3079 Comparison of Organ Weight in 11-to 12-Week-Old Sprague Dawley Rats from Different Geographical Regions

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This study was conducted to see if there were any differences in organ weights among the Sprague Dawley rat sourced from Taiwan and Beijing. Control group data from ongoing toxicology studies (N=140/sex/source) were used to see if there were any differences between those two sources of animals. The mean terminal body weight and organ weights were calculated. Analysis of the data showed statistical significant difference in organ weights included lower terminal body weight, heart weight (male only), liver weight (male only), kidney weight, spleen weight, thymus weight, thyroid glands with parathyroid gland(s) weight, pituitary gland weight, prostate gland weight, epididymides weight, and ovaries weight were noted in Taiwan rats; higher brain weight and uterus (including cervix) weight were noted in Taiwan female rats; lower organ weight/body weight ratio was noted in kidney (female only), thymus, thyroid glands with parathyroid gland(s), pituitary gland, prostate, and ovaries in Taiwan rats; higher organ weight/body weight ratio was noted in brain, liver (female only), testes, and uterus (including cervix) in Taiwan rats, when compared with Beijing rats. In addition, the organ weight/brain weight ratio was analyzed. The differences of organ weight/brain weight ratio reflected the changes seen in the absolute organ weight, with the exception that statistical lower heart/brain weight was noted in Taiwan female rats due to their higher brain weight, when compared to Beijing rats. These observed differences between the two sources of animals enforce the need to be consistent in the source of animals for a toxicology development program and also the need for maintaining separate back ground data bases.

3080 Platycodon Grandiflorum Derived Saponin Protect Agonist Eccentric Exercise-Induced Muscle Damage

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Platycodon grandiflorum contain a triterpenoid saponin as platycodin D and platyconin acid A with a multifold bioactive compound. Our previous research demonstrated that the platycodon grandiflorum derived saponin (PS) ameliorate against high fat diet-induced non-alcoholic steatohepatitis and inhibition of osteoclast differentiation. The pivotal effects of PS on inflammatory mechanism were suppressed NF-κB and matrix metalloproteinase (MMPs). However, the effect of PS on skeletal muscle damage are still unknown. Therefore, we investigated whether the PS extract protect from muscle damage. A significant reduction in eccentric exercise-induced muscle damage area and muscle damage related to the level of NF-κB p65 by PS (4 mg/kg for 2 weeks) was associated with the downregulation of ERK/p38/SMAD signaling. Also, PS supplementation was inhibited MMP-1, MMP-2 and MMP-9. Marked decreases in skeletal muscle damage, lactate dehydrogenase, creatine kinase and C-related protein. Taken together, our findings identify the PS protects against eccentric exercise-induced muscle damage. NF-κB p65 was suppressed via a p38, ERK and SMAD pathway, which provides a novel perspective on the biological function of PS against muscle damage.

3081 AChE-Independent Phosphoprotein Signaling in an Acute Mouse Model of Gulf War Illness

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Roughly 25-30% of veterans from the 1991 Persian Gulf War suffer from a persistent and amplified form of sickness behavior, classified as Gulf War Illness (GWI). Previous studies investigating GWI have suggested that exposure to organophosphates (OP) in theater, such as the irreversible acetylcholinesterase (AChE) inhibitor and chemical warfare agent, sarin, as well as other pesticides, may have contributed to GWI symptomatology. Additionally, concomitant exposure to high physiological stress in theater has been implicated in the initiation of the GWI phenotype. Traditionally, inhibition of AChE and the subsequent accumulation of acetylcholine (ACh) result in the activation of the cholinergic anti-inflammatory pathway. However, we have shown that the link between GWI and neuroinflammation appears to contradict this effect of AChE inhibitors. Therefore, it is plausible that exposure to OPs both alone and in combination with corticosterone (CORT; used as a physiological stress mimic) may target biomolecules other than AChE to induce the neuroinflammatory effects seen in our validated mouse model of GWI. To further investigate this phenotype, adult male C57BL/6J mice were exposed to CORT in the drinking water for 4 or 7 days. On the 5th or 8th day, mice were exposed to a single dose of a sarin surrogate, diisopropyl fluorophosphate (DFP; 4.0mg/kg, i.p.). To fully evaluate the brain-region specific effects of DFP and CORT+DFP on AChE, ACh concentrations were measured in cortex (CTX), hippocampus (HIP) and striatum (STR) using HILIC UPLC-MS/MS. Mice were euthanized using focused microwave irradiation to ensure rapid inactivation of AChE, as well as endogenous proteases and phosphatases. From these datasets, the alterations of ACh in the brain do not appear to correspond with the exacerbated neuroinflammation induced by CORT+DFP exposure. Therefore, interrogation of potential organophosphorylation targets and aberrant phosphoprotein responses of critical signaling pathways in the STR were conducted. Of the 28 phosphoprotein targets measured using multiplex ELISA, the GWI model (CORT+DFP) had numerous targets with increased phosphorylation over DFP alone (e.g., ERK1/2, GSK3, IkBa, JNK, MEK1), suggesting a need for measuring aberrant early intracellular signaling events to elucidate potential biomolecular drivers of GWI symptomatology.

3082 Geriatric Toxicology: Understanding Human Relevance of Toxicities Observed at Late-Stage of Long-Term Studies

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Toxicity testing in animals is traditionally conducted at fixed doses (*i.e.,* mg/kg/day) without adjustments for the occurrence of dose- and/or time-dependent systemic dose non-proportionality. The time-dependent dose non-proportionality is associated with age-dependent changes in physical, physiological and biochemical parameters possibly requiring a change in dosing for geriatric patients. Similar changes occur in animals, leading to higher than anticipated systemic dose resulting in "*late occurring*" toxicities in chronic studies. Determining the time of departure from dose proportionality is important to either adjust the external dose to maintain the anticipated systemic dose or interpret such toxicities in the context of systemic dose non-proportionality for better human health risk assessment. Pethoxamid, an herbicide, is >90% absorbed from the GI tract of rats and predominantly (~75%) eliminated through bile. In the rat carcinogenicity study, pethoxamid increased thyroid follicular cell hyperplasia (TFCH) and adenoma in male rats at the top dose (1600 ppm), only at termination (105 weeks) without such indication at interim sacrifice (after 27, 53, or 79 weeks of exposure). An increase in TFCH was observed in 13-week study at ~1.6- and ~3-fold higher doses [Pethoxamid: Draft Assessment Report, 16 August 2002]. The effects observed at the end of the carcinogenicity study were likely from geriatric changes (*e.g.*, metabolism, clearance) increasing the systemic dose to levels that caused TFCH in male rats in the 13-week dietary study. Similarly, in another study, rats showed sedation for several days at the start of exposure with propylene glycol monomethyl ether and recovered upon induction of enzymes; however, sedation again appeared after 12-18 months of exposure due to increasing systemic dose. Generating systemic dose data during the course of toxicology studies is recommended for better understanding of potential MoA and human relevance and consistent with the opinion that biological effects are best correlated with systemically available rather than the administered dose.

3083 Mouse Model of Intestinal Mucositis Induced by 5-Fluorouracil and Irinotecan

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Chemotherapy-induced mucositis is a common severe side effect experienced by colorectal cancer patients during treatment. We aimed to investigate the gastrointestinal toxicity of 5-fluorouracil and irinotecan in mice. Balb/C mice (n=8/group) were injected with saline, 5-fluorouracil (30 mg/kg, i.p.) for 5 consecutive days (males and females) or irinotecan (75 mg/kg, i.p.) for 4 consecutive days (males only). Body weight and diarrhea were assessed over the test period and inflammatory and histopathological responses were investigated 7 days after the first injection. 5-fluorouracil and irinotecan increased the diarrhea score compared to controls (5-fluorouracil: +2.3 and +2.4, $p<0.001$ for males and females respectively, and irinotecan: +0.9, $p<0.001$). 5-fluorouracil,

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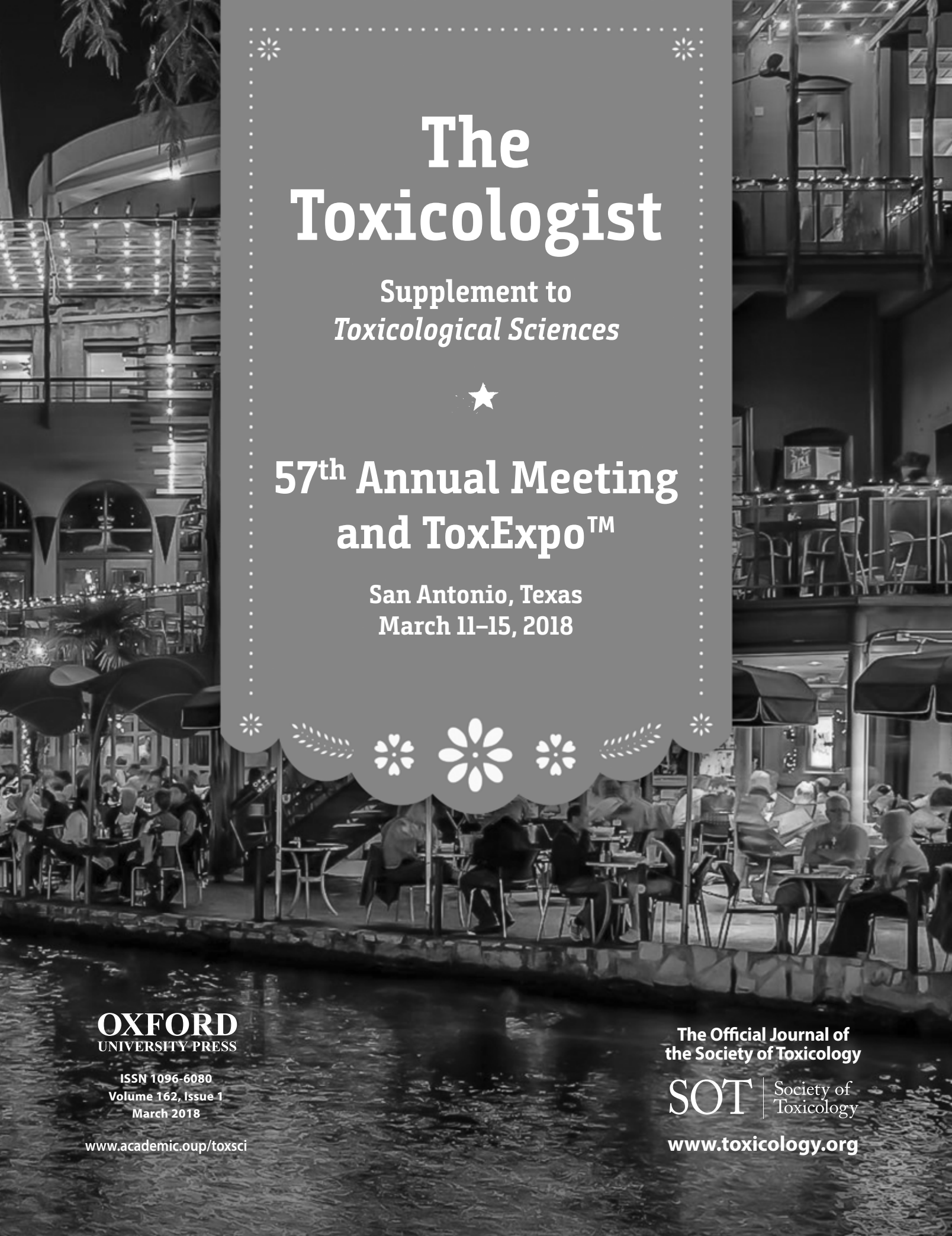

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