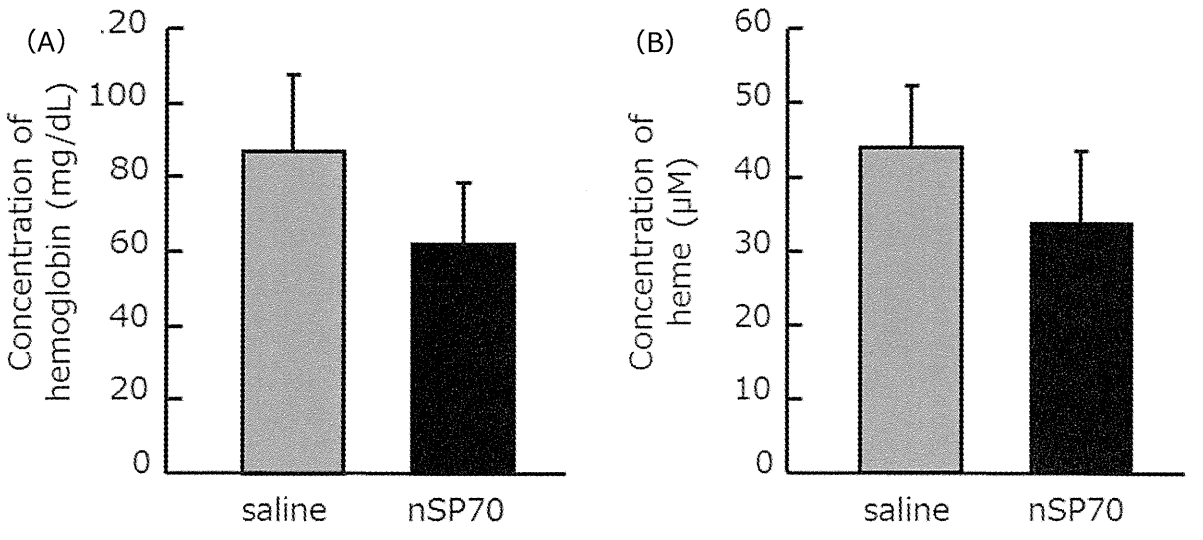

図 144. 血中 Hemoglobin 量、Heme 量の解析. BALB/ c マウスに nSP70 を 0.8 mg/mouse で尾静脈投与し、投与後 24 時間における血中 hemoglobin (A)、heme (B) 量を測定した。Data are presented as mean ± SEM (n=5-6).

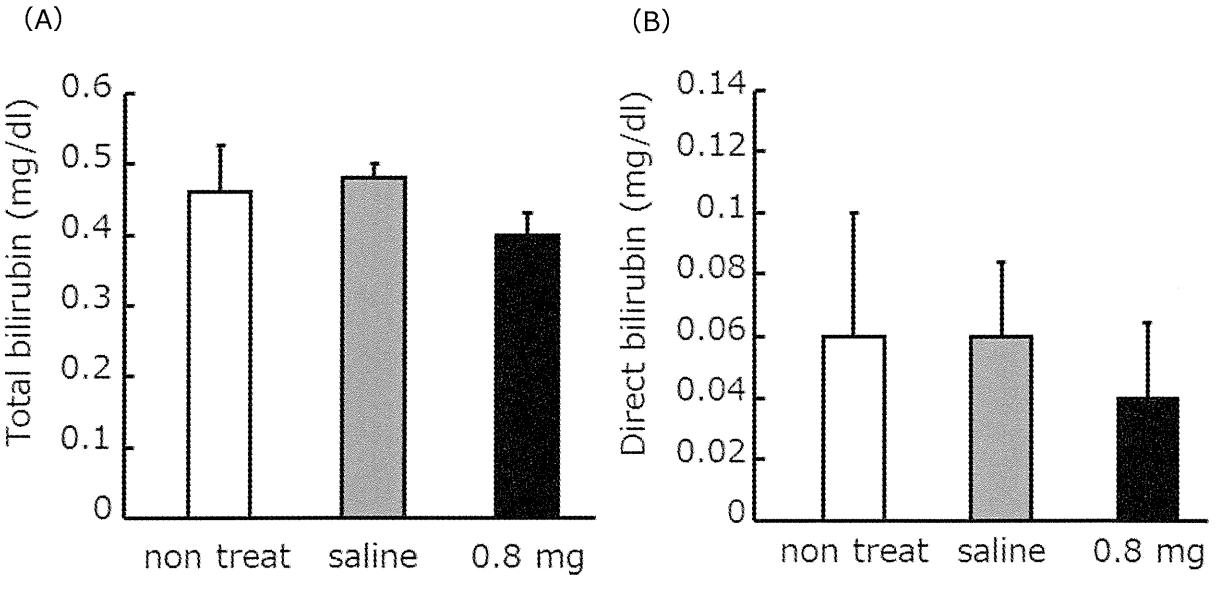

図 145. ナノシリカ投与時の溶血検査. BALB/ c マウスに nSP70 を 0.8 mg/mouse で尾静脈投与し、投与後 5 時間における総ビリルビン(A)、直接ビリルビン(B)量を測定した。Data are presented as mean ± SEM (n=5-6).

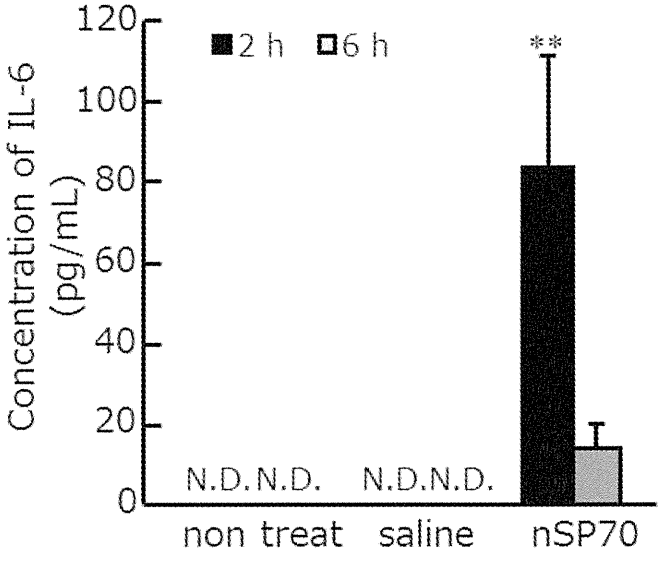

図 146. ナノシリカ投与時の血中 IL-6 量の測定. BALB/ c マウスに nSP70 を 0.8 mg/mouse で尾静脈投与し、投与後 2、6 時間における血中 IL-6 量を ELISA により測定した。Data are presented as mean ± SEM (n=5-6). **p <0.01 versus value for saline group by Bonferroni test)

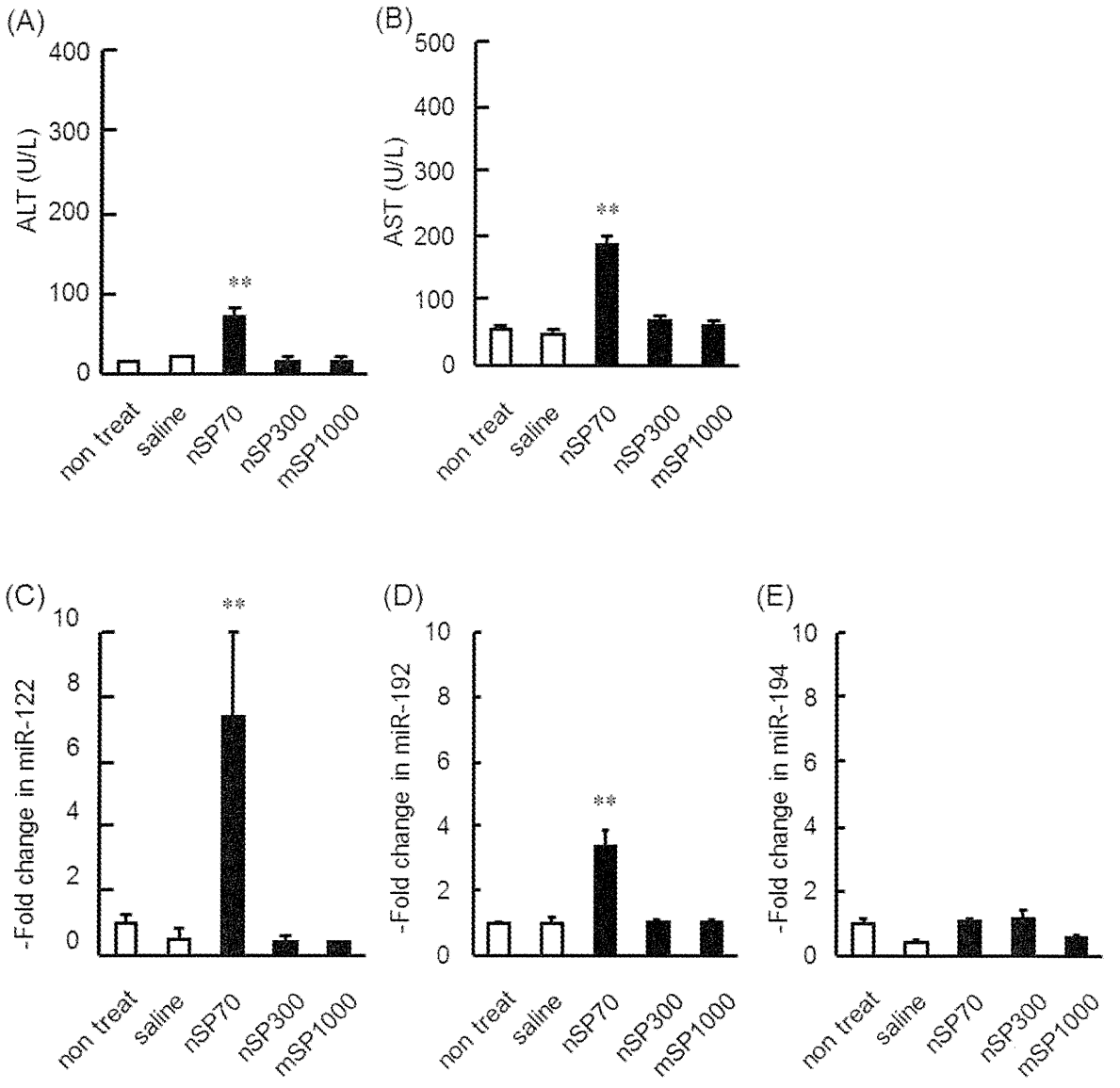

図 147. 非晶質ナノシリカ投与後の miR-122、mIR-192、miR-194 の発現変動解析
BALB/c マウスに nSP70、nSP300、mSP1000 を 40 mg/kg で尾静脈より投与し、投与後 8 時間における血液を回収した。従来の肝障害マーカーである（A）ALT、（B）AST は生化学検査により、（C）miR-122、（D）miR-192、（E）miR-194 はリアルタイム PCR により解析した。Bonferroni 法により有意差検定を行った。(**$P < 0.01$ *vs* non-treated group)

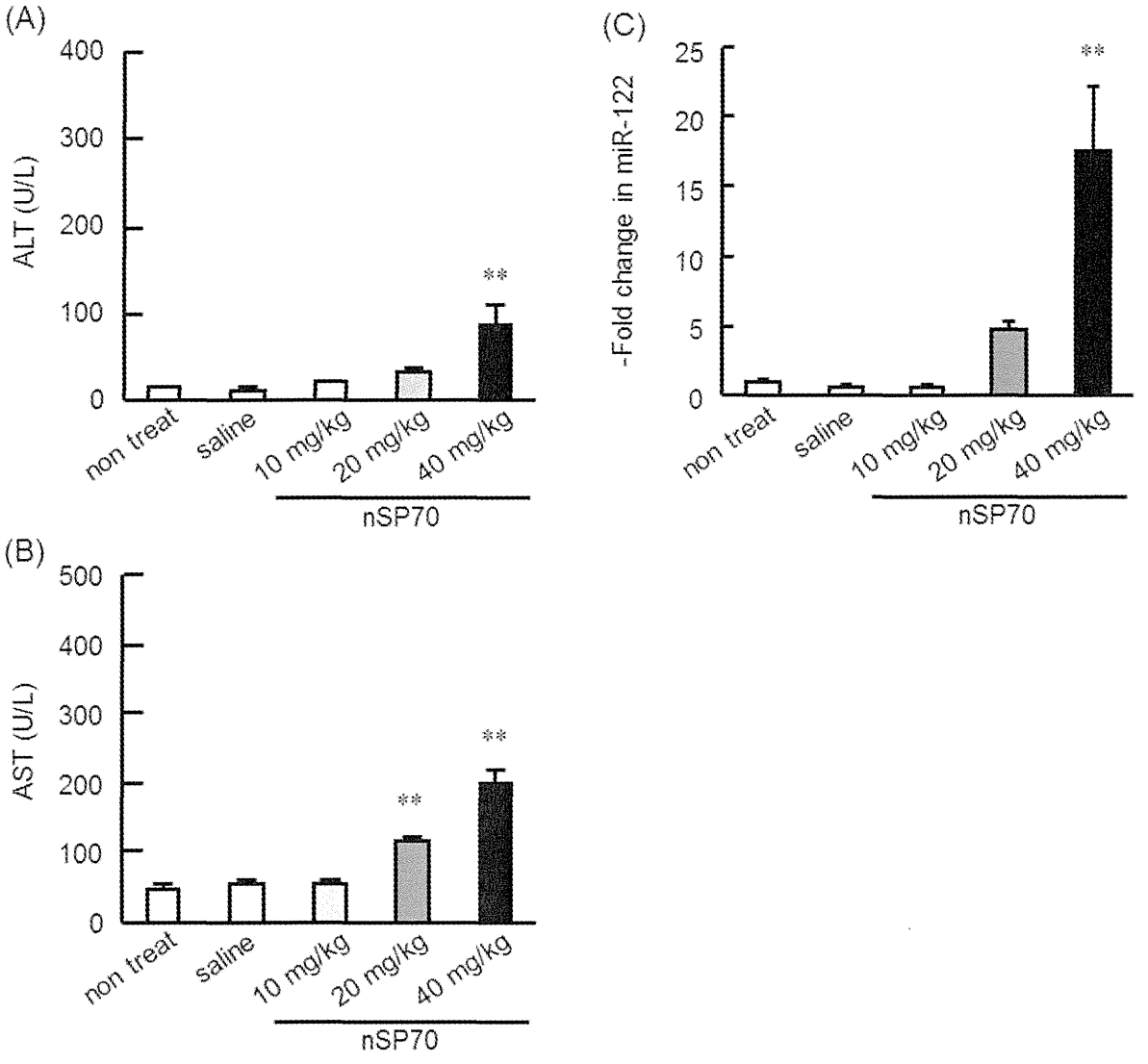

図 148. nSP70 の miR-122 の発現変動に対する投与量依存性の解析

BALB/c マウスに nSP70 を 10、20、40 mg/kg で尾静脈より投与し、投与後 8 時間における血液を回収した。従来の肝障害マーカーである（A）ALT、（B）AST は生化学検査により、（C）miR-122 はリアルタイム PCR により解析した。Bonferroni 法により有意差検定を行った。(**$P < 0.01$ *vs* non-treated group)

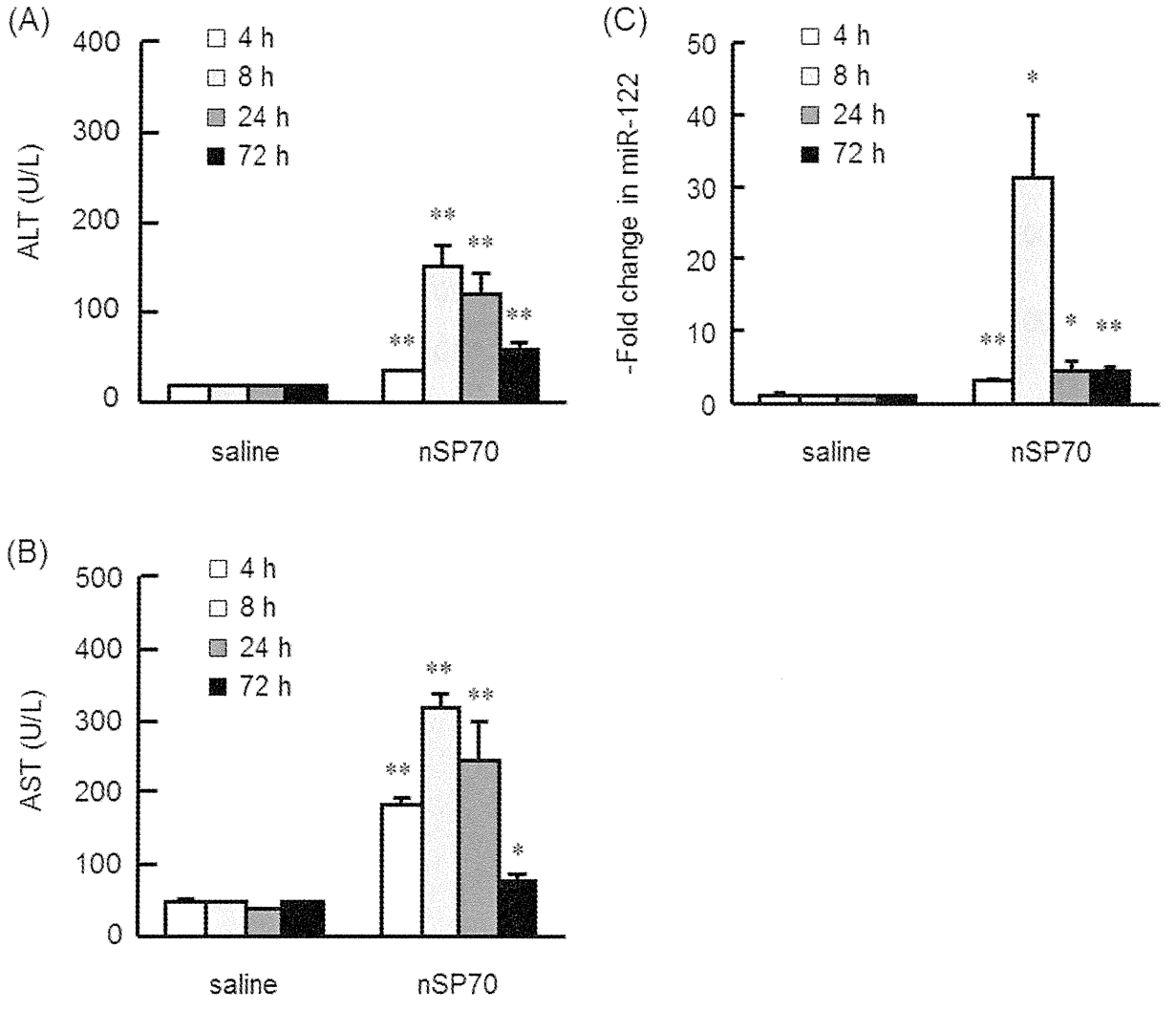

図 149. miR-122 の経時的な発現変動解析

BALB/c マウスに nSP70 を 40 mg/kg で尾静脈より投与し、投与後 4、8、24、72 時間における血液を回収した。従来の肝障害マーカーである(A) ALT、(B) AST は生化学検査により、(C) miR-122 はリアルタイム PCR により解析した。Bonferroni 法により有意差検定を行った。(**$P < 0.01$, *$P < 0.05$ *vs* saline-treated group)

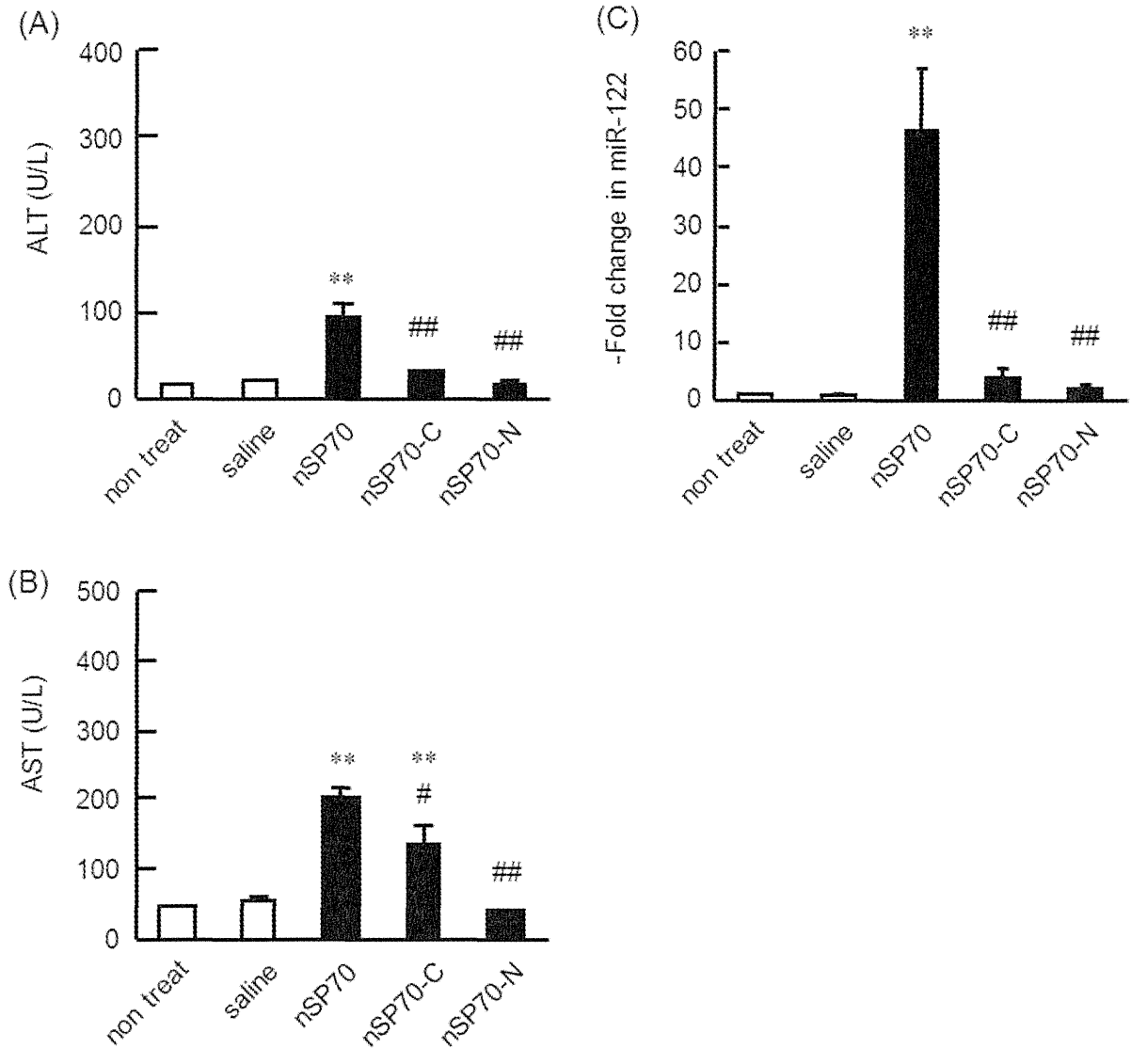

図 150. 表面修飾を施した nSP70 投与による miR-122 の発現変動解析

BALB/c マウスに nSP70、nSP70-C、nSP70-N を 40 mg/kg で尾静脈より投与し、投与後 8 時間における血液を回収した。従来の肝障害マーカーである（A）ALT、（B）AST は生化学検査により、（C）miR-122 はリアルタイム PCR により解析した。Bonferroni 法により有意差検定を行った。(**$P < 0.01$ *vs* non-treated group, $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ *vs* nSP70-treated group)

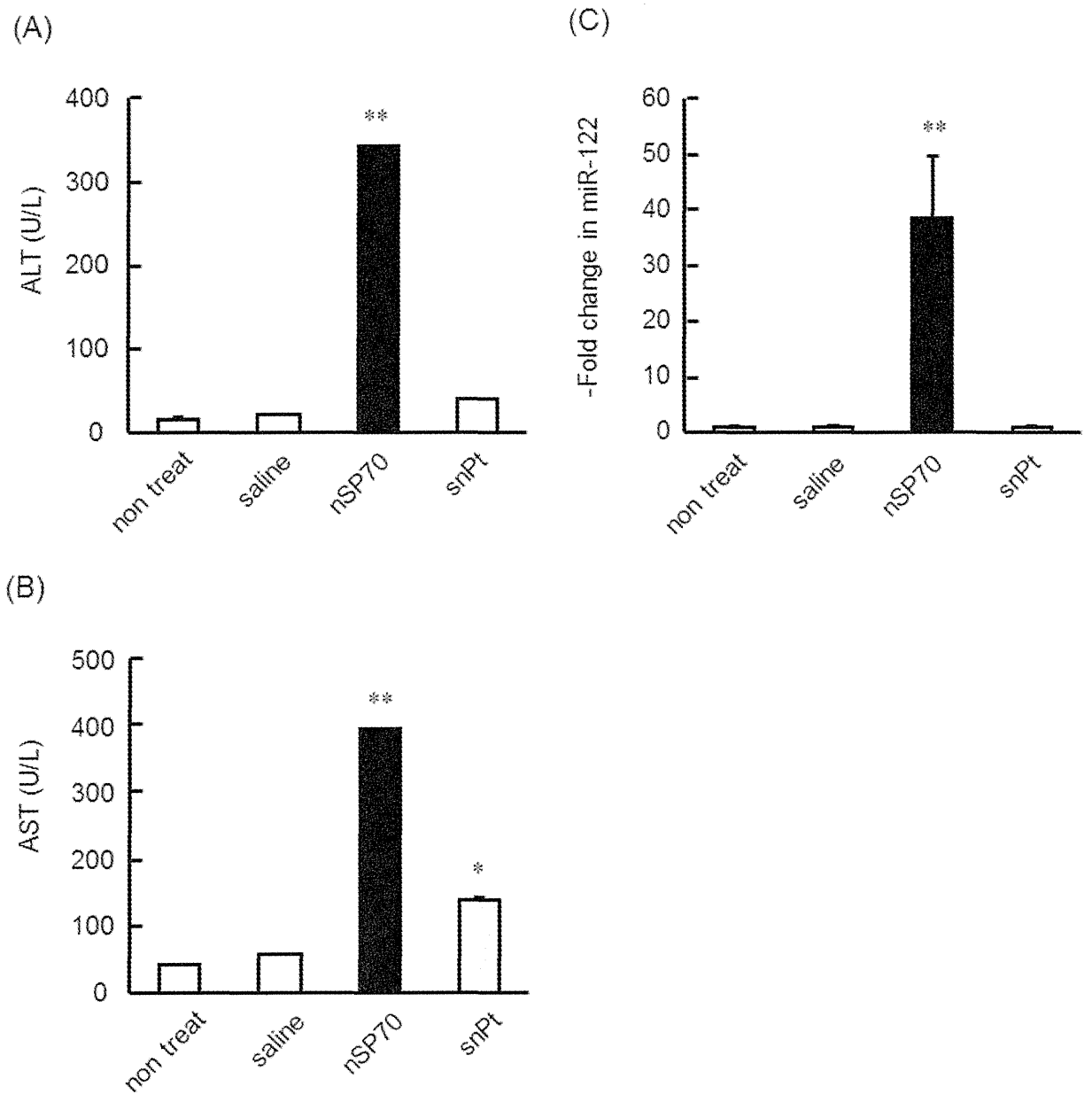

図 151. サブナノ白金投与による肝障害に対する血中 miR-122 の発現変動解析
BALB/c マウスに snPt を 20 mg/kg で尾静脈より投与し、投与後 8 時間における血液を回収した。従来の肝障害マーカーである（A）ALT、（B）AST は生化学検査により、（C）miR-122 はリアルタイム PCR により解析した。Bonferroni 法により有意差検定を行った。(**$P < 0.01$, *$P < 0.05$ *vs* non-treated group)

群	投与物質	溶媒	投与量 (mg/kg)	濃度 (w/v%)	投与容量* (mL/kg)	動物番号	
						雄	雌
対照群-1	ヒーン油		0	0	1	M01001～M01005	F01001～F01005
対照群-2	注射用水		0	0	1	M02001～M02005	F02001～F02005
3	CEO (Pistacia)	ヒーン油	1	0.09	1	M03001～M03005	F03001～F03005
4	PVP-CEO (Polymerized Pistacia vera oil)	注射用水	80	2.8	1	M04001～M04005	F04001～F04005
5	SW-CNT (Single-walled Carbon nanotube)	ヒーン油	1	0.05	1	M05001～M05005	F05001～F05005
6	MW-CNT (Multi-walled Carbon nanotube)	ヒーン油	1	0.05	1	M06001～M06005	F06001～F06005
7	PVP-K30 (Polymerized Povidone K30)	注射用水	80	2.8	1	M07001～M07005	F07001～F07005

*:最近時の体重測定に個体別の投与容量を算出した。

図152　群構成

図153　一般状態（雄）

Table 1. General conditions of male rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Group	Number of males and general conditions	Days of administration																												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Corn oil (control 1)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10 a)	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	10	5	5	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Distilled water (control 2)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	10	5	5	9	8	8	8	8	4	4	8	8	4
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2	2	2	1	1	2	2	1
C60	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	10	5	5	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PVP-C60	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	9	4	4	9	9	9	10	10	5	5	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	2	2	2	2	2
SWCNT	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	8	5	5	10	10	10	10	10	5	5	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	0	0	0	0	0	0	0	0	0	0
MWCNT	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	9	4	4	10	10	10	10	10	5	5	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0
PVP-K30	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	10	5	5	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a) Numerals represent the total number of animals showing clinical signs at pre- and post observations.

図154　一般状態（雌）

Table 2 . General conditions of female rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Group	Number of females and general conditions	Days of administration																												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Olive oil (control 1)	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	9	4	4	7	6	8	10	10	5	5	10	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	3	4	2	0	0	0	0	0	0	0	0
	General appearance, Hemorrhage from the wound	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Distilled water (control 2)	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	9	4	4	10	10	8	10	10	5	5	10	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	2	0	0	0	0	0	0	0	0
	General appearance, Hemorrhage from the wound	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C60	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	7	2	2	7	6	6	10	10	5	5	10	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3	3	3	4	4	0	0	0	0	0	0	0	0
	General appearance, Hemorrhage from the wound	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PVP-C60	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	8	3	3	8	6	6	9	10	5	5	10	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	2	2	4	1	0	0	0	0	0	0	0
	General appearance, Hemorrhage from the wound	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SW-CNT	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	9	4	4	9	5	8	8	5	4	4	10	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	1	2	2	1	1	0	0	0	0
	General appearance, Hemorrhage from the wound	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MW-CNT	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	8	3	3	9	9	10	9	9	4	4	10	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	1	1	0	1	1	1	1	0	0	0	0
	General appearance, Hemorrhage from the wound	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PVP-SA10	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	10	10	10	5	5	10	10	10	10	10	5	5	10	10	10	10	7	2	2	10	10	10	10	9	4	4	10	10	10	5
	Skin, crust formation by taping (except exposure area)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3	3	0	0	0	0	1	1	1	0	0	0	0
	General appearance, Hemorrhage from the wound	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0

a) Numerals represent the total number of animals showing clinical signs at pre- and post observations

図155　体重推移（雄）

Table 3　. Body weights of male rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Group	Corn oil (control 1)	Distilled water (control 2)	C60	PVP-C60	SW-CNT	MW-CNT	PVP-K30
Number of males	5	5	5	5	5	5	5
Days of administration							
1	198.4 ± 6.4	192.0 ± 4.4	196.5 ± 6.5	199.2 ± 3.9	197.7 ± 5.9	192.6 ± 6.0	194.3 ± 6.9
8	246.2 ± 12.4	241.8 ± 9.8	249.8 ± 9.7	248.9 ± 7.0	248.9 ± 14.2	245.0 ± 8.7	247.7 ± 14.4
15	287.7 ± 18.7	283.8 ± 10.0	302.2 ± 14.5	293.2 ± 20.4	294.3 ± 25.2	286.1 ± 12.0	295.2 ± 12.9
22	324.9 ± 22.1	317.9 ± 17.1	344.0 ± 19.4	330.8 ± 27.5	338.3 ± 27.9	326.4 ± 18.3	335.7 ± 18.9
28	352.7 ± 25.7	347.3 ± 23.6	378.6 ± 27.7	357.7 ± 34.1	366.9 ± 34.4	354.5 ± 21.9	363.5 ± 23.5

Each value shows mean (g) ± S.D.

図156　体重推移（雌）

Table 4　. Body weights of female rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Group	Corn oil (control 1)	Distilled water (control 2)	C60	PVP-C60	SW-CNT	MW-CNT	PVP-K30
Number of females	5	5	5	5	5	5	5
Days of administration							
1	151.3 ± 5.1	157.5 ± 7.9	159.6 ± 7.1	151.7 ± 9.1	152.2 ± 6.2	151.1 ± 5.7	153.3 ± 8.5
8	173.6 ± 13.1	176.4 ± 7.4	182.2 ± 7.6	168.5 ± 14.3	171.0 ± 9.8	177.5 ± 5.6	172.6 ± 15.1
15	191.3 ± 21.4	191.2 ± 7.7	198.7 ± 10.7	182.8 ± 14.6	188.5 ± 9.7	197.5 ± 9.5	195.7 ± 15.5
22	204.1 ± 22.1	208.8 ± 9.0	218.3 ± 16.9	196.0 ± 20.2	198.9 ± 13.7	215.5 ± 9.9	212.0 ± 17.9
28	219.8 ± 25.9	221.2 ± 11.2	232.9 ± 19.8	207.0 ± 22.2	213.1 ± 11.6	232.4 ± 9.0	226.8 ± 19.2

Each value shows mean (g) ± S.D.

図157　摂餌量（雄）

Table 5 . Food consumption of male rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Group	Corn oil (control 1)	Distilled water (control 2)	C60	FVP-C60	SW-CNT	MW-CNT	FVP-K30
Number of males	5	5	5	5	5	5	5
Days of administration							
2	24.8 ± 2.0	22.9 ± 1.5	23.1 ± 1.8	22.4 ± 1.0	24.3 ± 2.2	23.6 ± 1.0	23.5 ± 1.5
9	26.3 ± 2.9	24.6 ± 1.0	25.9 ± 1.6	26.9 ± 2.4	27.8 ± 1.2	25.4 ± 1.6	25.4 ± 2.1
16	30.0 ± 2.0	28.3 ± 2.3	28.5 ± 1.8	27.6 ± 3.0	30.1 ± 1.2	28.0 ± 0.9	27.4 ± 0.8
23	30.1 ± 3.6	28.2 ± 2.4	27.7 ± 2.6	28.6 ± 4.4	28.2 ± 2.3	28.1 ± 1.1	30.1 ± 3.5

Each value shows mean (g) ± S.D.

図158　摂餌量（雌）

Table 6 . Food consumption of female rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Group	Corn oil (control 1)	Distilled water (control 2)	C60	FVP-C60	SW-CNT	MW-CNT	FVP-K30
Number of females	5	5	5	5	5	5	5
Days of administration							
2	18.3 ± 3.2	19.6 ± 1.7	19.4 ± 1.2	16.7 ± 2.3	18.8 ± 1.4	19.1 ± 1.5	17.3 ± 1.7
9	19.4 ± 2.6	18.6 ± 1.7	19.8 ± 2.4	18.5 ± 1.4	19.1 ± 2.5	17.6 ± 2.3	18.6 ± 3.1
16	22.5 ± 1.6	20.7 ± 2.5	22.5 ± 2.6	19.6 ± 2.1	18.9 ± 2.6	21.8 ± 2.0	21.2 ± 2.7
23	23.5 ± 1.8	21.2 ± 2.4	23.1 ± 3.2	20.8 ± 3.6	21.6 ± 1.4	23.7 ± 0.9	22.9 ± 3.0

Each value shows mean (g) ± S.D.

図159　血液学検査（雄）

Table 7. Hematological findings of male rats in the repeated dose toxicity of nanomaterials by transcutaneous administration for 28 days

Group	Number of animals	RBC ($\times 10^4$/uL)	Hemoglobin (g/dL)	Hematocrit (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4$/uL)	PT (sec)	APTT (sec)
Corn oil (control 1)	5	781 ±34	14.8 ±0.2	44.3 ±0.8	56.8 ±2.4	19.0 ±0.6	33.4 ±0.6	102.7 ±10.9	18.9 ±3.6	22.2 ±1.6
Distilled water (control 2)	5	773 ±29	14.7 ±0.5	44.4 ±1.7	57.5 ±3.2	19.0 ±0.9	33.0 ±0.3	115.0 ±15.3	20.0 ±2.6	21.3 ±1.5
C60	5	790 ±28	14.9 ±0.3	45.2 ±0.9	57.3 ±2.4	18.8 ±0.6	32.8 ±0.5	105.4 ±6.6	19.4 ±3.9	21.9 ±2.2
PVP-C60	5	818 ±39	15.3 ±0.5	46.0 ±1.3	56.4 ±1.6	18.8 ±0.4	33.3 ±0.4	111.2 ±8.0	18.1 ±3.5	22.5 ±3.0
SW-CNT	5	762 ±50	14.9 ±0.7	45.0 ±2.4	59.1 ±1.5	19.6 ±0.5	33.1 ±0.4	115.3 ±14.7	18.5 ±4.1	22.7 ±1.2
MW-CNT	5	734 ±59	14.3 ±1.0	43.8 ±2.8	59.8 ±1.6	19.5 ±0.5	32.5 ±0.5	110.5 ±7.7	17.3 ±1.8	22.5 ±1.6
PVP-K30	5	771 ±28	14.9 ±0.5	45.4 ±0.7	58.9 ±1.5	19.3 ±0.3	32.8 ±0.6	103.3 ±9.4	18.8 ±3.9	23.4 ±2.3

Group	Number of animals	WBC (x100/uL)	Neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)	Reticulocyte (%)
Corn oil (control 1)	5	101.2 ±26.1	18.2 ±3.9	1.0 ±0.3	0.0 ±0.0	3.9 ±0.9	76.9 ±3.7	3.52 ±0.34
Distilled water (control 2)	5	98.7 ±40.6	18.6 ±6.5	1.0 ±0.4	0.0 ±0.1	4.0 ±0.8	76.3 ±7.0	3.71 ±0.32
C60	5	81.1 ±14.6	15.1 ±2.4	1.4 ±0.2	0.0 ±0.0	3.7 ±0.4	79.6 ±2.4	3.58 ±0.71
PVP-C60	5	85.1 ±17.1	17.9 ±4.9	1.5 ±0.4	0.1 ±0.1	4.3 ±1.1	76.2 ±4.5	3.60 ±0.27
SW-CNT	5	86.5 ±2.8	17.4 ±4.6	1.4 ±0.6	0.0 ±0.0	3.4 ±0.5	77.7 ±5.3	3.60 ±0.38
MW-CNT	5	92.4 ±32.3	15.1 ±8.6	1.3 ±0.3	0.0 ±0.1	2.8 ±0.7	80.7 ±8.6	4.17 ±1.03
PVP-K30	5	88.6 ±21.3	16.3 ±4.0	1.3 ±0.5	0.1 ±0.1	3.9 ±0.8	78.5 ±4.4	3.46 ±0.42

Each value shows mean±S.D.

図160　血液学検査（雌）

Table 8. Hematological findings of female rats in the repeated dose toxicity of nanomaterials by transcutaneous administration for 28 days

Group	Number of animals	RBC ($\times 10^4$/μL)	Hemoglobin (g/dL)	Hematocrit (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4$/μL)	PT (sec)	APTT (sec)
Corn oil (control 1)	5	763 ±48	14.7 ±0.7	43.5 ±1.6	57.1 ±2.0	19.3 ±0.6	33.9 ±0.6	102.0 ±9.1	12.7 ±0.9	16.6 ±1.5
Distilled water (control 2)	5	745 ±45	14.5 ±0.7	43.3 ±1.6	58.1 ±2.5	19.5 ±0.7	33.6 ±0.7	109.4 ±16.3	13.3 ±1.2	17.0 ±1.2
C60	5	757 ±32	14.5 ±0.2	42.8 ±0.8	56.6 ±2.4	19.1 ±0.6	33.8 ±0.5	106.9 ±11.5	13.3 ±0.9	16.7 ±1.3
PVP-C60	5	766 ±30	15.0 ±0.8	44.3 ±2.6	57.9 ±1.5	19.6 ±0.5	33.9 ±0.3	106.7 ±24.0	13.2 ±0.5	16.4 ±1.4
SW-CNT	5	798 ±25	15.4 ±0.5	46.1 * ±0.7	57.8 ±1.1	19.3 ±0.3	33.4 ±0.6	109.0 ±16.3	13.8 ±1.4	18.1 ±1.1
MW-CNT	5	779 ±71	15.0 ±1.1	44.4 ±3.0	57.2 ±2.1	19.3 ±0.5	33.7 ±0.4	124.0 ±20.9	12.9 ±0.7	18.5 ±1.4
PVP-K30	5	788 ±41	15.0 ±0.6	45.1 ±1.5	57.3 ±1.7	19.1 ±0.7	33.4 ±0.4	112.3 ±16.8	12.9 ±0.7	19.1 ± ±1.1

Group	Number of animals	WBC ($\times 100$ μL)	Neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)	Reticulocyte (%)
Corn oil (control 1)	5	53.0 ±17.7	10.4 ±2.3	2.0 ±0.4	0.0 ±0.0	2.9 ±1.1	84.7 ±2.7	3.04 ±0.31
Distilled water (control 2)	5	65.7 ±9.4	14.4 ±4.4	2.1 ±0.5	0.0 ±0.0	2.3 ±0.5	81.3 ±5.0	3.02 ±0.61
C60	5	58.1 ±20.9	13.5 ±5.5	2.1 ±1.0	0.0 ±0.0	3.0 ±0.6	81.4 ±5.9	2.71 ±0.64
PVP-C60	5	52.7 ±10.5	12.1 ±2.5	1.5 ±0.3	0.0 ±0.0	2.5 ±0.7	83.9 ±2.7	2.83 ±0.56
SW-CNT	5	63.1 ±14.0	10.1 ±4.2	2.0 ±0.8	0.0 ±0.0	2.6 ±0.4	85.3 ±4.5	3.00 ±0.77
MW-CNT	5	66.5 ±10.1	14.3 ±8.0	2.8 ±0.7	0.0 ±0.0	3.0 ±1.3	79.8 ±8.4	3.08 ±0.53
PVP-K30	5	71.1 ±23.0	14.4 ±4.4	2.0 ±1.4	0.0 ±0.0	3.4 ±0.9	80.2 ±5.3	2.71 ±0.45

Each value shows mean±S.D.

Significantly different from the control group (±P<0.03; control 2, *P<0.02; control 1)

図161　血液生化学検査（雄）

Table 9. Biochemical findings of male rats in the repeated dose toxicity of nanomaterials by transcutaneous administration for 28 days

Group	Number of animals	Total protein (g/dL)	Albumin (g/dL)	Total cholesterol (mg/dL)	Triglyceride (mg/dL)	Phospholipid (mg/dL)	Glucose (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)
Corn oil (control 1)	5	5.2 ±0.3	3.7 ±0.2	41 ±7	25 ±6	75 ±9	137 ±12	14 ±3	0.4 ±0.1	0.05 ±0.01	790 ±133
Distilled water (control 2)	5	5.3 ±0.1	3.6 ±0.1	40 ±6	32 ±18	70 ±6	126 ±4	14 ±2	0.4 ±0.0	0.04 ±0.01	612 ±51
C60	5	5.2 ±0.1	3.6 ±0.2	42 ±9	19 ±10	70 ±13	119 ±8	14 ±2	0.4 ±0.0	0.04 ±0.01	820 ±241
PVP-C60	5	5.3 ±0.2	3.7 ±0.1	38 ±9	23 ±14	68 ±10	126 ±7	15 ±2	0.4 ±0.0	0.05 ±0.01	728 ±118
SW-CNT	5	5.1 ±0.2	3.5 ±0.1	40 ±9	35 ±31	70 ±15	120 ±6	13 ±0	0.3 ±0.1	0.05 ±0.01	575 ±131
MW-CNT	5	5.3 ±0.2	3.6 ±0.1	39 ±9	22 ±12	66 ±9	124 ±9	13 ±3	0.4 ±0.1	0.04 ±0.00	526 * ±107
PVP-K30	5	5.4 ±0.2	3.7 ±0.1	41 ±8	24 ±6	73 ±10	126 ±19	15 ±1	0.4 ±0.0	0.05 ±0.01	687 ±84

Group	Number of animals	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Ca (mg/dL)	Inorganic phosphorus (mg/dL)	A/G	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Corn oil (control 1)	5	76 ±4	36 ±2	0 ±1	63 ±12	9.3 ±0.3	7.7 ±0.4	2.42 ±0.17	143.5 ±0.8	3.91 ±0.37	105.9 ±1.3
Distilled water (control 2)	5	75 ±10	34 ±5	0 ±1	81 ±48	9.6 ±0.2	7.6 ±0.7	2.12 ±0.26	145.0 ±1.2	3.94 ±0.13	106.6 ±1.3
C60	5	84 ±31	32 ±7	0 ±0	91 ±30	9.7 ±0.2	7.6 ±0.5	2.32 ±0.29	145.0 ±1.0	3.83 ±0.22	107.0 ±0.9
PVP-C60	5	97 ±49	42 ±17	0 ±0	126 ±80	9.7 ±0.2	7.7 ±0.3	2.26 ±0.09	144.0 ±1.0	3.92 ±0.08	106.8 ±0.7
SW-CNT	5	66 * ±5	28 * ±3	0 ±0	54 ±8	9.6 ±0.3	7.9 ±0.4	2.22 ±0.26	144.2 ±1.3	3.79 ±0.21	106.0 ±1.6
MW-CNT	5	65 * ±4	26 * ±5	0 ±1	60 ±36	9.6 ±0.2	7.9 ±0.5	2.15 ±0.12	144.4 ±0.7	3.77 ±0.16	106.5 ±1.1
PVP-K30	5	74 ±9	32 ±3	0 ±0	113 ±78	9.6 ±0.3	7.5 ±0.5	2.21 ±0.16	144.6 ±0.8	3.60 ±0.22	107.4 ±1.5

Each value shows mean±SD

Significantly different from the control group (*P<0.02; control 1)

図162　血液生化学検査（雌）

Table 10. Biochemical findings of female rats in the repeated dose toxicity of nanomaterials by transcutaneous administration for 28 days

Group	Number of animals	Total protein (g/dL)	Albumin (g/dL)	Total cholesterol (mg/dL)	Triglyceride (mg/dL)	Phospholipid (mg/dL)	Glucose (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)
Corn oil (control 1)	5	5.5 ±0.2	3.8 ±0.2	46 ±10	10 ±5	85 ±13	120 ±14	16 ±1	0.5 ±0.1	0.06 ±0.01	440 ±102
Distilled water (control 2)	5	5.4 ±0.2	3.7 ±0.3	46 ±11	10 ±4	86 ±17	113 ±12	16 ±1	0.4 ±0.0	0.05 ±0.01	373 ±87
C60	5	5.3 ±0.3	3.7 ±0.2	41 ±9	10 ±3	79 ±13	117 ±10	16 ±3	0.4 ±0.0	0.06 ±0.01	422 ±73
PVP-C60	5	5.3 ±0.5	3.8 ±0.4	46 ±11	9 ±4	84 ±20	116 ±11	16 ±1	0.4 ±0.0	0.06 ±0.01	328 ±80
SW-CNT	5	5.2 ±0.4	3.6 ±0.3	52 ±14	11 ±4	91 ±20	125 ±6	14 ±2	0.4 ±0.0	0.06 ±0.01	441 ±60
MW-CNT	5	5.5 ±0.1	3.8 ±0.1	44 ±8	10 ±1	79 ±10	118 ±11	18 ±7	0.5 ±0.1	0.05 ±0.01	461 ±46
PVP-K30	5	5.5 ±0.3	3.8 ±0.1	55 ±14	13 ±5	97 ±23	115 ±5	15 ±1	0.4 ±0.0	0.06 ±0.01	482 ±64

Group	Number of animals	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Ca (mg/dL)	Inorganic phosphorus (mg/dL)	A/G	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Corn oil (control 1)	5	74 ±8	26 ±2	1 ±0	80 ±23	9.3 ±0.4	6.6 ±0.7	2.29 ±0.12	143.9 ±1.2	3.65 ±0.20	107.1 ±2.2
Distilled water (control 2)	5	71 ±7	27 ±4	1 ±0	80 ±20	9.2 ±0.2	7.1 ±0.4	2.13 ±0.27	144.4 ±1.0	3.70 ±0.24	107.8 ±0.6
C60	5	76 ±11	24 ±3	1 ±0	69 ±33	9.2 ±0.3	6.8 ±0.3	2.31 ±0.16	143.0 ±0.6	3.71 ±0.13	107.8 ±1.6
PVP-C60	5	87 ±37	42 ±35	1 ±0	87 ±30	9.3 ±0.4	7.5 ±0.5	2.53 ± ±0.11	144.5 ±0.6	3.72 ±0.21	108.1 ±1.6
SW-CNT	5	74 ±4	26 ±2	1 ±0	85 ±39	9.4 ±0.2	7.5 ±0.6	2.37 ±0.38	143.3 ±1.1	3.62 ±0.14	107.6 ±1.5
MW-CNT	5	79 ±13	25 ±5	1 ±0	84 ±30	9.6 ±0.1	7.4 ±0.4	2.40 ±0.29	143.6 ±1.5	3.71 ±0.23	106.8 ±1.1
PVP-K30	5	81 ±8	33 ±15	1 ±0	59 ±11	9.6 ±0.3	7.5 ±0.8	2.28 ±0.23	143.5 ±0.8	3.65 ±0.29	107.0 ±0.3

Each value shows mean±SD

Significantly different from the control group (±P<0.03; control 2)

図163　尿検査（雄）

Table 11. Urine findings of male rats in the repeated dose toxicity of nanomaterials by transcutaneous administration for 28 days

Group	Number of animals	pH					protein				glucose		ketone body			Bilirubin	occult blood			urobilinogen	
		6.0	6.5	7.0	7.5	8.0	−	±	1+	2+	−	1+	−	±	1+	−	−	1+	2+	±	1+
Corn oil (control 1)	5	0	3	2	0	0	0	0	5	0	5	0	0	3	2	5	5	0	0	2	3
Distilled water (control 2)	5	0	0	5	0	0	0	0	5	0	5	0	0	5	0	5	4	1	0	3	2
C60	5	0	1	4	0	0	0	0	5	0	5	0	2	3	0	5	5	0	0	2	3
PVP-C60	5	0	2	2	0	1	0	0	4	1	5	0	3	0	2	5	5	0	0	3	2
SW-CNT	5	0	3	1	1	0	0	1	2	2	5	0	1	1	3	5	5	0	0	1	4
MW-CNT	5	0	2	3	0	0	0	0	5	0	5	0	1	2	2	5	4	1	0	3	2
PVP-K30	5	0	1	3	1	0	0	0	5	0	5	0	1	4	0	5	5	0	0	3	2

Each value shows mean±S.D.

図164　尿検査（雌）

Table 12. Urine findings of female rats in the repeated dose toxicity of nanomaterials by transcutaneous administration for 28 days

Group	Number of animals	pH					protein				glucose		ketone body			Bilirubin	occult blood			urobilinogen	
		6.0	6.5	7.0	7.5	8.0	−	±	1+	2+	−	1+	−	±	1+	−	−	1+	2+	±	1+
Corn oil (control 1)	5	0	3	2	0	0	0	4	1	0	5	0	4	1	0	5	5	0	0	5	0
Distilled water (control 2)	5	1	3	0	0	1	0	2	3	0	5	0	2	3	0	5	5	0	0	4	1
C60	5	0	5	0	0	0	0	2	3	0	5	0	2	3	0	5	5	0	0	2	3
PVP-C60	5	0	3	2	0	0	0	3	2	0	5	0	2	2	1	5	4	0	1	4	1
SW-CNT	5	1	4	0	0	0	0	2	3	0	5	0	3	2	0	5	5	0	0	3	2
MW-CNT	5	0	3	1	1	0	1	1	3	0	5	0	2	3	0	5	5	0	0	2	3
PVP-K30	5	1	1	1	2	0	2	1	2	0	5	0	3	1	1	5	5	0	0	3	2

Each value shows mean±S.D.

図165　器官重量（雄）

Table 13　. Organ weights of male rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Group		Control (vehicle)	Distilled water (control 2)	CB0	FVB-CB0	SWCNT	MWCNT	FVB-R20
Number of males		5	5	5	5	5	5	5
Body weight	(g)	318.4 ± 13.6	325.1 ± 21.9	317.6 ± 14.2	326.6 ± 33.5	333.2 ± 13.0	331.3 ± 21.5	331.7 ± 23.0
Brain	(mg)	1919.7 ± 91.8	1919.5 ± 32.2	1942.7 ± 42.0	1908.9 ± 99.4	1860.7 ± 63.5	1901.7 ± 86.7	1912.5 ± 61.6
	(mg/g)	6.055 ± 0.567	5.779 ± 0.395	5.777 ± 0.407	5.884 ± 0.601	5.625 ± 0.705	5.759 ± 0.465	5.779 ± 0.475
Thymus	(mg)	501.9 ± 65.6	568.6 ± 87.9	461.9 ± 130.0	474.1 ± 110.7	482.5 ± 53.9	594.1 ± 114.0	495.5 ± 110.3
	(mg/g)	1.585 ± 0.185	1.676 ± 0.047	1.419 ± 0.291	1.445 ± 0.276	1.397 ± 0.197	1.801 ± 0.390	1.509 ± 0.386
Liver	(mg)	10054.1 ± 946.2	10631.9 ± 1455.5	9606.9 ± 425.9	9710.8 ± 1702.5	10116.9 ± 1212.5	10616.1 ± 597.6	10057.0 ± 859.0
	(mg/g)	31.556 ± 1.418	31.510 ± 3.013	28.518 ± 1.047 *	29.624 ± 3.190	30.384 ± 1.488	32.116 ± 0.555	30.260 ± 1.668
Kidney (R)	(mg)	1291.0 ± 53.7	1349.0 ± 124.9	1226.1 ± 51.6	1240.7 ± 116.6	1215.3 ± 51.9	1295.7 ± 95.5	1209.5 ± 76.3
	(mg/g)	4.071 ± 0.313	4.048 ± 0.284	3.643 ± 0.223	3.806 ± 0.188	3.661 ± 0.265	3.918 ± 0.256	3.651 ± 0.118
Kidney (L)	(mg)	1271.5 ± 64.6	1316.4 ± 142.8	1208.4 ± 53.3	1240.5 ± 103.6	1256.5 ± 91.2	1206.1 ± 114.5	1239.9 ± 94.9
	(mg/g)	4.009 ± 0.312	3.953 ± 0.335	3.592 ± 0.270	3.807 ± 0.142	3.675 ± 0.169	3.642 ± 0.254	3.690 ± 0.171
Spleen	(mg)	599.6 ± 120.1	921.0 ± 296.0	515.3 ± 161.0	674.7 ± 152.9	791.8 ± 174.6	722.6 ± 64.9	787.9 ± 159.0
	(mg/g)	1.208 ± 0.404	2.746 ± 0.782	1.408 ± 0.535	2.045 ± 0.515	2.390 ± 0.550	2.191 ± 0.269	2.375 ± 0.491
Testis (R)	(mg)	1574.4 ± 109.5	1544.7 ± 73.8	1605.6 ± 70.4	1565.5 ± 135.0	1540.5 ± 160.2	1570.1 ± 74.5	1540.7 ± 123.0
	(mg/g)	4.959 ± 0.414	4.651 ± 0.329	4.774 ± 0.575	4.859 ± 0.669	4.645 ± 0.488	4.746 ± 0.278	4.676 ± 0.622
Testis (L)	(mg)	1577.0 ± 107.1	1545.7 ± 55.5	1596.6 ± 64.0	1572.3 ± 109.7	1560.6 ± 152.9	1605.0 ± 139.5	1547.0 ± 96.1
	(mg/g)	4.958 ± 0.450	4.647 ± 0.290	4.749 ± 0.350	4.861 ± 0.646	5.002 ± 0.580	4.856 ± 0.547	4.691 ± 0.547
Adrenal gland (R)	(mg)	25.0 ± 2.0	27.5 ± 4.5	31.4 ± 3.9 *	29.7 ± 1.4	32.2 ± 3.6 *	28.3 ± 3.2	28.2 ± 2.6
	(mg/g)	0.078 ± 0.005	0.082 ± 0.011	0.094 ± 0.012	0.093 ± 0.015	0.097 ± 0.012 *	0.085 ± 0.005	0.086 ± 0.005
Adrenal gland (L)	(mg)	26.5 ± 2.3	27.0 ± 4.7	32.9 ± 3.8 *	29.1 ± 2.9	34.2 ± 3.5 *	29.4 ± 3.7	27.3 ± 2.7
	(mg/g)	0.083 ± 0.007	0.081 ± 0.011	0.098 ± 0.011	0.090 ± 0.015	0.103 ± 0.009 *	0.089 ± 0.008	0.082 ± 0.004

Each value shows mean ± SD

Significantly different from the control group (* P<0.05, control 1)

図166　器官重量（雌）

Table 14 . Organ weights of female rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Group		Control (control 1)	Distilled water (control 2)	C60	FVP-C60	MW-CNT	MW-CNT	FVP-ALO
Number of female		5	5	5	5	5	5	5
Body weight	(g)	197.2 ± 24.6	199.5 ± 5.5	211.9 ± 18.5	189.3 ± 10.5	194.4 ± 9.5	208.2 ± 9.2	204.5 ± 21.4
Brain	(mg)	1728.7 ± 56.5	1752.8 ± 53.6	1745.3 ± 91.3	1769.7 ± 51.6	1752.5 ± 68.5	1758.7 ± 50.1	1771.4 ± 55.2
	(mg/g)	8.868 ± 1.052	8.779 ± 0.289	8.256 ± 0.501	9.418 ± 0.972	9.028 ± 0.599	8.456 ± 0.548	8.721 ± 0.599
Thymus	(mg)	408.6 ± 81.1	422.2 ± 48.0	445.3 ± 117.5	335.1 ± 65.0	416.7 ± 64.6	449.4 ± 64.2	407.6 ± 147.1
	(mg/g)	2.054 ± 0.175	2.121 ± 0.297	2.088 ± 0.422	1.784 ± 0.233	2.157 ± 0.247	2.159 ± 0.291	1.969 ± 0.637
Liver	(mg)	5921.8 ± 961.2	6066.2 ± 606.5	6346.2 ± 434.7	5564.6 ± 566.5	5094.9 ± 204.9	6209.9 ± 359.1	6215.8 ± 555.2
	(mg/g)	30.428 ± 1.192	30.332 ± 2.451	30.018 ± 1.465	29.529 ± 1.554	31.591 ± 1.195	29.816 ± 0.946	30.506 ± 1.654
Kidney(R)	(mg)	842.7 ± 115.8	861.5 ± 40.9	888.5 ± 94.1	770.6 ± 33.6 ±	816.3 ± 25.1	817.1 ± 70.1	848.8 ± 107.4
	(mg/g)	4.275 ± 0.339	4.312 ± 0.123	4.239 ± 0.773	4.084 ± 0.238	4.206 ± 0.304	3.927 ± 0.329	4.143 ± 0.388
Kidney(L)	(mg)	838.7 ± 122.3	844.5 ± 36.9	876.1 ± 65.0	745.9 ± 57.8 ±	819.6 ± 47.5	797.5 ± 59.9	844.9 ± 118.7
	(mg/g)	4.255 ± 0.353	4.230 ± 0.164	4.160 ± 0.563	3.945 ± 0.175 ±	4.218 ± 0.352	3.832 ± 0.240	4.121 ± 0.295
Spleen	(mg)	455.6 ± 78.1	508.7 ± 53.5	535.2 ± 98.0	429.2 ± 40.7	518.1 ± 79.5	500.4 ± 34.2	515.4 ± 106.1
	(mg/g)	2.300 ± 0.155	2.548 ± 0.278	2.529 ± 0.358	2.273 ± 0.224	2.662 ± 0.364	2.411 ± 0.239	2.498 ± 0.320
Ovary(R)	(mg)	49.4 ± 5.4	39.1 ± 6.9	55.7 ± 5.5	36.5 ± 5.0	45.2 ± 10.2	46.1 ± 5.1	46.5 ± 15.3
	(mg/g)	0.252 ± 0.052	0.196 ± 0.030	0.264 ± 0.055	0.194 ± 0.029	0.250 ± 0.054	0.222 ± 0.025	0.223 ± 0.045
Ovary(L)	(mg)	39.4 ± 2.9	38.6 ± 4.5	53.7 ± 7.5 *	40.5 ± 10.5	44.0 ± 9.5	49.6 ± 4.5 *	40.0 ± 10.1
	(mg/g)	0.201 ± 0.015	0.194 ± 0.023	0.255 ± 0.037	0.216 ± 0.054	0.226 ± 0.049	0.238 ± 0.023	0.194 ± 0.035
Adrenal gland (R)	(mg)	36.5 ± 7.5	33.1 ± 3.9	33.7 ± 2.4	27.4 ± 7.2	34.6 ± 4.7	35.3 ± 5.4	35.7 ± 5.4
	(mg/g)	0.185 ± 0.045	0.165 ± 0.015	0.160 ± 0.022	0.144 ± 0.031	0.178 ± 0.020	0.169 ± 0.025	0.175 ± 0.027
Adrenal gland (L)	(mg)	37.9 ± 4.2	33.2 ± 3.2	35.0 ± 2.2	29.7 ± 5.7	33.3 ± 4.6	33.5 ± 6.3	37.1 ± 8.2
	(mg/g)	0.193 ± 0.011	0.166 ± 0.017	0.167 ± 0.022	0.156 ± 0.022	0.171 ± 0.022	0.161 ± 0.030	0.182 ± 0.030

Each value shows mean ± S.D.

Signi ficantly different from the control group (± P<0.05; control 2, * P<0.02; control 1)

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Table 15. Macroscopic findings of male rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Findings	Group / Grade	Corn oil (control 1) -	Corn oil (control 1) P	Distilled water (control 2) -	Distilled water (control 2) P	C60 -	C60 P	PVP-C60 -	PVP-C60 P	SW-CNT -	SW-CNT P	MW-CNT -	MW-CNT P	PVP-K30 -	PVP-K30 P
Kidney															
Enlargement		5	0	4	1	5	0	5	0	5	0	5	0	5	0
Liver															
Whitish area		5	0	5	0	5	0	4	1	5	0	5	0	5	0
Lymph node, submandibular															
Enlargement		5	0	4	1	5	0	5	0	4	1	5	0	4	1
Skin															
Crust[a)]		5	0	4	1	5	0	5	0	5	0	5	0	5	0
Spleen															
Enlargement		5	0	4	1	5	0	5	0	5	0	5	0	5	0

Notes) - : No abnormal changes P : Non-graded change

a) By taping (except exposure area)

Numerals represent the number of animals.