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The effects of o,p'-DDT on cytochrome P450 1A1 expression was investigated in cultured mouse hepatoma Hepa-1c1c7 cells. o,p'-DDT alone did not affect P450 1A1-specific 7-ethoxyresorufin O-deethylase (EROD) activity. In contrast, the TCDD-inducible EROD activities were markedly reduced upon concomitant treatment with TCDD and o,p'-DDT in a dose dependent manner. Treatment with ICI 182.780, an estrogen-receptor antagonist, did not affect the suppressive effects of o,p'-DDT on TCDD-inducible EROD activity. TCDD-inducible P450 1A1 mRNA levels were markedly suppressed upon treatment with TCDD and o,p'-DDT, and this consistent with their effects on EROD activity. A transient transfection assay using dioxin-response element (DRE)-linked luciferase and an electrophoretic mobility shift assay revealed that o,p'-DDT reduced the transformation of the aryl hydrocarbons receptor to a form capable of specifically binding to the DRE sequence in the promoter region of the P450 1A1 gene. These results suggest that the down regulation of P450 1A1 gene expression by o,p'-DDT in Hepa-1c1c7 cells might be an antagonism of the DRE binding potential of the nuclear aryl hydrocarbon receptor but is not mediated through the estradiol receptor.

[PA4-4] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Sphinganine 1-phosphate , New biomarker of fumonisin B1 exposure

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Fumonisins are produced by fusarium verticilloides and other fusarium that grow on corn worldwide. They cause liver cancer promotion and subchronic liver and kidney effects in rats, mice, rabbits, horses and swine. The impact of fumonisins on human health remains unclear, but epidemiologic evidence suggests that consumption of fumonisin-contaminated corn contributes to human esophageal cancer and neural tube defects in southern africa and china. On molecular level, fumonisins inhibit ceramide synthase and disrupt sphingolipid metabolism including the accumulation of sphinganine(Sa).
Recently, we studied the effect of fumonisin B1 on sphinganine 1-phosphate(Sa1P) by using HPLC method in vitro and in vivo.
In vitro, HaCaT cells and LLC-PK1 celle were sensitive to fumonisin B1. In HaCaT cells and LLC-PK1 cells treated with fumonisin B1 50uM, Sa1P was elevated by 23-fold and 300-fold at 72 hr, respectively. But, CHO cells and Chang cells did not go through cell death even 50uM fumonisin B1 exposure. Interestingly, although there was a big increase in sphinganine, no increase in Sa1P was observed in CHO and Chang cells.
In vivo study, we compared the effects of fumonisin B1 on Sa1P elevation with Sa.
Mice (n=8) were cut the abdomen open after 1hr (acute) and 5 days (chronic) of given fumonisin B1 (0.5 and 5 mg/kg body weight) by i.p injection. The increase in sphinganine 1-phosphate were significantly observed than sphinganine in all tissues except liver. In brain, sphinganine 1-phosphate was increased although the elevation of sphinganine did not observed.
This study may settle limitation of using Sa elevation as a biomarker of fumonisin B1 exposure and may be suggested as a new biomarker of fumonisin B1 exposure.

[PA4-5] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

In vitro effects of polychlorinated biphenyls on the AhR and ER activity.

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Polychlorinated biphenyls (PCBs) are persistent environmental contaminants that elicit a broad spectrum of toxic effects in mammals and other vertebrate species. Because of their lipophilicity, chemical stability and resistance to biodegradation, PCBs tend to accumulate in the food chain and environmental matrices including human adipose tissues, blood and milk.
Certain congeners of PBCs exert dioxin-like activities such as immuno-, reproductive-, neuro-, dermal-, and hepatotoxicity and carcinogenesis through interacting with aryl hydrocarbon receptor (AhR). In vivo and in vitro studies have shown that some PCB mixtures, individual congeners and their metabolites exhibit

estrogenic or antiestrogenic activity. However, evidence for interaction of single PCB congeners with nuclear receptors has been sparse.
Here we examined the effects of four PCB congeners, PCB118(2,3',4,4'5-pentachlorobiphenyl), PCB138 (2,2',3',4,4'5-hexachlorobiphenyl), PCB153 (2,2',4,4',5,5'-hexachlorobiphenyl) and PCB180 (2,2'3,4,4'5,5'-heptachlorobiphenyl) and mixture effects of PCB congeners and TCDD on the AhR mediated gene expression (cytochrome P450 1A1 mRNA level and AhR responsive reporter gene assay) and enzyme activity (EROD activity) in the two hepatocarcinoma cell lines: HepG2 and Hepa1c1c 7. In addition, we evaluate the effects of PCB congeners on the estrogen receptor (ER) activity by E-screen assay and ERE-Luc reporter gene assay. In this study, we present evidence that PCB congeners exhibiting a variety of chlorine substitution patterns, have pleiotypic effects on the AhR and ER activity.

[PA4-6] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Suppression of iNOS expression by nonylphenol in macrophages

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In this study, we investigated the effect of 4-nonylphenol on the regulation of inducible nitric oxide synthase (iNOS) in murine macrophages. 4-Nonylphenol alone did not affect the expression of iNOS, in contrast, suppressed the LPS-induced gene expression of iNOS, in a dose-dependent manner. Nitric Oxide (NO) production was assessed by measurement of nitrites in the medium. The level of NO was found to correlate well with a decrease in transcripts of iNOS. Since the promoter in iNOS gene contains binding motifs for NF-kB, the effect of 4-nonylphenol on the inactivation of this transcripts factor was determined by transient transfection assay. Employing a transfection and reproter gene expression system with p(NF-kB)3-Luciferase, the treatment of 4-nonylphenol produced a dose-dependent inhibition of luciferase activity in RAW 264.7 murine macrophages cell line. These results suggest that suppression of iNOS gene expression by 4-nonylphenol might be mediated by the inhibition of NF-kB activation.

[PA4-7] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Evaluation of skin sensitization to sunscreens by local lymph node assay in Balb/c mice

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The use of sunscreens have been recently increased in various kinds of cosmetic products, although there were some reports that sunscreens might cause skin allergies and photoallergies. A murine lymph node assay (LLNA) has been developed as an alternative to guinea pigs for contact sensitization potential. This study was carried out to investigate the skin sensitization potential of four chemical sunscreens, butyl methoxy dibenzoylmethane, octyl methoxycinnamate, 3-(4-methyl benzyliden) camphor, octyl salicylate, by LLNA using non-radio isotopic endpoint. Female Balb/c mice were exposed topically to allergen, dinitrochlorobenzene (DNCB), irritant, sodium lauryl sulfate (SLS) and four sunscreens following LLNA protocol. Lymph node (LN) weight and cell proliferation in ears and auricular lymph node using BrdU (Bromodeoxyuridine) immunohistochemistry were evaluated. As results, LN weights were significantly increased at the DNCB (0.25, 0.5, 1%) and SLS (10, 25%), compared to control. Allergen DNCB(0.5, 1%) elicited 3-fold or greater increase in cell proliferation of lymph node as well as increase in cell proliferation of ear by BrdU immunohistochemistry. However, irritant SLS did not increase cell proliferation of lymph node. In the sunscreen agents, there were no significant changes in LN weight and cell proliferation in ear and lymph node of mice treated with 10 and 20% four sunscreens compared to control. These results show that these four sunscreens do not have contact sensitization potential at tested concentration in Balb/c mice by LLNA.

[PA4-8] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]