The Japanese Society of Toxicology
Fundamental Toxicological Sciences

2015-Vol。2 No. 4

バック

2015-Vol。2

原著

[ラットにおけるβ-ブロモスチレンの反復投与28日間経口毒性試験]

Vol.2、No.4、p.191-200

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リリース：2015年9月29日

概要 全文PDF [202K]

β-ブロモスチレンの反復投与経口毒性の可能性とその可逆性に関する情報を得るために、Crl：CD（SD）ラットにβ-ブロモスチレンを0、30、125、500 mg / kg /日で28回強制経口投与した。数日、その後14日間の回復期間が続きます。500 mg / kg群では、最初の投与日にすべての雌雄で自発運動の減少が観察され、1匹の雌ラットが3日目に死亡した。体重または摂餌量に有意な変化はなかった。125 mg / kg以上を投与された雄で尿量の増加と尿浸透圧の低下が観察され、500 mg / kgを投与された雌で尿量の増加が観察された。血液生化学的検査では、総コレステロール、リン脂質、トリグリセリド、総タンパク質、アルブミン、無機リン、および/または塩素が125および/または500mg / kg群で観察された。組織病理学的には、尿細管細胞の好酸球体および/または尿細管変性が、125および500 mg / kg群の雄の腎臓で観察された。甲状腺では、125 mg / kg以上を投与された雌と、500 mg / kgを投与された雄で卵胞細胞の肥大が観察されました。さらに、小葉中心性肝細胞肥大は、500mg / kgを投与された雌雄で観察された。投与期間の終わりに観察されたこれらの変化は、回復期間後に消失または減少した。これらの結果に基づき、β-ブロモスチレンの無毒性量は雌雄ともに30mg / kg /日と判断された。尿細管細胞の好酸球体および/または尿細管変性が、125および500 mg / kg群の雄の腎臓で観察された。甲状腺では、125 mg / kg以上を投与された雌と、500 mg / kgを投与された雄で卵胞細胞の肥大が観察されました。さらに、小葉中心性肝細胞肥大は、500mg / kgを投与された雌雄で観察された。投与期間の終わりに観察されたこれらの変化は、回復期間後に消失または減少した。これらの結果に基づき、β-ブロモスチレンの無毒性量は雌雄ともに30mg / kg /日と判断された。尿細管細胞の好酸球体および/または尿細管変性が、125および500 mg / kg群の雄の腎臓で観察された。甲状腺では、125 mg / kg以上を投与された雌と、500 mg / kgを投与された雄で卵胞細胞の肥大が観察されました。さらに、小葉中心性肝細胞肥大は、500mg / kgを投与された雌雄で観察された。投与期間の終わりに観察されたこれらの変化は、回復期間後に消失または減少した。これらの結果に基づき、β-ブロモスチレンの無毒性量は雌雄ともに30mg / kg /日と判断された。小葉中心性肝細胞肥大は、500mg / kgを投与された雌雄で観察された。投与期間の終わりに観察されたこれらの変化は、回復期間後に消失または減少した。これらの結果に基づき、β-ブロモスチレンの無毒性量は雌雄ともに30mg / kg /日と判断された。小葉中心性肝細胞肥大は、500mg / kgを投与された雌雄で観察された。投与期間の終わりに観察されたこれらの変化は、回復期間後に消失または減少した。これらの結果に基づき、β-ブロモスチレンの無毒性量は雌雄ともに30mg / kg /日と判断された。

ページトップ

原著

[ラットにおける長鎖パーフルオロアルキルカルボン酸の反復投与および生殖/発生毒性：パーフルオロヘキサデカン酸およびパーフルオロテトラデカン酸]

Vol.2、No.4、p.177-190

平田睦子小泉、藤井咲子、加藤ひな、松本真理子、高橋美香、斧アツシ、広瀬明彦
リリース：2015年9月28日

概要 全文PDF [369K]

Perfluoroalkyl carboxylic acids (PFCAs) are global environmental contaminants that are the cause of concern due to their possible effects on wildlife and human health. Since few studies have investigated the toxicity of long-chain PFCAs, we have performed combined repeated dose toxicity studies with the

reproduction/developmental toxicity screening tests. We previously examined perfluoroundecanoic acid (C11), perfluorododecanoic acid (C12), and perfluorooctadecanoic acid (C18). We herein reported our results for perfluorotetradecanoic acid (PFTeDA; C14) and perfluorohexadecanoic acid (PFHxDA: C16). Male and female rats were administered PFTeDA at 1, 3 or 10 mg/kg/day or PFHxDA at 4, 20 or 100 mg/kg/day by gavage, and each female was then mated with a male in the same dose group after 14 days. Males were dosed for a total of 42 days and females were dosed throughout the gestation period until day 5 after parturition. PFTeDA and PFHxDA caused hepatocyte hypertrophy and/or fatty changes in the liver at the middle and high doses. PFTeDA also induced follicular cell hypertrophy in the thyroid at the middle and high doses. The only reproductive/developmental effect observed was an inhibited postnatal body weight gain in pups in the 10 mg/kg/day PFTeDA group. Based on these results, the NOAELs for the repeated dose and reproductive/developmental toxicity were concluded to be 1 and 3 mg/kg/day for PFTeDA and 4 and 100 mg/kg/day for PFHxDA, respectively. Our current and previous results indicate that the toxicity of PFCAs decreases with increases in the carbon chain length from 12 to 18.

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Letter

Health survey of workers in a 2,4,6-trinitrotoluene explosives factory in Fuxin, China — Vol.2, No.4, p.171-175

Yasuhiro Shinkai , Song Li , Tomohiro Kikuchi , Nobuhiro Shimojo , Yoshito Kumagai
Released: September 15, 2015

Abstract Full Text PDF[172K]

2,4,6-Trinitrotoluene (TNT) is a serious occupational and environmental pollutant. We conducted a cross-sectional health survey of workers in a TNT explosives factory in Fuxin, China. For each subject, we determined their blood pressure, hematotoxicity parameters, glutathione concentration, lipid hydroperoxide concentration, superoxide dismutase activity, and nitrite/nitrate (NOx) concentration in serum. Significantly fewer white blood cells were found in samples from male workers exposed to TNT than in samples from control male workers, but hematological parameters (such as the amount of hemoglobin present, the hematocrit value, and the formation of methemoglobin) varied little between the exposed and control workers. Exposure of male workers to TNT was found to cause their blood pressure to decrease significantly, concomitant with a tendency towards increased NOx concentrations in serum. On the other hand, lipid hydroperoxide (an oxidative stress marker) concentrations were significantly higher in female workers exposed to TNT than in control female workers. Our results suggest that TNT has different, deleterious effects in males and females, causing hematotoxic stress in males and oxidative stress in females.

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Original Article

Toxicogenomic prediction with group sparse regularization based on transcription factor network information — Vol.2, No.4, p.161-170

Keisuke Nagata , Yoshinobu Kawahara , Takashi Washio , Akira Unami
Released: September 15, 2015

Abstract Full Text PDF[1M]

Regression analysis such as linear regression and logistic regression has often been employed to construct toxicogenomic predictive models, which forecast toxicological effects of chemical compounds in human or animals based on gene expression data. While in general these techniques can generate an accurate and sparse model when a regularization term is added to a loss function, they ignore structural relationships behind genes which form vast regulatory networks and interact with each other. Recently, several reports proposed structured sparsity-inducing norms to incorporate prior structural information and make a model reflecting relationships between variables. In this study, assuming that genes regulated by the same transcription factor should be selected together, we applied the latent group Lasso technique on toxicogenomic data with transcription factor networks as prior knowledge. We compared generated

classifiers for liver weight gain in rats between the latent group Lasso and Lasso. The latent group Lasso was comparable or superior to the Lasso in terms of predictive performances (balanced accuracy: 74% vs. 72%, sensitivity: 62% vs. 62%, specificity: 86% vs. 83%). Besides, groups selected by the latent group Lasso suggested involvement of Wnt/β-catenin signaling pathway. Such mechanism-related analysis could not have been possible with the Lasso and is one of the advantages of the latent group Lasso.

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Letter

Effects of rofecoxib on lipid oxidation in plasma and aortas of rats Vol.2, No.4, p.155-159

Atsushi Miyajima , Yasuha Amano , Takeyoshi Kamamoto , Masahiro Okamoto , Takashi Hirota
Released: September 07, 2015

Abstract Full Text PDF[243K]

A selective cylooxygenase-2 (COX-2) inhibitor, rofecoxib, was withdrawn from the worldwide market due to an increased risk of cardiovascular (CV) events. A hypothesis has been proposed that rofecoxib promotes lipid oxidation, which increases the risk of CV events. However, this hypothesis was only predicated on *in vitro* experiments using isolated human low density lipoprotein and diluted human plasma. In the present study we investigated the effect of rofecoxib on the *in vitro* and *in vivo* production of thiorbarbituric acid reacting substance (TBARS) as an indicator of oxidation in plasma and aortas in rats. *In vitro* experiment, the TBARS production in plasma and aortic homogenate was not changed by the addition of rofecoxib at 2 μM, which concentration is around the maximum plasma concentration at clinical doses, or even at 200 μM. In addition, the production was not increased by rofecoxib in the presence of $FeSO_4$ as a typical oxidant. Meanwhile the TBARS production in the aorta of rats after 4-weeks administration of 10 mg/kg/day rofecoxib was comparable to that of the control rats. These results *in-vitro* and *in-vivo* experiments suggest that rofecoxib would have no or very weak effect on lipid oxidation in clinical usage, and it is thought that the increase of CV events already reported stemmed from causes other than oxidative stress.

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Letter

In vitro comet assay in cultured human corneal epithelial cells Vol.2, No.4, p.147-153

Hideyuki Sakaki , Masaki Kakehi , Kazuyo Sadamoto , Shingo Nemoto , Masaaki Kurata
Released: September 04, 2015

Abstract Full Text PDF[1M]

Topical drug treatment of the eye exposes ocular tissues to a high drug concentration. Genotoxicity assessment in ocular tissues has not been established to date. Therefore, we investigated the *in vitro* comet assay by incubating cultured human corneal epithelial (HCE-T) cells with known mutagens. The alkaline comet assay was conducted to measure the DNA strand breakage yield. When the cells were incubated with methyl methanesulfonate (MMS) for 1 hr, hydrogen peroxide (H_2O_2) for 15 min and actinomycin D (AMD) for 1 hr, statistically significant increases of percentage (%) DNA in the tail were noted in MS-, H_2O_2-, and AMD-treated cells at 100, 10, and > 10 μM, respectively. When the cells were treated with mitomycin C (MMC) or 5-bromouracil (5-BrU), %DNA in the tail was unchanged even at the highest concentration. Hedgehog cells were found in MMS- and H_2O_2-treated cells at 1000 and > 100 μM, respectively. The response to each compound was consistent with results previously reported in other cells. In conclusion, the *in vitro* comet assay using HCE-T cells can detect DNA strand breakage induced by mutagens. This method has a possibility to become a conventional screening tool to assess the genotoxicity of drugs applied to ocular surface.

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Original Article

Effects of cisplatin on testicular enzymes and Sertoli cell function in rats Vol.2, No.4, p.137-145

Zhifei Liu , Yingbiao Sun , Li Su , Yifan Sun , Shibo Kong , Xuhong Chang , Fang Guo , Wei Li , Junjie Guo , Jin Li
Released: August 25, 2015

Abstract Full Text PDF[1M]

Cisplatin (CP) is one of important tumour chemotherapeutic agents in humans. Previous reports claim that CP can cause testicular toxicity. The aim of this study was to evaluate the potential effects of CP in the testes of rats. Male Wistar rats were intraperitoneally administered CP at 1.0, 2.5, and 5.0 mg/kg for three consecutive days. After exposure, CP significantly inhibited the testicular activities of succinate dehydrogenase (SDH) and malate dehydrogenase (MDH), but it significantly elevated the activities of acid phosphatase (ACP), alkaline phosphatase (AKP), and lactate dehydrogenase (LDH) in the 5.0 mg/kg group. The decreased levels of superoxide dismutase (SOD), total antioxidant capacity (T-AOC), and metallothionein-1 (MT-1) mRNA as well as the increased levels of malondialdehyde (MDA) and haemoxygenase-1 (HO-1) mRNA showed that CP could increase oxidative stress in rat testes. Western blot analysis showed that the levels of transferrin, vimentin, androgen binding protein (ABP) and inhibinβ-B decreased significantly in the CP 2.5 and 5.0 mg/kg groups compared with the control group. These findings indicated that the inhibited enzymes, oxidative stress, and the down-regulation of Sertoli cell function-related proteins play pivotal roles in CP-induced testicular damage.

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