ubiquitous in the environment because of their efficacy in crop protection against destruction from insects, yet they are one of the suspected players in the development of neurobehavioral disorders. OPs act as neurotoxins because they inhibit acetylcholinesterase (AChE) activity and in humans can cause death and paralysis in high doses. Little is known about the effects of low sub-chronic doses of OPs during development that do not inhibit AChE activity. There is indication that in both humans and animal models exposed to low doses of OPs neonatally there are resultant changes in behavior and brain development, especially because their immune systems have not fully developed. However, anxiety-related behavioral changes in the zebrafish have not been documented after exposure to low levels of OPs. Using zebrafish for a model system is useful because the embryos can be exposed to OPs directly after fertilization and can be collected in large numbers. Using a high-throughput assay unique to our lab, we show that a widely used OP, chlorpyrifos, at 0.1μM and 0.01μM administered for 7 consecutive days after fertilization (dpf) decreased thigmotaxis, an anxiety-related behavior, and also decreased swim speed while body morphology remained unchanged in zebrafish larvae at 7dpf. At 1 μM, chlorpyrifos caused the tail of the larvae to curl upwards and larvae could not swim normally. The lowest level of chlorpyrifos administered, 0.001 μM elicited no changes in anxiety-related behavior, body morphology or swimming speed when compared to the DMSO control group. The results indicate that even low levels of chlorpyrifos have the potential to impact behavior when administered during a critical period of development. Future studies will include confocal brain imaging to detect neural patterning changes after chlorpyrifos exposure.

PS 2564 REGIONAL BRAIN DOSIMETRY FOR THE ORGANOPHOSPHORUS INSECTICIDE CHLORPYRIFOS IN THE PREWEANLING RAT.

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Infants and children may be sensitive to adverse effects of pesticide exposure associated with ingestion of residues on food. Organophosphorus (OP) insecticides, like chlorpyrifos (CPF), have been implicated as developmental neurotoxins; however, aspects of dose-response relationships are poorly understood particularly with regards to critical window(s) of vulnerability and target tissue (i.e. brain) dosimetry. Ongoing research is focused on evaluation of in vivo/in vitro brain chlorpyrifos dosimetry in the preweanling rat pup and for comparison in adult male rats. At post-natal day-10 (PND-10), both male and female pups were orally administered CPF at 1 or 5 mg/kg/day for 5 consecutive days and humanely sacrificed 4 hours after the last dose, adult male rats were likewise orally dosed at 5 mg CPF/kg/day (5 doses). Whole brains and brain regions (forebrain, midbrain and cerebellum) were analyzed for CPF and its major metabolite trichloropyridinol (TCP), its major metabolite. In addition, brain region acetylcholinesterase (AChE) activity was determined in PND-15 pups. In vitro metabolism studies were conducted with hepatic and brain microsomes and whole brain homogenates prepared from naïve adult male rats. A comparison of whole brain dosimetry (5 mg CPF/kg/day) suggests that the concentration of CPF and TCP in the brain of preweanling rats is comparable to adults following oral exposure. In both male and female PND-15 pups, regional brain CPF concentration tended to be forebrain > midbrain > cerebellum; whereas, the concentration of TCP was fairly comparable across gender and brain regions. In vitro brain metabolism studies support both the bioactivation of CPF to the neurotoxic metabolite CPF-oxon and detoxification of CPF to TCP. The importance of localized brain metabolism is highly relevant for lipophilic pesticides that potentially sequester in the brain where localized brain disposition and metabolism may be critically important for understanding target tissue dosimetry. Supported by CDC/NIOSH grant R01 OH008173.

PS 2565 PATTERN OF INHIBITION OF BRAIN ENDOCANNABINOID METABOLIZING ENZYMES FOLLOWING DEVELOPMENTAL CHLORPYRIFOS EXPOSURE.

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The endogenous cannabinoids 2-arachidonylglycerol (2-AG) and anandamide (AEA) play vital roles during nervous system development including regulating axonal guidance and synaptogenesis. The degradation of 2-AG and AEA is mediated by monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively. We have previously reported that developmental repeated exposure to low levels of chlorpyrifos (CPS) results in inhibition of these enzymes as well as accumulation of endocannabinoids in rat forebrain at 4hrs post exposure. However, it is not clear if these effects are persistent or transient. To determine this, 10 day old rat pups were exposed daily for 7 days to either corn oil or increasing dosages of CPS (1, 2.5, or 5 mg/kg) by oral gavage. FAAH and MAGL activity was inhibited in a dose dependent manner at 4hrs after the last dose and this level of inhibition persisted through 12hrs. By 24hrs, some recovery of activity was observed with the two higher dosages but not the lowest dosage. This persistent inhibition suggests that if daily exposure was occurring, the activities of these enzymes would not have the opportunity to return to control levels. Forebrain 2-AG and AEA levels were significantly elevated at 4hrs in a dose related manner and continued to increase to peak levels at 12hrs. Substantial recovery had occurred by 24hrs but levels remained significantly elevated above control levels. Thus, repeated exposure to CPS results in a persistent inhibition of the endocannabinoid metabolizing enzymes and a cyclic pattern of elevation of the endocannabinoids themselves. This alteration of endocannabinoid signaling during brain maturation could exert long term effects, leading to permanent alterations in neuronal brain circuits and behavioral responses.

PS 2566 EVALUATION OF DEVELOPMENTAL NEUROTOXICITY OF MANCOZEB IN RATS.

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Mancozeb, a widely used fungicide, was evaluated for potential developmental neurotoxicity (DNT) in rats in accordance with OECD test guideline 426. In a dose-range finding study, female CD rats were given dietary mancozeb at doses of 0, 5, 30 or 60 mg/kg/day (mkd) from gestation day (GD) 6 through GD 20 (5/dose) or through lactation day (LD) 21 (10/dose). At 30 and 60 mkd, gestation body weight gains were decreased (14% and 37%), and on LD 21 thyroid follicular cell hypertrophy was increased (44% and 50% vs. 20% incidence in control) with decreased serum thyroxine (24% and 44%). There were no treatment-related effects on reproductive or litter parameters. Postnatally, pup growth rates were decreased at these dose levels. Mancozeb, and ethylene thiourea (ETU), which is a metabolite of toxicological concern especially from a developmental perspective, were both present in plasma of dams and offspring, and in maternal milk during lactation. Based on these results, 30 mkd was selected as the high dose for the definitive DNT study. In the definitive DNT study, female CD rats (25/dose) were given dietary mancozeb at doses of 0, 5, 15 or 30 mkd from GD 6 to post-natal day (PND) 21-28 and the offspring were assessed for effects on nervous system structure and function. High-dose dams had no treatment-related effects on any parameters investigated except decreased gestation body weight gain [GD 6-9 (42%), 6-12 (26%) and 6-20 (9%)], increased relative thyroid weight (9%) and thyroid follicular cell hypertrophy (44% vs. 25% incidence in control). There were no treatment-related effects on offspring, including litter parameters, survival, clinical signs, functional observational battery, growth, neurobehavioral ontogeny, puberty onset, motor activity, startle response, learning and memory, brain morphometry and neuropathology of the central and peripheral nervous system. Thus, the NOEL for maternal systemic toxicity was 15 mkd, whereas the NOEL for developmental neurotoxicity was 30 mkd, the highest dose level tested. The study demonstrated that mancozeb does not cause developmental neurotoxicity.

PS 2567 ISOFORM-SPECIFIC DOWNREGULATION OF SODIUM CHANNELS FOLLOWING DEVELOPMENTAL DELTAMETHRIN EXPOSURE.

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The pyrethroid pesticides are a commonly used class of insecticides worldwide. Due to the unique susceptibility of developing animals to the toxicity of these compounds there is increasing concern over the potential developmental neurotoxicity of pyrethroid exposure. However, few data are available on molecular mechanism(s) of developmental pyrethroid neurotoxicity Previous work from our laboratory has shown that in utero exposure to the type II pyrethroid deltamethrin can produce persistent downregulation of voltage-gated sodium channel (Na(v)) mRNA and acute exposure can transiently downregulate Na(v) protein in an age-dependent fashion. In this current work PND 1-10 rats were exposed to deltamethrin at 0 or 0.1 mg/kg in corn oil, by oral gavage daily. At PND 10 the animals receiving deltamethrin were divided; 1 group continued receiving 0.1 mg/kg daily, while the second group began receiving 0.5 mg/kg daily until weaning at PND 21. Animals were sacrificed at PND 30 and samples were probed for Na(v) protein levels via western blot. Animals showed approximately 30% reduction in total Na(v) protein at 0.1 mg/kg and approximately 40% reduction at 0.5 mg/kg in the striatum. Individual Na(v) isoforms were measured using isoform-specific antibodies. Na(v) 1.1 protein levels were reduced approximately 30% at 0.1 mg/kg and 45% at 0.5 mg/kg, while Na(v) 1.2 protein showed no such downregulation. These data show an isoform-specific response to developmental deltamethrin exposure that corre-

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