sponse. Compensatory tissue repair, an opposing but dynamic event that follows injury, also showed a dose-dependent increase, with a maximum at 48 h. The timely stimulation of tissue repair helps the animals to escape from the progression of liver injury and mortality due to the toxic challenge. By comparing the toxic and tissue repair responses of individual components of the binary mixture, it appears that the interaction between the components in the binary combination resulted in additive biological responses. (Supported by ATSDR # U61/ATU 681482)

1853 EFFECTS OF CADALENE ON C-100 CELLS TREATED WITH TCDD AND B(A)P.

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2, 3, 7, 8-tetrachlorodibezo-p-dioxin (TCDD) and benzo(a)pyrene [B(a)P] is generated mainly from combustion of fossil fuel and considered as important environmental pollutant, food contaminants, carcinogen and endocrine disruptor. In the present study, to understand effect of TCDD and B(a)P on the cholesterol biosynthesis, monoclonal antibody against squalene synthase was made and C100 cells, the SV-40-transformed baby hamster kidney cells, that express high level of squalene synthase was used. Cadalene, originated from wood Zelkova serata, was used as a potential protective compound against TCDD/B(a)P-induced toxicity. TCDD 30 nM and/or B[a]P 3 ¥ÏM were treated on C100 cells to elucidate the combined effects of such two important environmental toxicants, then squalene synthase activity and expression, cell cycle analysis, Northern blot and GSH level was measured. Cadalene treatment induced the decrease of squalene synthase activity compared to TCDD/B(a)P alone. Also, squalene synthase gene expression increased as a function of time in all groups. GSH level decreased as time elapsed. Cadalene-treated groups showed increased G0/G1 cell population as compared with cadalene-nontreated group. In conclusion, combined treatment of TCDD and B(a)P increased squalene synthase activity and this increase might be responsible for the enhanced toxicity. And treatment of cadalene increased G0/G1 cell population significantly and decreased G2/M cell population. Our monoclonal antibody was quite useful for the detection of squalene synthase activity in the cell. For better understanding of the precise mechanism of combined toxicity of TCDD and B(a)P in terms of cholesterol biosynthesis, further studies are needed. Supported by BK21.

1854 ARYL HYDROCARBON RECEPTOR-MEDIATED DISRUPTION OF ANDROGEN RECEPTOR SIGNALLING IN LNCAP CELLS.

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Several mechanisms have been proposed to explain how the aromatic hydrocarbon receptor (AHR) interferes with steroid-regulated functions. These mechanisms include: (1) enhancing ligand metabolism, (2) altering hormone synthesis, (3) down-regulating receptor levels, and (4) interfering with hormone-induced gene transcription and cell proliferation in hormone-responsive tissues. In male rats exposed in utero or lactationally and, to a lesser extent, in adult rats, the AHR ligand, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) decreases growth of the testis, epididymis, and accessory organs. These effects do not correlate with decreases in circulating androgen or androgen receptor (AR) levels, which suggests that TCDD does not interfere with androgen synthesis or metabolism, or with the levels of AR. Because androgens exert their effect on the cell cycle by regulating the expression and activity of genes controlling G1-S progression, we hypothesized that TCDD interferes with AR-mediated gene expression and cell proliferation. We have begun to test this hypothesis utilizing androgen-dependent human Lymph Node Cancer of the Prostate (LNCaP) cells. Our studies indicate the activation of the AHR is sufficient to block androgen-dependent cell proliferation. In addition, the activated AHR can block the androgen-dependent activity of the human PSA (prostate specific antigen) gene promoter and of the MMTV (mouse mammary tumor virus) LTR in LNCaP as well as in African green monkey CV-1 cells. Furthermore, experiments in estrogen-responsive MCF-7 cells indicate that the AHR induces expression of p21WAF1/CIP1, a major inhibitor of cyclin-dependent kinases that govern G1-S cell cycle progression. These results point to a possible role of the AHR in disruption of androgen-mediated responses regulating cell proliferation. Supported by NIH Grants RO1 ES06273 and P30 ES06096.

1855 TRANSCRIPTIONAL ACTIVATION OF CDC25A PHOSPHATASE IN MCF-7 CELLS BY 17β-ESTRADIOL AND INHIBITION BY TCDD.

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Studies in this laboratory showed that 17β-estradiol (E2) induced proliferation of MCF-7 human breast cancer cells, and this was paralleled by increased progression of cells from the G_0/G_1 to S phase of the cell cycle and increased expression of cell cycle genes/proteins. Cyclin-dependent kinases are activated, in part, by cdc25-dependent phosphatases, and E2 induces cdc25a protein in MCF-7 cells. In transient transfection studies in MCF-7 cells, E2 induced luciferase (reporter gene) activity (> 10-fold) in cells transfected with a construct (pcdc25a-1) containing a -460 to +129 insert from the cdc25a gene promoter, and E2-responsiveness requires co-transfection with a human estrogen receptor α (ERα) expression plasmid. Identification of the E2-responsive regions of the promoter were determined by deletion analysis using constructs containing the following cdc25a gene promoter inserts: -390 to +129 (pcdc25a-2); -209 to +129 (pcdc25a-3); -184 to +129 (pcdc25a-4); -31 to +129 (pcdc25a-5). The results indicate that at least two regions of the promoter -390 to -209 and -184 to -31 are E2-responsive, and both sequences contain GC-rich motifs and other transcription factor binding sites, but estrogen responsive elements (EREs) were not identified in the region of the promoter. In addition, E2-induced luciferase activities in MCF-7 cells were inhibited after cotreatment with E2 plus 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The mechanisms and promoter element(s) required for ER action and inhibitory Ah receptor-ERa crosstalk are being investigated. (Supported by NIH ES04176 and ES09106)

1856 ACETAMINOPHEN AND ESTRADIOL DIFFERENTIALLY ALTER THE EXPRESSION OF ESTROGEN-RESPONSIVE GENES IN HUMAN BREAST CANCER CELLS.

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Studies from this lab have reported that acetaminophen stimulates proliferation of estrogen-responsive (E2-responsive) MCF-7 breast cancer cells, but does not stimulate proliferation of E2-nonresponsive MDA-MB-231 breast cancer cells. Furthermore, acetaminophen-induced breast cancer cell proliferation is inhibited by antiestrogens, indicating acetaminophen alters breast cancer cell proliferation by an estrogen receptor (ER)-mediated pathway. However, ER binding assays demonstrate that acetaminophen does not compete with E2 for ER binding. It is possible that acetaminophen activates the ER as a transcription factor *via* an alternative pathway. This study tested the hypothesis that acetaminophen activates the ER as a transcription factor by a mechanism other than directly binding ER. Ribonuclease protection assays were used to establish the effects of E2 and acetaminophen on expression of various genes in E2-responsive (MCF-7) and nonresponsive (MDA-MB-231) breast cancer cells. In MCF-7 cells, E2 significantly induced the level of c-myc, bcl-2, c-fos, bax and GADD45 RNAs, but acetaminophen only induced expression of c-myc RNA. Furthermore, the magnitude and time course of acetaminophen and E2 induction of c-myc expression were different: E2 induced c-myc ~2-fold at 1 hour, while acetaminophen induced c-myc ~1.45 fold at 2-4 hours. In MDA-MB-231 cells, E2 did not alter the expression of any of the genes examined, while acetaminophen treatment resulted in small, but significant, increases in bax, GADD45, and p21 expression. The finding that acetaminophen induces c-myc RNA expression in MCF-7 cells, but not in MDA-MB-231 cells, is consistent with a stimulatory effect of this drug on E2-responsive breast cancer cell proliferation. However, the different effects of acetaminophen and E2 on expression of other genes indicates ER is differentially activated by E2 and acetaminophen as a transcription factor.

1857 EFFECTS OF DIETARY GENISTEIN ON CELL CYCLE OF OVARIAN TISSUE IN RATS.

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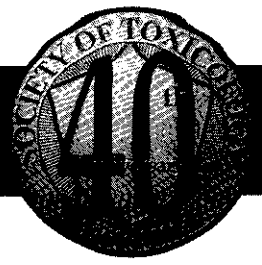
Genistein is a naturally occurring isoflavone. Genistein has been reported to affect the development of the reproductive tract and mammary glands in rats. This study is to evaluate the effects of dietary genistein on ovarian tissue in rats by flow cytometric cell cycle analysis. Genistein was fed in a soy-free casein-containing diet at 0, 25, 250, or 1250 ppm to F0 dams beginning on gestation day (GD) 7 and contin-



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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 40th Annual Meeting of the Society of Toxicology, held at the Moscone Convention Center, San Francisco, California, March 25–29, 2001.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

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