研究業績

論文等

一般毒性学

A Study for Collecting Background Data on Wistar Hannover [Crl:WI(Han)] Rats in General Toxicity Studies - Comparative Data to Sprague Dawley Rats -

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The Journal of Toxicological Sciences, 2013; **38(6)**: 855-873

The purpose of the present study was to collect background data from repeated dose toxicity studies in Wistar Hannover [Crl:WI(Han)] (hereafter Wistar Han) rats with dosing periods of 4, 13 and 26 weeks from four safety research facilities of pharmaceutical companies and contract research organizations participating in the International Genetic Standardization (IGS) rat forum supported by Charles River Laboratories Japan, Inc. The data from Wistar Han rats were compared with those from Sprague Dawley Crl:CD(SD) rats. In addition, the effects of restricted feeding of SD rats were also investigated by one facility. As a result, body weights and food consumption in Wistar Han rats were lower than those of SD rats. White blood cell (WBC), neutrophil, lymphocyte, monocyte and eosinophil counts were almost half of those noted for SD rats and platelet counts were almost 20% less than those in SD rats. Minimal strain differences were noted in several biochemical parameters including aspartate aminotransferase (AST), alanine aminotransferase, total cholesterol, triglyceride and phospholipids, and in thymus, ovary and testis weights. Ophthalmologic or histopathologic examinations revealed a higher incidence of corneal opacities or corneal mineralization in Wistar Han rats. Restricted feeding of SD rats resulted in intermediate values for body weights and food consumption between the *ad libitum* fed SD and Wistar Han rats, and WBC and AST were lower than those in the *ad libitum* fed SD rats. Based on these results, some strain differences might be ascribable to reduced food consumption and associated body weight changes in Wistar Han rats.

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生殖・発生毒性学

An antioxidant, N,N'-diphenyl-p-phenylenediamine (DPPD), affects labor and delivery in rats: A 28-day repeated dose test and reproduction/developmental toxicity test

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Food and Chemical Toxicology, 2013; **56**: 290-296

A 28-day repeated dose toxicity test and reproduction/developmental toxicity test for N,N'-diphenyl-p-phenylenediamine (DPPD) were conducted in [Crl:CD(SD)] SPF rats. Male and female rats were dosed with DPPD by gavage for 28 days at 0, 100, 300, or 1000 mg/kg bw/day or for a total of 42−46 days at 0, 8, 50, or 300 mg/kg bw/day. No significant adverse effects were observed in the repeated dose toxicity study up to 1,000 mg/kg bw/day in both sexes. In the reproduction/developmental toxicity study, two females showed piloerection, hypothermia, and pale skin; one died and the other showed dystocia on day 23 of pregnancy at 300 mg/kg bw/day. Another female delivered only three live pups at 300 mg/kg bw/day. A significantly prolonged gestation period was observed at 50 and 300 mg/kg bw/day. The NOAELs of repeated dose toxicity and reproduction/developmental toxicity were considered to be 1,000 and 8 mg/kg bw/day, respectively.

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Developmental effects of oral exposure to diethylstilbestrol on mouse placenta

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Journal of Applied Toxicology, 2013; **33(11)**: 1213-1221

Placental growth and function are of biological significance in that placental tissue promotes prenatal life and the maintenance of pregnancy. Exposure to synthetic estrogens causes embryonic mortality and placental growth restriction in mice. The aim of the present study was to examine the effects of diethylstilbestrol (DES) on placenta in mice. DES at 1, 5, 10 or 15 μg/kg/day, or 17 β-estradiol (E2) at 50 μg/kg/day, was administered orally to ICR mice on days 4 through to 8 of gestation. Expression of ER_{α}, ER_{β}, ERR_{β} or ERR_{γ} mRNA in the junctional or labyrinth zone of the placentas on day 13 was assessed using RT-PCR, as well as the embryonic mortality, embryonic and placental weight, histological changes of labyrinth and ultrastructural changes of the trophoblast giant cells (TGCs). Embryo mortalities in the DES 10 and 15 μg/kg/day groups were markedly increased. No significant changes in embryonic and placental weight were observed in any DES- or E2-exposed groups. Expression of ER_{α} mRNA in the junctional zone with male embryos in the 5 μg/kg/day group was significantly higher than that in the control, whereas expression was not determined in the 15 μg/kg/day group. Histological observation revealed that the placentas exposed to DES at 10 μg/kg/day lacked the developing labyrinth. Ultrastructural observation of the TGCs showed poor rough-surfaced endoplasmic reticulum in the DES 10 μg/kg/day group. The present data suggest that developmental changes induced by DES may be related to interference with the nutrition and oxygen exchange between mother and embryo or decreased protein synthesis, resulting in a high frequency of embryo mortality.

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A Study for Collecting Background Data on Wistar Hannover [Crl:WI(Han)] Rats in Embryo-fetal Development Studies - Comparative Data to Sprague Dawley Rats -

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The Journal of Toxicological Sciences, 2013; **38(6)**: 847-854

The purpose of the present study was to collect the background data on Wistar Hannover [Crl:WI(Han)] (hereafter Wistar Han) rats in embryo-fetal development studies from the 6 safety research facilities of pharmaceutical companies and contract research organizations. In each facility, 20 or 22 female rats were dosed with vehicle solution during the organogenesis period. As a result, no abnormalities in clinical signs and necropsy findings in dams were found. Body weights and food consumption in dams were lower than those in Sprague Dawley (SD) rats. The number of corpora lutea (13.3 vs. 16.0 in SD) and implantations (11.8 vs. 14.7) were fewer, and fetal body weights (3.66 vs. 3.70) and placental weights (0.42 vs. 0.45) tended to be lower than those in SD rats. Regarding the fetal abnormalities, the incidence of several findings such as the persistent left umbilical artery (10.4% vs. 1.1 %) and cervical (5.2% vs. 0.4%), full (7.4% vs. 0.9%) or short supernumerary (64.5% vs. 9.9%) and wavy ribs (6.6% vs. 0.3%) was higher than that in SD rats. Our present study showed that they maintained a sufficient number of live fetuses and the difference in the fetal sex ratio was not observed. In conclusion, Wistar Han rats were considered to be a suitable strain for embryo-fetal development toxicity study. Since the incidence of several abnormalities was higher than that in SD rats, it may be said that to accumulate background control data is important to evaluate the embryo-fetal development toxicity study using Wistar Han rats.

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細胞毒性学

Studies on mechanism of wear in micro-beads, and food-safety of fine particles caused by wear in a micro-beads mill

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Powder Technology, 2013; **240**: 74-78

The characteristics of wear in micro-beads were studied by focusing on projections on the surfaces of the micro-beads. Food safety associated with the presence of fine wear particles was studied by cytotoxicity tests reusing micro-beads with the projections worn away. It was shown that the smaller projections on the micro-beads surface were removed in a shorter time than the larger one and that if the beads diameter was less than about 60 μm, the size of the projections reached the submicron-level. Also, it was shown that fine particles formed by wear in micro-beads made of yttrium partially stabilized zirconia did not show cytotoxicity.

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食品衛生学

微生物検査の外部精度管理

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食品機械装置, 2014; **51(3)**: 57-60

ダイズおよびトウモロコシ抽出DNAの精製度の検討

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日本食品化学学会誌, 2013; **20(3)**: 203-208

The quality and yield of DNA extracted from soybean and maize samples were compared using two commercial DNA extraction kits, the DNeasy Plant Mini kit (Mini kit) and the GM quicker kit. Subsequent quantification of the extracted DNA samples by UV spectrophotometry and fluorometry revealed that the yields of soybean DNA extracted using the Mini kit were approximately three times higher when determined by UV spectrophotometry than when they were determined by fluorometry. Conversely, the yields of soybean DNA extracted using the GM quicker kit were only slightly higher when determined by UV spectrophotometry than when they were determined by fluorometry. However, the relative DNA yields of maize DNA samples estimated by UV spectrophotometry and fluorometry were 1.77 with the Mini kit and 1.52 with the GM quicker kit. To validate the soybean DNA yields obtained using both extraction kits, DNA samples were analyzed by agarose gel electrophoresis and real-time PCR of a reference gene. These analyses indicated that the Mini kit yields estimated by UV spectrometry were overestimated, due to more low-intensity bands and fewer gene copies being observed, compared to DNA extracted with the GM quicker kit. Conversely, the maize DNA yields obtained using the Mini and GM quicker kits showed only slight differences between the real-time PCR and agarose gel electrophoresis analyses. The extracted DNA samples were then analyzed by size-exclusion chromatography. The results showed that the soybean DNA extracted using the Mini kit contained more low-molecular weight impurities than the DNA extracted using the GM quicker kit and maize extracts obtained with both extraction kits. Therefore, it appears that the presence of low-molecular weight impurities in soybean DNA extracted with the Mini kit interferes with the UV quantification of DNA.

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食品分析の信頼性を確保するための外部精度管理について

渡辺卓穂

計測標準と計量管理, 2014; **63(4)**: 6-11

食品添加物検査の外部精度管理調査について

渡辺卓穂

食品衛生学雑誌, 2014; **55(1)**: J10-J14

医療機器

第6章：非臨床安全性試験・臨床試験における評価

【第1節】非臨床試験の評価　[1]非臨床試験で実施される安全性試験の概要

小島幸一

再生医療における臨床研究と製品開発, 技術情報協会, 東京(2013), pp.367-374

第13章 研究, 試験に関わる規制・ガイドラインの最新トピックと今後の動向　第5節 医療機器GLP

小島幸一

実験者/試験検査員の誤ったデータの取扱い・試験誤操作防止策, 技術情報協会, 東京(2014), pp. 505-511

発達神経毒性学

Chapter 5 Sexual Dimorphism in Monoamine Metabolism in BrdU-Treated Rats Showing Behavioral Dopamine Hypersensitivity: An Animal Model of Schizophrenia

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Sexual Dimorphism, InTech, (2013), pp. 81-96

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薬効薬理

Tranexamic acid induces kaolin intake stimulating a pathway involving tachykinin neurokinin 1 receptors in rats

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European Journal of Pharmacology, 2014; **723**: 1-6

Tranexamic acid suppresses post-partum haemorrhage and idiopathic menorrhagia through its anti-fibrinolytic action. Although it is clinically useful, it is associated with high risks of side effects such as emesis. Understanding the mechanisms underlying tranexamic acid-induced emesis is very important to explore appropriate anti-emetic drugs for the prevention and/or suppression of emesis. In this study, we examined the receptors involved in tranexamic acid-induced kaolin intake in rats, which reflects the drug's clinical emetogenic potential in humans. Further, we examined the brain regions activated by administration of tranexamic acid and elucidated pivotal pathways of tranexamic acid-induced kaolin intake. We examined the effects of ondansetron, a 5-hydroxytryptamine 3 receptor antagonist, domperidone, a dopamine 2 receptor antagonist, and aprepitant, a tachykinin neurokinin 1 (NK1) receptor antagonist, on tranexamic acid-induced kaolin intake in rats. Then, we determined the brain regions that showed increased numbers of c-Fos immunoreactive cells. Finally, we examined the effects of an antagonist(s) that reduced tranexamic acid-induced kaolin intake on the increase in c-Fos immunoreactive cells. Aprepitant significantly decreased tranexamic acid-induced kaolin intake. However, neither ondansetron nor domperidone decreased kaolin intake. Tranexamic acid significantly increased c-Fos immunoreactive cells by approximately 5.5-fold and 22-fold in the area postrema and nucleus of solitary tract, respectively. Aprepitant decreased the number of c-Fos immunoreactive cells in both areas. Tranexamic acid induced kaolin intake possibly via stimulation of tachykinin NK1 receptors in rats. The tachykinin NK1 receptor could be targeted to prevent and/or suppress emesis in patients receiving tranexamic acid.

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その他

フロアからの発言

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日本薬理学雑誌, **142(5)** (2013), pp. 207-208

学会発表等

免疫毒性学

粒子径の異なるナノ白金のLLNA試験

森村智美, 関　剛幸, 高岡　裕, 青木聡子, 又吉　健, 西垣嘉人, 吉岡靖男[1], 堤　康央[1], 桑形麻樹子

第40回日本毒性学会学術年会 2013.6.17～6.19(千葉)

同会講演要旨集, pp. S334

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In vitro 皮膚感作性試験代替法:KeratinoSens assayのJaCVAM第三者評価委員会における検証状況

金澤由基子[1], 安達玲子[2], 小島幸一, 筒井尚久[3], 佐藤一博[4], 森本隆史[5], 武吉正博[6], 牧　栄二[7], 小島　肇[2]

第20回日本免疫毒性学会学術大会 2013.9.12～9.13(東京)

同会講演要旨集, p.49

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In vitro 皮膚感作性試験代替法:Direct Peptide Reactivity Assay(DPRA)のJaCVAM第三者評価委員会における検証状況

武吉正博[1], 佐藤一博[2], 森本隆史[3], 筒井尚久[4], 安達玲子[5], 金澤由基子[6], 小島幸一, 牧　栄二[7], 小島　肇[5]

第20回日本免疫毒性学会学術大会 2013.9.12～9.13(東京)

同会講演要旨集, pp.50-51

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毒性病理学

ステント留置血管の治癒における初期の組織反応

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第30回日本毒性病理学会 2014.1.30～1.31(徳島)

同会講演要旨集, p. 112

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Developmental Origins of Health and Disease(DOHaD)説に基づいた新生児期栄養変化による生後発達への影響

桑形麻樹子, 瀬沼美華, 熊谷文明, 柴藤淳子[1], Rakwal Randeep[1], 斉藤義明, 丸茂秀樹, 小川哲郎[2], 塩田清二[1]

第30回日本毒性病理学会 2014.1.30～1.31(徳島)

同会講演要旨集, p. 113

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一般毒性学

ラットにおいてトラネキサム酸により誘発されるカオリン摂取とそのメカニズムの解明

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第156回日本獣医学会学術集会 2013.9.20～9.22(岐阜)

同会講演要旨集, p. 377

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酸化チタンナノ粒子の点鼻投与がラットの行動に及ぼす影響

横田俊二, 瀬沼美華, 根倉　司, 古谷真美, 吉田由香, 堀内伸二, 安藤栄里子

日本薬学会第134年会2014.3.27～3.30(熊本)

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生殖・発生毒性学

Hatano高および低回避雌ラットの性成熟, 性周期および体重推移に及ぼす新生児期ジエチルスチルベストロール曝露の影響

太田　亮, 根倉　司, 大向英夫, 新藤智子

環境ホルモン学会第16回研究発表会 2013.12.12～12.13(東京)

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食品衛生学

食品添加物検査の外部精度管理調査について

渡辺卓穂
第105回日本食品衛生学会 2013.5.17～5.18(東京)
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食品衛生外部精度管理調査のための残留動物用医薬品調査試料の作成検討について

渡辺卓穂, 高坂典子, 鈴木達也, 小島幸一
日本食品化学学会第19回総会・学術大会 2013.8.29～8.30(名古屋)
同会講演要旨集, p. 104

動物実験代替法

IL-8 Luc assayの施設間差試験およびデータセットの作製

木村　裕[1], 渡辺美香, 斎藤るみ子, 鈴木紀之[2], 岩城知子[3], 山影康次, 斎藤幸一[2], 中島芳浩[3],
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日本動物実験代替法学会第26回大会 2013.12.19～12.21(京都)
同会プログラム/講演要旨集, p. 116

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IL-8 Luc assayにおけるばらつきを考慮した判定基準の提案

丸谷あおい[1], 相場節也[2], 木村　裕[2], 渡辺美香, 鈴木紀之[3], 岩城知子[4], 山影康次, 斎藤幸一[3],
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同会プログラム/講演要旨集, p. 117

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Vitrigel-EIT(Eye Irritancy Test)法のプレバリデーション研究

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同会プログラム/講演要旨集, p. 150

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その他

DOHaD 説に基づいた精神疾患のリスクに関与する遺伝子の検索

瀬沼美華, Rakwal, Randeep[1], 柴藤淳子[1], 齋藤智美[1], 宗岡克政[1], 小川哲郎[1], 塩田清二[1], 桑形麻樹子
第53回日本先天異常学会学術集会 2013.7.21～7.23(大阪)
同会プログラム・要旨集, p. 84
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Developmental Origins of Health and Disease(DOHaD)責任遺伝子の解析

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同会プログラム・要旨集, p. 84
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