diets containing up to 1250 ppm genistein or 2000 ppm nonylphenol from gestation day 7 of the dams until postnatal day 77 of their offspring. At dose levels that decreased maternal and offspring body weight, there were subtle alterations in some sexually dimorphic behaviors, especially fluid intake of a sodium solution. Moderate doses of either agent also decreased the volume of the sexually dimorphic nucleus of the hypothalamus in male offspring.

The role of the hormonal activity of weak estrogens in the overall toxicity profile of chemicals to which humans are exposed is very important in order that regulatory agencies such as the FDA may conduct sound, scientifically based risk assessments.

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THYROID HORMONE OF MATERNAL ORIGIN DIRECTLY AFFECTS FETAL BRAIN DEVELOPMENT. R. Thomas Zoeller. *Department of Biology, University of Massachusetts, Amherst, MA*

Thyroid hormone clearly plays essential roles in brain development. This statement is most commonly justified by citing clear and in some cases severe neurological impairments associated with cretinism and with congenital hypothyroidism. However, until the beginning of this decade, it was believed that thyroid hormone only exerted effects on postnatal brain development, and that the fetus was not sensitive to thyroid hormone action. Several observations have caused a revision of this view. First, it was found that children born without a thyroid gland, or genetically incapable of synthesizing thyroid hormone, have normal levels of thyroid hormone at birth but become severely hypothyroid at a rate predicted by clearance of the hormone from blood. This observation showed that thyroid hormone of maternal origin reaches the fetus. Second, it was found that fetal brain express thyroid hormone receptors before the onset of fetal thyroid function, and that these receptors are occupied by thyroid hormone. Most recently, it was shown that pregnant women with undiagnosed hypothyroidism gave birth to children with measurable deficits in various neurological measures including "IQ" and measures of attention. Despite the clinical evidence that thyroid hormone plays important roles in fetal brain development, there were no experimental studies illustrating the mechanisms of thyroid hormone action on the developing brain or the developmental processes affected. Therefore, we initiated a project designed to identify thyroid hormone-responsive genes in the fetal cortex and to use these genes as markers of thyroid hormone action within the fetal brain. We have identified a number of genes expressed in the fetal cortex that are selectively regulated by thyroid hormone of maternal origin. The genes identified have provided the first clues about the developmental processes affected by thyroid hormone.