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PRESENTATION TYPE: Symposium

Secondary Pres Type - Proposal: Symposium

IAT/ITS Designation:

TITLE:

Mode of Action Associated with Induction of Endothelial Cell Tumors - Hemangiosarcoma

ABSTRACT BODY:

Hemangiosarcoma is an aggressive, malignant tumor of endothelial cells that is rare in humans. In the 12 regions of the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, the incidence rate of hemangiosarcoma between 1996 and 2000 was 0.21 new cases per 100,000 people (0.00021%). Hemangiosarcoma in humans commonly occurs on head and neck and is associated with skin structures. Liver hemangiosarcoma is associated with exposure to genotoxic compounds such as Thorotrast or vinyl chloride. In contrast, hemangiosarcoma occurs spontaneously in liver, spleen, bone marrow, lymph nodes and skin at a high incidence in rodents. The background incidence in B6C3F1 mice reported from the National Toxicology Program database is 5.4% in males and 2.7% in females with a range from 0% to 12%. The incidence in Wistar rats ranges from 0 - 3.4 %. These data suggest that mice are more susceptible to development of spontaneous hemangiosarcoma than rats and much more susceptible than humans. Hemangiosarcoma in rodents, primarily mice, has been reported in the labeling of a number of marketed drug products and in the literature with several chemicals. Some of these compounds demonstrated genotoxic potential in nonclinical testing and thus a plausible mechanism for tumor induction. Others, however, are clearly nongenotoxic and a mode of action is more difficult to establish. Regardless, findings of hemangiosarcoma have significant impact on decisions made regarding further development of these agents and future usage. Recent research has provided a great deal of information on epigenetic mechanisms of tumorigenesis relating to these compounds. Species differences in hemangiosarcoma incidence may be related to factors responsible for normal endothelial homeostasis and thus provide a basis for risk assessment. This symposium will focus on characterization of unique biological aspects of hemangiosarcoma, current issues and impact on drug and chemical development, and case studies describing recent research on tumorigenic mechanisms with relevance to human risk assessment.

CATEGORY: Carcinogenesis, Regulatory and Safety Evaluation, Mechanisms, Toxicologic & Exploratory Pathology

CHAIR/PRESENTER INFORMATION:

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Role: Presenter 1

Member Type: Non-member

Funding: SOT funding requested

Presentation Title: Comparative Pathology Of Hemangiosarcoma

Presentation Description: This presentation will be an overview of the comparative histological, biological, and molecular biological aspects of benign and malignant neoplasms arising from blood vessel endothelium (i.e. hemangioma/angioma and hemangiosarcoma/angiosarcoma) in man and animals. There will be a brief review of the terminology and useful diagnostic criteria, potential and known etiologies, as well as emphasis on the incidence and behavior of endothelial neoplasms in man, dog, cat, rat, and mouse. Data from

recent retrospective studies of the rat and mouse from the U.S. National Toxicology Program will be presented and discussed.

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Funding: No SOT funding required
Presentation Title: The Induction Of Hepatic Hemangiosarcoma By Vinyl Chloride: Dose-Response And Mode Of Action.
Presentation Description: This talk will review the induction of hepatic hemangiosarcoma in humans and laboratory animals exposed to vinyl chloride. It will also discuss the roles of cell proliferation and the induction of DNA adducts, their repair and relationship to identical endogenous DNA adducts that arise from oxidative stress.

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Funding: No SOT funding required
Presentation Title: Epigenetic Mechanisms Of Hemangiosarcoma Induction
Presentation Description: In mouse liver, chronic exposure to several hemolytic agents results in the induction of hemangiosarcoma. Concomitant with hemangiosarcoma induction is an increase in hemosiderin deposition in Kupffer cells. Studies have demonstrated that one of these agents, 2-butoxyethanol, induces a dose dependent increase in endothelial cell proliferation. The endothelial cell proliferation appears dependent upon Kupffer cell activation, probably via hemolyzed blood cells and iron deposition. Thus, Kupffer cells appear to mediate the increase in cell proliferation seen with selected nongenotoxic agents that induce hemangiosarcoma in mouse liver. In this presentation the hypothesis that Kupffer cell derived oxidative stress or growth factor release mediates this effect and that Kupffer cells, therefore, may play a central role in the induction of liver hemangiosarcomas by nongenotoxic agents, will be discussed.

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Funding: No SOT funding required

Presentation Title: Investigative Approaches to Understanding the Mode of Action for, and Human Relevance of, PPAR γ Agonist Induced Hemangiosarcomas

Presentation Description: Peroxisome Proliferation Associated Receptor gamma (PPAR γ) agonists, and PPAR α , dual agonists, developed for the treatment of insulin resistance in type II diabetes, have shown carcinogenic potential in 2-year rodent studies. Two tumor types of concern associated with chronic treatment with PPAR γ agonists are carcinomas in transitional urothelium in rats and hemangiosarcomas in mice. Whereas the weight of evidence indicates that neither the agonists nor their metabolites have genotoxic activity, the focus has been on elucidating direct or indirect mechanisms of non-genotoxic carcinogenesis. The hemangiosarcoma response in mice, first reported for troglitazone (Tox. Appl. Pharm. 156:106-112, 1999), is characterized by a multi-organ involvement with subcutaneous tissue and liver being the highest incidence sites. Whereas no evidence for ras oncogene or p53 tumor suppressor gene mutations was found for these tumors, current mechanistic investigations are focused on promotion of spontaneous lesions by epigenetic mechanisms associated with PPAR agonist-mediated changes in gene expression. Since the response is specific to mouse (and hamster), but is not seen in rats, the focus of the talk will be on elements in the mouse genome that may predispose to the development of these lesions when endothelial progenitor cell populations are subject to stimulation from angiogenic growth factors released as part of the normal program of PPAR γ -stimulated adipogenesis.

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Funding: No SOT funding required

Presentation Title: Regulatory Perspective on PPAR-Induced Rodent Tumors including Hemangiosarcoma

Presentation Description: Drug-induced hemangiosarcomas have been observed with 9 of the 12 PPAR agonists with completed 2-year carcinogenicity studies (4/6 gamma agonists, 5/6 dual agonists). These tumors have been observed in CD-1 and B6C3F1 mice and hamsters. Increased incidences of sarcomatous tumors at other sites (e.g., adipose, skin, stomach, uterus, renal tubules) have also been observed in both rats and mice with multiple compounds. The tumors are located at sites of high PPAR distribution, tumorigenicity correlates with exposures associated with significant PPAR activation (> EC 50), and the mechanism of PPAR-mediated tumor induction is unknown. Therefore, the FDA is concerned about the potential human relevance of the rodent tumor findings and the clinical safety implications for patients enrolled in long-term studies. The available rodent carcinogenicity data and current regulatory recommendations developed to insure patient safety will be discussed.

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Role: Chair

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Funding: No SOT funding required

Presentation Title: Induction Of Hemangiosarcoma In Mice Treated With Pregabalin By A Novel Epigenetic Mode Of Action

Presentation Description: A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin in the diet for two years. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years. Pregabalin is a single species, single tumor type epigenetic carcinogen. A novel mode of action for tumor induction with pregabalin will be discussed in this presentation.

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Funding: No SOT funding required

Presentation Title: No

Presentation Description: No