Toxic bile salts are known to exert hepatocyte toxicity by inducing apoptosis. Although it has been reported that Fas- death receptor pathway is the predominant pathway of apoptosis in cholestasis, the precise mechanism of bile salt-mediated apoptosis is still not fully understood. We investigated cellular localization and expression of proteins involved in the bile salt-mediated apoptosis in bile duct-ligated (BDL) rats by immunohistochemistry and Western blot analysis. Activated stellate cells, responsible for liver fibrosis, were ncreased in portal and periductular areas in BDL rats over 8 weeks. In sham controls, Fas was weekly expressed in cytoplasm of hepatocytes but not in bile duct epithelial cells (BEC). The expression was inhanced by BDL for first 3 days, and remained constituitively expressed over 8 weeks. Bax was expressed in a punctate manner indicative of mitochondrial localization in BEC and hepatocytes of sham controls. Bax was increased by BDL, and then its expression was decreased with time. Antiapoptotic protein Bcl-2 was detected only in BEC of sham controls. At day 3 after BDL, de novo Bcl-2 expression was observed in hepatocytes, and the strong immunoreactivity was observed in hepatocytes located along the bile ductules. After BDL for two weeks, expression of Bcl-2 showed a marked increase in BEC and also showed strong expression in periportal hepatocytes. Expression pattern of p53, a transcription factor, was very similar to that of Bax expression. We demonstrated that Fas was strongly expressed in the cytoplasm of hepatocytes in BDL rats, indicating the involvement of soluble Fas molecules. Expression pattern of Bax showed a good inverse correlation with that of Bcl-2 expression. Also expression of Bax may be regulated by p53.

[PA3-13] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Comparison of corresponding human intake giving biochemical toxicity induced by TCDD in risk Assessment

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The most sensitive biochemical effect dioxin and related chemicals are CYP1A1/2 induction, EGF-receptor down regulation and oxidative stress. Currently, the body burden giving rise to specific toxicological endpoint has been used for calculation of human external intake in dose-response assessment in field of risk assessment improved by PB-PK model. The animal body burden giving rise to statistically significant effect related with CYP1A1/2 induction, and EGF receptor down-regulation induced by TCDD using animal data have reported as range of 3~10ng/kg by WHO (1998). U.S.EPA(2000) suggested corresponding animal body burden (0.17~12.3ng/kg) giving biochemical toxicity like CYP1A1/2 induction and EGF receptor down regulation from dose-response model. This study has compared difference of above two value using conversion equation which can human intake level from animal body burden : Intake(ng/kg/day) = body burden(ng/kg)×ln2 / half-life×absorption rate (ln2=0.693, half-life 7.5years, absorption rate 50%). The range of corresponding human intake giving biochemical toxicity based on WHO and U.S.EPA data were 1.52~5.06pg/kg/day and 0.086~6.23pg/kg/day, respectively.
If above two values regard and apply uncertainty factor 10 (human variability), tolerable daily intake 0.009~0.62pg/kg/day can be used as possible human intake without giving rise to biochemical toxicity induced by TCDD.

[PA4-1] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

The Role of Rat Plasma in Manifesting Toxicity of Erythrocytes by Water -Soluble Menadione: Further Evidence of Free Radical Generation

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