molecular mass of 75.2 kDa. Phylogenetic analysis shows that AHRRs (mammals and fish) form a third clade within the AHR family, along with AHR1 (mammals and fish) and AHR2 (fish only); these three vertebrate AHR-like genes descended from a single invertebrate AHR. Thus, mammalian AHRR is not the ortholog of fish AHR2. We show here that *in vitro*-expressed AHRR proteins from human, mouse, and *Fundulus* all fail to bind [^{3}H]TCDD or [^{3}H]-beta-naphthoflavone. In transient transfection experiments in COS-7 cells using a DRE-luciferase reporter gene, *Fundulus* AHRR had a concentration-dependent inhibitory effect on TCDD-dependent transactivation by both AHR1 and AHR2. *Fundulus* AHRR mRNA is widely expressed and is inducible by TCDD or PCBs. The *Fundulus* AHRR promoter contains three putative dioxin-response elements. Both AHR1 and AHR2 activated transcription of luciferase driven by the AHRR promoter, and AHRR could repress its own promoter. Thus, AHRR is an evolutionarily conserved, TCDD-inducible repressor of AHR1 and AHR2 function. [NIH Superfund ES07381 and NIH ES06272]

1068 GRIP1 ENHANCES AHR SIGNALING IN HEPA1C1C7 CELLS.

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Exposure to 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds produces a variety of tissue and species specific toxic and biological effects, most of which are mediated *via* the aryl hydrocarbon receptor (AhR) signaling pathway. The AhR is a ligand-dependent transcription factor that regulates gene expression *via* its binding to the dioxin responsive element (DRE) as a heteromeric complex with the AhR nuclear translocator (ARNT) protein. The events necessary for transcriptional activation by the DNA-bound AhR complex remain to be elucidated. As part of our effort to identify nuclear factor(s) which can modulate the transcriptional activity of the AhR complex, we have examined the ability of the glucocorticoid receptor interacting protein 1 (GRIP1) cofactor to affect AhR/ARNT-dependent signal transduction. GRIP1, like the AhR and ARNT, contains a basic helix-loop-helix/PAS domain located near the N-terminus and two transcriptional activation domains, AD1 and AD2, near the C-terminus. Cotransfection of Hepa1c1c7 cells with a DRE-reporter construct and a GRIP1 expression plasmid results in a 5-8 fold increase in reporter activity over cotransfection with the empty parent vector alone. However, when these cells were cotransfected with a GRIP1 lacking AD1, reporter activity was not enhanced, suggesting a role for AD1 in the augmentation of AhR signaling. Co-immunoprecipitation and GST pull-down techniques revealed strong interactions between GRIP1 and the AhR in at least two regions. The addition of GRIP1 also enhanced AhR:ARNT:DNA complex formation as assessed by gel retardation analysis. These results demonstrate that GRIP1 acts as a coactivator of the nuclear AhR complex. Supported by NIEHS (ES07072, ES05707 and ES04699).

1069 CROSS-TALK BETWEEN THE ARYL HYDROCARBON RECEPTOR AND SIGNAL TRANSDUCTION PATHWAYS: A ROLE FOR NF-κB.

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Activation of gene expression by 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related chemicals is mediated by the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor. Previously, a role for protein kinase C (PKC) in AhR signal transduction was demonstrated, with PKC inhibition blocking AhR functionality and phorbol-12-myristate-13-acetate (PMA)-dependent PKC activation enhancing AhR-dependent gene expression. In the present study we have extended these analyses and demonstrate that the PMA enhancement of AhR signaling in mouse hepatoma (Hepa1c1c7) cells is dependent upon the AhR DNA-binding site and is transient, occurring within the first eight hours after PMA treatment. While the enhancing effect appears directly related to gene transcription, the inhibition of PKC is associated with decreases in nuclear AhR and gene expression. PMA is also a potent activator of nuclear factor-κB (NF-κB)-dependent reporter gene expression in these cells. Not only do three chemical inhibitors of NF-κB (pyrrolidinedithiocarbamate (PDTC), (E)-capsaicin (CAPS), and caffeic acid phenethyl ester (CAPE)) block PMA-induced expression from an NF-κB reporter gene, but they inhibit both normal and PMA-enhanced AhR-dependent gene expression. Although gel retardation analysis reveals that inhibition of PKC by chelerythrine chloride reduced AhR nuclear translocation, NF-κB inhibition by PDTC had no effect on nuclear AhR levels. These results demonstrate a role for both PKC and NF-κB in the regulation of AhR-dependent gene expression. (Supported by NIEHS grant ES07685)

1070 TNF-α TREATMENT SUPPRESSES CYP1A1 TRANSCRIPTION BY INHIBITING ACETYLATION OF HISTONE H4 AND PHOSPORYLATION OF THE C-TERMINAL DOMAIN OF RNA POLYMERASE II.

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It has been known that TNF-α and lipopolysaccharide (LPS) suppress the gene expression of cytochromes P450 1A1(cyp1a1). In earlier studies, we demonstrated that activation of NF-KB is a critical event leading to the suppression of cyp1a1 gene expression, thus establishing a cross-interaction between the Ah receptor and NF-KB signal transduction pathways. In the present study, we demonstrated that Ah receptor/NF-KB interactions converges at level of transcription involving two steps of transcriptional regulation: (1) chromatin remodeling and (2) transcriptional elongation by RNA polymerase II (RNA Pol II). Specifically, using cyp1a1 transcription in Hepa1c1c7 cells as a model system, we demonstrated that dioxin treatment (10 nM, 2 hrs) causes significant histone H4 acetylation which is associated with chromatin remodeling activity. TNF treatment (5 ng/ml) markedly suppresses this histone acetylation activity, especially around the TATA box region, suggesting that NF-KB activation inhibits the histone H4 acetylation at cyp1a1 promoter. Furthermore, we demonstrated dioxin treatment causes phosphorylation of the C-terminal domain (CTD) of RNA PolII. The phosphorylation of RNA Pol II is a critical step of transcriptional elongation. TNF-α treatment significantly suppresses the dioxin-induced RNA Pol II phosphorylation, especially at serine 2 of YSPTSPS motif of the RNA Pol II CTD. These results established a mechanism for the inflammatory cytokin-induced inhibition of chytochrome P450 1A1, suggesting the involvement of chromatin remodeling and transcriptional elongation in the "cross-talk" between Ah receptor and NF-KB signaling pathways. Supported in part by NIEHS Grant ES09859 and NIEHS Center Grant ES05022.

1071 MECHANISM OF HORMONAL ACTIVATION OF EARLY GROWTH RESPONSE-1 (*egr-1*) IN BREAST CANCER CELLS.

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Egr-1 is induced by 17β-estradiol (E2) in estrogen receptor (ER)-positive MCF-7 breast cancer cells, and analysis of the *egr-1* gene promoter indicates that there are multiple *cis*-elements that could be activated by ER through genomic and non-genomic pathways. The E2-responsive -650 to +12 region of the promoter does not contain an estrogen response element (ERE), and direct binding of ER to the *egr-1* promoter has not been detected. 5'-Deletion analysis of the promoter showed that the -460 to -164 region of the promoter was essential for E2-responsiveness, and this sequence contains 3 serum response elements (SREs) and two Ets motifs. Identification of E2-responsive motifs was further investigated using a series of deletion constructs (pEgr-1f-i) containing the -460 to -283, -383 to -283, and -460 to -383 regions of the *egr-1* gene promoter, respectively. In transient transfection studies in MCF-7 cells, E2 induced reporter gene activity in cells transfected with pEgr-1f (-460 to -283) (7.5-fold), and only weak induction (< 2-fold) was observed in cells transfected with pEgr-1g (-383 to -283). The remaining constructs were not hormone-responsive suggesting that the upstream SRE was the major site of E2-induced transactivation. These results are similar to those recently reported for non-genomic activation of the proximal SRE in the *c-fos* gene by E2 and, in MCF-7 cells transfected with pEgr-1f, hormone-induced activation was blocked by the MAPK inhibitor PD98059. Current studies are focused on characterizing the SRE-binding transcription factors and the pathway for E2-dependent MAPK activation of Egr-1. (Supported by NIH ES09253 and ES09106)

1072 *IN VIVO* STRESS ACTIVATES JAK-STAT IN LIVER BUT NOT BRAIN.

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The Janus kinase-signal transducers and activators of transciption (JAK-STAT) signaling pathways are believed to be crucial signalling pathways in the physiological changes induced by stress. Various stressors (e.g., UV) have been shown to activate the JAK-STAT pathway, *in vitro*, but only a few reports have examined the JAK-STAT pathway using stress models, *in vivo*. Here C57BL6/J female mice were exposed to restraint, vibration or cold stress. To preserve steady-state phosphorylation, the mice were killed by focused microwave irradiation. The activation state of STAT 3, 5 and 6 was assessed from blots of tissue homogenates probed with phospho state-specific antibodies as well as antibodies directed against the context-independent state of the various STATs to assess their total tissue levels. Quantification

was achieved by densitometry of bands generated by enhanced chemiluminescence. No changes in the activation (phosphorylation) state of any of the STATs were evident in brain; however, large increases in phosphoSTAT3 were evident in liver, with restraint and cold providing the largest magnitude changes (~ 300%). STAT3 levels did not change with any of the stressors. Restraint of adrenalectomized mice caused an even larger increase in phosphoSTAT3 (~ 500%). Immunohistochemical examination of STAT3 confirmed that restraint resulted in the nuclear location (i.e. activation) of STAT3, which was substantially greater in adrenalectomized mice. These data suggest that effects of physiological stressors are mediated through a STAT3 pathway that may involve the HPA axis and/or sympathetic nervous system.

1073 COSTS AND BENEFITS OF COMPLIANCE WITH ALTERNATIVE REMEDIATION STANDARDS AT HEXAVALENT CHROMIUM–CONTAMINATED SITES.

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The New Jersey Department of Environmental Protection (NJDEP) requires varying levels of soil remediation at hazardous waste sites depending on the pathway of exposure. For example, sites which contain hexavalent chromium [Cr(VI)] in soil, must comply with either uniform default or site-specific health-based standards for inhalation, dermal, and oral exposures. NJDEP currently relies on an "averaging" approach when evaluating the increased cancer risk from inhalation of suspended soil (i.e., the 95th percentile upper confidence limit of the mean concentration is not allowed to exceed the inhalation standard) and a "bright line" approach when evaluating allergic contact dermatitis (ACD), an acute effect, from dermal contact with Cr(VI) in soil or puddles (i.e., no single soil sample is allowed to exceed the dermal standard). NJDEP also relies on this latter "bright line" approach when evaluating the long-term non-cancer risks associated with incidental soil ingestion, although this is inconsistent with USEPA risk assessment guidelines. The current analysis evaluates whether the extra costs required to comply with NJDEP's approach are justified by the associated benefits. Cost estimates are based on average costs for site remediation and the difference in the volume of soil requiring treatment to meet the oral standard as either a "bright line" or an "average." Benefits are estimated as the expected change in health risk associated with NJDEP's approach, and assumptions about the population affected and value per fatal and nonfatal event averted. The results of the cost-benefit analysis indicate that NJDEP's approach for site remediation yields negative net benefits—i.e., estimated costs are about $100, 000 per site examined as compared to estimated benefits of about $100. Sensitivity analyses, which incorporate a range of possible costs and benefits, also suggest that NJDEP's approach is not cost-beneficial. These findings are important for evaluating the appropriateness and limitations of alternative approaches for complying with soil remediation standards.

1074 INVESTIGATION OF ASBESTOS IN CONSUMER PRODUCTS: CHILDREN'S PLAYSAND.

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The US Consumer Product Safety Commission (CPSC) regulates 15, 000 types of consumer products, including products made with mined materials. Recently, CPSC staff obtained a convenience sample of six playsand products from three companies in five states. Under contract, two independent laboratories analyzed the sand by polarized light microscopy (PLM) and transmission electron microscopy (TEM) for the presence of asbestos fibers. The bulk of each sample was nonfibrous and consisted of quartz, with smaller amounts of rutile, sphene, zircon, horneblende, rock fragments, and opaque grains. Two samples from the same company contained chrysotile and tremolite asbestos (<0.001%). Fibers were small, about 1 µm long and 0.05-0.2 µm in diameter. Small chamber experiments were conducted to determine if asbestos fibers could be released into the air. Air filters were analyzed by TEM using the USEPA AHERA (Asbestos Hazard Emergency Response Act) protocol. Estimated asbestos fiber release from the two playsand samples was 210, 000-2.5 million fibers per minute. Airborne fibers had the same mineralogy and physical characteristics as fibers detected in the bulk samples. Thus, despite the relatively small proportion of asbestos structures in the sand, large numbers of fibers were released into the air during a simulated play activity. Indoor air modeling based on one hour of play in a daycare or classroom setting resulted in projected air concentrations of 0.03 to 0.35 fibers/mL. Although the staff concludes that the very short fibers detected in these samples are not a health concern, we will continue to monitor playsand and other mineral-containing consumer products for the presence of potentially hazardous asbestos fibers. (The opinions expressed by the authors do not necessarily represent the views of the Commission. This abstract is in the public domain and may be freely copied or reprinted.)

1075 DERMAL ABSORPTION OF PCBs IN RHESUS MONKEYS FROM SOIL CONTAMINATED WITH AROCLOR 1260.

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Dermal absorption is routinely evaluated as a potential pathway for absorption of contaminants when conducting human health risk assessments for Superfund sites. For PCB-contaminated soil, the US Environmental Protection Agency uses a dermal absorption factor of 14%, a factor derived from a 1993 study of the dermal absorption of Aroclors 1242 and 1254 from contaminated soil by Rhesus monkeys. In comparison to the 1993 study, the current study varied several parameters that can influence the dermal absorption of lipophilic hydrocarbons, including soil organic content, soil particle size, skin residence time and contaminant "aging" in the soil. The study consisted of four groups of four female Rhesus monkeys exposed to ^{14}C-radiolabeled Aroclor 1260. One group was exposed intravenously to PCBs in propylene glycol (100% absorption) and 3 groups were exposed dermally to PCB-spiked soil. Two dermal exposure groups were exposed for 12 or 24 hours, respectively, to PCBs that had been aged in soil. These groups exhibited percutaneous absorption of 3.43 ± 0.35% and 4.26 ± 0.52%, respectively, of the applied dose. The remaining dermal group was exposed for 24 hours to soil freshly spiked with PCBs and exhibited dermal absorption of 4.07 ± 0.46% of the applied dose. It has been reported that soil organic content is an important factor in modulating the percutaneous absorption of highly lipophilic compounds from soil. The soil used in the current study had an organic content of 5-6%, a value typical for US soil, and a value that contrasts sharply with the 0.9% soil organic content used in the 1993 study upon which the current 14% dermal absorption factor for PCBs is based. Therefore, the current dermal absorption factor used by EPA appears to substantially overestimate the fraction of PCBs available for absorption from soils with typical organics content.

1076 EPA'S INTEGRATED RISK INFORMATION SYSTEM (IRIS).

S. H. Rieth and A. L. Mills. *USEPA, Washington, DC.* Sponsor: D. Singh.

IRIS is an EPA database that contains consensus scientific positions on potential human health effects that may result from chronic exposure to chemical substances. IRIS assessments present summaries of qualitative and quantitative health effects information, including reference doses (RfDs) and reference concentrations (RfCs) for the noncarcinogenic effects of chemicals and cancer slope factors and unit risks. Quantitative assessments in IRIS are used extensively in combination with specific situational exposure assessment information to evaluate potential public health risks. The IRIS database currently contains assessments for over 500 chemical substances. Approximately 80 assessments are underway or will be initiated in FY 2002; these include assessments for chemicals new to IRIS and updates of existing summaries that provide new scientific information and application of more current risk assessment methodologies. The IRIS Program continues to explore ways to improve its assessments, the process by which the assessments are prepared, and the database itself. Two such initiatives are the re-engineering of the IRIS Web site and an IRIS "Needs Assessment." The Web site (www.epa.gov/iris) was redesigned to be a more user-friendly Web-enabled database, with extensive hyperlinks and search interfaces. Users can request a "QuickView" version, which provides essential values with links to full IRIS summary text and supporting documents. The Needs Assessment is intended to define the needs of the public and EPA program offices/regions for new and revised IRIS health assessments. Issues being examined include: what additional chemical substance assessments are needed; which assessments currently on IRIS are in greatest need of scientific update; what additional types of information would be of value (e.g., acute and subchronic values); and to what extent should EPA collaborate with external parties as a means of developing IRIS assessments. Input from this Needs Assessment will be used by EPA in developing the 2002-5 IRIS agenda and resource needs.

1077 EVALUATION OF NON-CARCINOGENIC EFFECTS OF SOLUBLE NICKEL SALTS.

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A risk assessment for chronic toxicity of soluble nickel(reference dose; RfD) *via* oral exposure was prepared by USEPA in 1987 and is available on EPA's Integrated Risk Information System (IRIS). The RfD was based on a two year feeding study in rats given 0, 100, 1000 or 2500 ppm nickel in the diet (estimated as 0, 5, 50 and 125 mg/kg/day). No significant effects were reported at 100 ppm (5 mg Ni/kg/day). At 1000 ppm, body weight was significantly reduced in both sexes; at 1000 pm, females had significantly higher heart-to-body weight ratios and lower liver-to-body weight ratios than controls. The two year survival was poor, particularly in control

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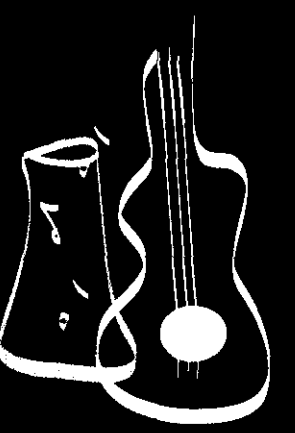

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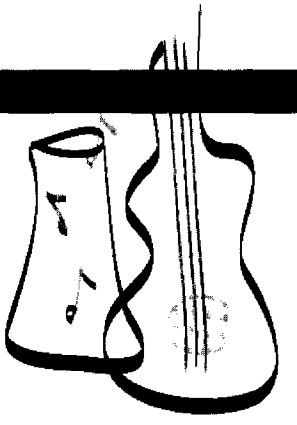

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Preface

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 41st Annual Meeting of the Society of Toxicology, held at the Opryland Hotel and Convention Center, Nashville, Tennessee, March 17–21, 2002.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 385.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 411.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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