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ies in the serum (Khan *et al.*, Toxicol. Appl. Pharmacology134, 155-160, 1995). In the present study, we measured anti-malondialdehyde antibodies (AMDA) in the serum of TCE or DCAC-treated mice in order to understand the contribution of lipid peroxidation to this AI response. Female MRL +/+ mice (5 weeks old) received i.p. injections of 10 mmol/kg TCE or 0.2 mmol/kg of DCAC in corn oil (100 Fl) every 4th day for 6 weeks, while controls received an equal volume of vehicle only, and AMDA was measured in the sera of these animals by an ELISA established in our laboratory. While TCE treatment caused only marginal induction of AMDA, DCAC treatment elicited a consistent and stronger AMDA response. Furthermore, a time-response study of DCAC (0.2 mmol/kg, every 4th day, for 2, 4, 6 or 8 weeks) showed an induction of AMDA (3/4) after 4 weeks of treatment, which was even greater at both 6 and 8 weeks of DCAC treatment (5/5). These findings were further substantiated by the presence of AMDA in SLE-prone MRL-lpr/lpr mice as early as 6 weeks of age. Presence of AMDA, as observed in this study, not only indicates increased lipid peroxidation (oxidative stress), but also suggests a putative role of oxidative stress in inflammatory autoimmune diseases.

672 EFFECTS OF MURINE RIL-2 IN (NZB X NZW)F1 FEMALE MICE.

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The exacerbation of pre-existing autoimmune diseases is a potential toxic effect of immunoactive drugs. An apparent increase in the frequency of autoimmune thyroiditis has been noted in patients treated with human recombinant interleukin-2 (rIL-2). In contrast, human rIL-2 tends to protect mice from autoimmunity. However, the effects of murine rIL-2 on autoimmunity have not been reported in mice. Therefore female (NZB x NZW)F1 mice, which are genetically predisposed to develop a spontaneous lupus-like disease, were treated intraperitoneally with 20,000 IU of murine rIL-2, twice weekly for 13 weeks, beginning at 15 weeks of age. Under our experimental conditions, there was no evidence of an exacerbating effect of murine rIL-2 on the lupus disease of (NZB x NZW)F1 mice. This treatment regimen had no effect on the mean survival or the mean body weights of the animals. Compared with saline-injected control (NZB x NZW)F1 mice, no major differences were observed in either anti-DNA antibody production or antinuclear antibodies. These results show that: 1) like human rIL-2, murine rIL-2 does not exacerbate auto-immunity in mice; 2) the biological effects of human as well as murine rIL-2 in mice differ to some extent from those seen with human rIL-2 in man. These latter findings suggest that the selection of the relevant animal species for immunotoxicity studies with recombinant cytokines and derivatives may be less straightforward than previously thought.

673 PATHOLOGICAL CHANGES IN (NZB/NZW)F1 MICE.

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As a prelude to a series of studies on autoimmunity a study was set up to investigate the pathological changes in the female (NZB/NZW)F1 mouse under our laboratory conditions. Fifty 10-week-old mice from Harlan, France were housed individually in plastic cages and fed diet and water *ad libitum.* Groups of mice were scheduled for sacrifice at 24, 28, 32 and 47 weeks of age. Animals were weighed weekly and blood samples were taken every 4 weeks and urine samples were taken every two weeks. A fully autopsy was performed on all animals. From 24 weeks of age all mice showed some level of mesangial thickening in the renal glomerulus. This was however very variable in extent at all time points, only being at a significant level in 2/12 at 24 weeks and only in 5/15 sacrificed at 32 weeks of age. Of the seven mice that died or were sacrificed at greater than 32 weeks of age all had severe glomerular lesions. In many of the affected kidneys this was accompanied by plasma cell aggregations. Ten mice died or were sacrificed in a moribund condition related to renal lesions from 26 weeks of age. In the lymphoid tissue both the spleen and lymph nodes showed a general hyperplasia in many animals and a slight increase in hematopoiesis in the spleen. In the liver the majority of mice greater than 24 weeks of age had fatty vacuolation of hepatocytes that was extensive in several cases. In eight of the 50 mice there was hemorrhagic necrosis in the liver and this was particularly seen in those sacrificed at 24 week old. This study established that the expected lesions in this strain were obtained, but the degree of individual variation in the extent of the glomerular change was greater than expected. The necrosis in the liver had been reported, but the extent was not anticipated nor was the high incidence of fatty vacuolation. The individual variation would mean that large group sizes would be necessary in study designed to investigated modification of this disease process.

674 BENZO(A)PYRENE-INDUCED ANEMIA AND SPLENOMEGALY IN THE FEMALE NZB/WF1 MOUSE.

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Benzo(a)pyrene (BaP) is an universal environmental pollutant formed during the incomplete combustion of organic materials. At high doses, BaP is known to suppress the immune system; however, low dose studies revealed that BaP enhances the immune response in rodents. Accordingly, studies were conducted to determine if BaP had the ability to exacerbate autoimmune disease in a genetically-predisposed mouse strain, the NZB/WF1. Five week old female NZB/WF1 mice were dermally exposed to BaP for thirty days. BaP, at doses of 0.02, 0.2, 2.0, and 20 mg/kg, did not increase markers of autoimmunity including total serum IgG, anti-DNP (dinitrophenol) antibodies, anti-dsDNA antibodies, and anti-laminin antibodies. Hematological evaluation revealed a significant decrease in erythrocytes, hemoglobin, and hematocrit. Conversely, there was an increase in both mean corpuscular volume (MCV) and red cell distribution width (RDW), consistent with autoimmune hemolytic anemia (AIHA). A parent strain of the NZB/WF1, the NZB, spontaneously develops AIHA. Although the observed anemia could be potentially autoimmune-mediated, follow-up studies utilizing flow cytometry, Coombs' tests, and a hemolytic assay using serum from treated mice indicated that the BaP-induced anemia was most likely not autoimmune-mediated. However, an increase in spleen weight was consistently observed at the 20 mg/kg dose. The observed increase in spleen weight was not due to a change in total spleen cell number. Histopathology revealed an expansion of the red pulp in spleens from mice treated with BaP, consistent with extramedullary hematopoiesis. Furthermore, a significant increase in CFU-e number was seen in spleens from mice treated with high doses of BaP when compared to vehicle mice. Although BaP did not exacerbate autoimmunity in the NZB/WF1 mouse model, exposure to BaP did induce anemia and extramedullary hematopoiesis in the spleen. (This work was supported in part by NIEHS Contract ES55387.)

675 CONCURRENT EXPOSURE TO N,N-DIETHYL-*m*-TOLUAMIDE (DEET), PYRIDOSTIGMINE BROMIDE (PYR), AND JP-8 JET FUEL EFFECTS ON BIOMARKERS OF IMMUNE FUNCTION IN B6C3F1 MICE.

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Approximately 5,000 to 80,000 of the U.S. service personnel involved in the Persian Gulf War have complained of a variety of nonspecific symptoms since their return in 1991. These symptoms have been collectively labeled Gulf War syndrome and include muscle fatigue, general malaise, myalgia, impaired cognition, ataxia, headaches, fever, joint pain, skin rash, gastrointestinal disturbances, sleep disturbances, and respiratory difficulties. The exact cause of this syndrome is still unclear; however, it has been suggested that psychological stress, chemical exposure, or infectious exposure may be possible causes. While on duty service personnel were exposed to both stressful events and environmental chemicals. Three of the compounds soldiers were exposed to during the war were PYR, DEET and JP-8. Previous range finding studies in this lab have determined a LOEL for these three exposures. In this study mice were exposed daily to the LOEL or 2 times the LOEL for 14 days. For both the LOELs (15.5 mg/kg DEET, 2 mg/kg PYR, and 500 mg/kg JP-8) and the 2xLOELs (31 mg/kg DEET, 5 mg/kg PYR, and 1000 mg/kg JP-8), no effect was noted in thymic or splenic weights or cellularity, in peripheral WBC or differential counts, in CD4/CD8 lymphocyte subpopulations or in NK-cell activity. T-cell proliferation was significantly suppressed following treatment with JP-8 at both treatment levels (LOEL and 2xLOEL) and the PFC-response was suppressed by PYR, DEET, JP-8 and the mixture at both treatment levels. Interactions in the tertiary mixtures were not additive for any of the endpoints.

~~676~~ A COMPARATIVE STUDY EVALUATING THE EFFECTS OF TRICHLOROETHYLENE ON IMMUNOLOGICAL FUNCTION IN NZB/NZW AND B6C3F1 MICE.

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Trichloroethylene (TCE) is an industrial solvent that contaminates ground water supplies potentially resulting in human exposure. The present study investigates the role of TCE in the development of autoimmune disease. Autoantibody production, mitogenic lymphocyte proliferation and humoral antibody responses were assessed