第1表

LD_{50} of 2,3,7,8,-Tetrachlorodibenzo-p-dioxin(TCDD) after a single administration

Species/strain	Sex	Age	Route	Vehicle	LD50 (μg/kg)	Time to death(days)	Reference
Rat							
Sharman	M	NR	oral	corn oil/	22	9-27	Schwetz et
	F	NR	oral	aceton(9:1)	45	13-43	al 1973
F-334/CR	M	11-12(w)	oral	corn oil	164	25	Ealden et
F-344/F	M	11-12(w)	oral	corn oil	303	26	al 1985
F-334/H	M	11-12(w)	oral	corn oil	340	28	
CD/CR	M	10-11(w)	oral	corn oil	297	25	
Han/Wistar	M	NR	oral	corn oil	>3000	NR	Pohjanvirta et al 1986
Sprague-	M	Adult	ip	olive oil	60	NR	Beatty et
Dawley	F	Adult	ip	olive oil	25	NR	al 1978
	M	25 days	ip	olive oil	25	NR	
Guinea-pig							
Hartley	M	NR	oral	corn oil/	0.6	5-34	Schwetz et
	M	NR	oral	aceton(9:1)	2.1	9-42	al 1973
Hartley	M	3-4 (w)	oral	corn oil	2	17-20	McConnel et al 1978
Hartley	F	NR	oral	corn oil	2.5	32-42	Silkworth
Hartley	F	NR	oral	CMC	19	12-427	et al 1982
Mouse							
C57BL/6j	M		oral	corn oil	182	24	Chapman et
DBA/2	M		oral	corn oil	2570	21	al 1985
B6D2F1	M		oral	corn oil	296	25	
C57BL/6j	M		ip	corn oil	132	NP	Neal et al
DBA/2	M		ip	corn oil	620	NP	1982
B6D2F1	M		ip	corn oil	300	NP	
Rhesus monkey	F		oral	corn oil	< 70	14-34	McConnel et al 1978
Golden Syrian Hamster	M		oral	olive oil	1157	2-47	Olson et al 1980
	M		oral	corn oil/ aceton(9:1)	5051	9-43	Henck et al 1981
	M		ip	corn oil/	> 3000	1-5	Olson et al
	F		ip	aceton(9:1)	> 3000	14-32	1980

* NR : No Reported

第2表　TCDD の薬物動態

1. 血中に吸収された TCDD は速やかに肝、脂肪組織に移行する。

Metabolism and excretion of TCDD in several animal species

Species/Strain	Dose and Route	Ratio of % of dose excreted (feces/urine)	Half-life (Whole body) (days)	Reference
Rat				
Sprague-Dawley	50μg/kg, po	4.0	17.4	Pirkle et al 1989
	1μg/kg, po	9.9	31	Rose et al 1976
Han/Wistar	5μg/kg, ip	14.1	21.9	Pohjanvirta et al 1990
Long-Evans	5μg/kg, ip	12.0	28.8	Pohjanvirta et al 1990
Guinea pig				
Hartley	0.5μg/kg, ip	15.7	32.2	Gasiewicz et al 1979
Hartley	0.5μg/kg, ip	11.2	93.7	Olson et al 1986
Mouse				
C57BL/6J	0.5μg/kg, po	2.1	9.7	Birnbaum et al 1980
DBA/2J	0.5μg/kg, po	6.8	11.1	Birnbaum et al 1980

Total tritium excretion in the 7 days following administration of a single ip dose of H_3-TCDD to three groups of experimental animals (Van Miller 1976)

Route of excretion	^3H excretion (% of dose) in Adult monkeys	Infant monkeys	Rays
Urine	1.06±0.25	1.96±0.42	0.51±0.05
Faeces	3.75±0.91	1.26±0.34	4.96±0.30

TCDD concentrations in liver and adipose tissue following different doses, and calculated concentration ratios (liver/adipose tissue). Concentrations were measured 7 days after injection (Abraham et al 1988)

Dose (ng/kg)	n	TCDD Concen. liver (ng/g)	TCDD Concen. adipose tissue (ng/g)	Concen. ratio: liver/adipose tissue
1	6	0.0031±0.0009		
3	6	0.0102±0.0020	0.0139±0.0015	0.74±0.15
10	12	0.0406±0.0121	0.0494±0.0084	0.82±0.20
30	6	0.162 ±0.032	0.139 ±0.021	1.16±0.07
100	6	0.699 ±0.130	0.335 ±0.065	2.10±0.27
300	6	3.38 ±0.22	0.819 ±0.075	4.14±0.31
1000	6	10.7 ±2.2	2.02 ±0.17	5.27±0.96
3000	5	27.9 ±2.4	3.66 ±0.31	7.65±0.64

第３表　TCDD の薬物動態 (2)

2. TCDD は肝で代謝を受けて、より毒性の低い代謝物に変わる。

Effect on hepatic mixed-function oxidase activity and toxicity of 2,3,7,8 tetrachlorodibenzo-p-dioxin of castration of male rats or testosterone traetment of female rats (Beatty et al 1978)

Sex	Treatment	Aminopyrine demethylase	Aniline hydroxylase	LD_{50} (μg/kg, mean±SE)
Male	None	1.641±0.209	0.0143±0.0007	60.2±7.8
	Castration	1.207±0.043	0.0098±0.0007	39.1±2.1
Female	None	1.089±0.148	0.0084±0.0007	24.6±2.0
	Testosterone	1.298±0.185	0.0124±0.0015	44.5±1.5

Microsomal mixed-function oxidase activity and toxicity of TCDD to male weanling rats pretreated with phenobarbital, 3-methylcholanthrene or TCDD (Beatty et al 1978)

Treatment	Aniline hydroxylase	Benzopyrene hydroxylase	LD_{50} (μg/kg, mean±SE)
None	0.012±0.001	10.3±3.68	25.2±1.4
Phenobarbital	0.015±0.001	55.4±8.35	40.9±1.3
3-methycholanthrene	0.014±0.000	213±25.4	44.1±1.2
TCDD	0.028±0.001	226±0.001	36.8±1.8

Rate of ^{14}C-TCDD metabolite formation in isolated hepatocytes in suspension (Worblewshi et al 1985)

	pmol mg hepatocyte protein^{-1}hr^{-1}		
	Control	TCDD pretreated	Phenobarbital pretreated
Rat	0.70±0.10	2.26±0.43	0.98±0.13
Guinea pig	0.25±0.07	0.26±0.14	ND

第4表　TCDD の薬物動態 (3)-1

3. サルでは、ラットに比較すると TCDD の主な標的臓器である皮膚への移行率が高く、毒性の現れ難い肝への移行率は低い。

Tissue concentrations of tritium in three groups of experimental animals 7 days after administration of a single ip dose of TCDD (Van Miller 1976)

	^{3}H level (% of dose/g tissue)# in		
Tissue	Adult monkeys	Infant monkeys	Rats
Liver	0.09±0.06***	0.13±0.07***	4.54±0.45
Brain	0.006±0.004**	0.018±0.019**	0.13±0.04
Kidney	0.017± - **	0.051±0.037***	0.33±0.07
Lung	0.009±0.003*	0.030±0.014*	0.21±0.09
Spleen	0.008±0.004*	0.031±0.021**	0.83±0.36
Stomach	0.010±0.007*	0.059±0.043*	0.30±0.13
Small intestine	0.015±0.006*	0.059±0.025	0.17±0.08
Large intestine	0.015±0.003*	0.051±0.026	0.18±0.07
Thymus	−	0.15±0.06	0.44±0.15
Adrenal	0.096±0.058	0.19±0.05	−
Muscle	0.004±0.001	0.096±0.05	0.058±0.03
Skin	0.028±0.014**	0.24±0.07**	0.13±0.02
Adipose tissue	0.16±0.06***	0.49±0.12***	3.46±0.21

Values are means ±SD for groups of three adult monkeys, four infant monkeys and five rats. Those marked with asterisks differ significantly (Student's T test) from the corresponding value for the rats:* P<0.02; ** P<0.01; ***P<0.001

Tritium retention in tissue of three groups of experimental animals 7 days after administration of a single ip dose of TCDD (Van Miller 1976)

	^{3}H level (% of dose/total weight of tissue)# in		
Tissue	Adult monkeys	Infant monkeys	Rats
Liver	10.4±6.9***	4.51±1.60***	43.0±4.7
Brain	0.58±0.34	1.41±1.40	0.21±0.07
Spleen	0.028±0.013*	0.026±0.004**	0.48±0.17
Small intestine	0.87±0.39	1.47±0.64	0.93±0.44
Large intestine	1.29±0.12**	0.64±0.24	0.45±0.21
Muscle	8.62±2.39	35.6±14.4**	4.63±2.52
Skin	13.1±4.9*	22.7±8.8**	4.39±0.52
Adipose tissue	16.2±5.8	−	−

Values are means ±SD for groups of three adult monkeys, four infant monkeys and five rats. Those marked with asterisks differ significantly (Student's T test) from the corresponding value for the rats:* P<0.02; ** P<0.01; ***P<0.001

第4表　TCDD の薬物動態 (3)-2

4. TCDD に対する感受性の高いモルモットでは、感受性の低いラットに比較すると脂肪組織への移行率が高く、半減期も長い。

Liver, kidney and adipose tissue distribution of TCDD in rat and guinea pig

Species/Strain	Dose and Route	1 day			15 day		
		% Liver	Li/Ap	Ki/Ap	% Liver	Li/Ap	Ki/Ap
Rat							
Han/Wistar	5μg/kg, ip a)	10.75	2.02	0.12	10.75	2.02	0.12
Long-Evans	5μg/kg, ip a)	9.41	0.98	0.18	9.41	0.98	0.18
Guinea pig							
Hartley	2μg/kg, ip b)	11.4	0.34	0.09	11.4	0.34	0.09

Species/Strain	Dose and Route	32 day			45 day		
		% Liver	Li/Ap	Ki/Ap	% Liver	Li/Ap	Ki/Ap
Rat							
Han/Wistar	5μg/kg, ip a)	10.56	1.42	0.12			
Long-Evans	5μg/kg, ip a)	12.59	1.53	0.08			
Guinea pig							
Hartley	0.5μg/kg, ip c)				7.01	0.23	0.08

a) Pohjanvirta et al 1990　b) Gasiewicz et al 1979　c) Olson et al 1986

第5表

Species difference in toxic responses following exposure to TCDD

(R. Pohjanvirta & J. Tuomisto 1994)

	Rat	Mouse	Guinea Pig	Monkey	Rabbit
LD_{50} (μg/kg)	22-340	114-284	0.6-2.5	< 70	115-275
Time to death (day)	9-43	15-38	12-42	14-34	6-39
Body weight loss (Wasting syndrome)	+	+	+	+	+
Serum glucose	↓	↓	→	↓	
Serum triglyceride	↑	→	↑	↑	↑
Serum cholesterol	↑	↓	↑	↓	
Hypoplasia/atrophy/necrosis					
Thymus and lymphatic organs	+	+	+	+	
Bone marrow	+	+	+	+	
Testis	-	+	+	-	
Adrenal cortical necrosis	-	-	+	-	
Liver hepatic cell necrosis	+	+#	-	-	+
Hyperplasia/metaplasia					
Urinary tract	-	-	+	+	
Skin (chloracne)	-	+	-	+	+
Other responses					
Pophyria	+	+	-	-	
Edema	-	+	-	-	
Hormonal imbalance	+	NP	NP	NP	NP
Hemorrhage	-	-	+	-	

* NP : data not provided

chronic toxicity

第6表－(1)

Two-year chronic toxicity and oncogenicity study of TCDD in Sprague-Dawley rats (Kochiba 1978)

Pathological lesions	Dose (μg/kg/day)							
	0		0.1		0.01		0.001	
	M	F	M	F	M	F	M	F
Hepatotoxicity								
hepatocellular deg/necrosis	-	-	+	+	-	-	-	-
foci of cellural alteration	-	-	+	+	-	+	-	-
swelling of hepatic cells	-	-	+	+	-	+	-	-
inflammation	-	-	+	+	-	-	-	-
Neoplastic lesions								
hepatocelllar hyperplastic nodules	6	8	2	23	3	18	0	3
hepatocellular carcinoma	2	1	1	11	0	2	0	0
bile duct adenoma	0	0	1	2	0	0	0	1
squamous cell carcinoma of hard plate/nasal turbinates	0	0	4	4	0	1	0	0
squamous cell carcinoma of lung	0	0	1	7	0	0	0	0

18-month carcinogenicity testing of TCDD in male Swiss mice (Toth 1979)

Pathological lesions	Dose (μg/kg/day)							
	0		7.0		0.7		0.007	
Skin lesions	0/38		25/43		13/44		5/44	
with amyloidosis	0/38		17/43		10/44		5/44	
Neoplastic lesions								
liver	7/38	(18)	13/43	(30)	21/44	(48)	13/44	(29)
lung	15/38		11/43		18/44		27/44	
lymphoma	6/38		12/43		12/44		10/44	
other organs	7/38		4/43		4/44		6/44	

第6表－(2)

実験動物を用いた慢性毒性実験におけるTCDDの無毒性量、最小毒性量（宮田 1997）

動物（系統）	性	対象病変	無毒性量または最小毒性量	報告者または研究期間
ラット (SD)	雄	肝機能障害、病理所見	1 ng/kg/day*	Kociba ら (1978,79)
	雌	肝機能障害、病理所見	1 ng/kg/day*	
マウス (Swiss)	雄	アミロイドーシス、皮膚症状	1 ng/kg/day**	Toth ら (1979)
マウス (B6C3F1)	雄	肝機能障害、病理所見	1.4 ng/kg/day*	NTP (1982)
	雌	肝機能障害、病理所見	6 ng/kg/day*	
サル (Macca mullata)	雌	血液学的障害 皮膚症状	2～3 ng/kg/day**	Allen ら (1977,78,79)

*: 無毒性量、**: 最小毒性量

各国におけるダイオキシン類の耐容1日摂取量（TDI）または実質安全量（VSD）（宮田 1997）

国名あるいは規制機関名	TDI または VSD(pgTEQ/kg/day)
日本	10
カナダ	10
WHO 欧州地域事務局	10
オランダ	10（現在1を提案中）
スウェーデン	5*
ドイツ	10（目標値1）
イギリス	10
イタリア	1
米国環境保護庁	0.01**
米国カリフォルニア州	0.007**
米国食品医薬品庁	0.06*

*:実際の規制値である 35 pgTEQ/kg/week を1日当たりに換算した値

**:ダイオキシン類を発癌物質として、閾値なしの立場で設定した値

第7表

人に対する TCDD の毒性 (ATSDR 1997)

Duration of exposure	System	Effect	Body burdens ng/kg body weight	Reference
< 1 year	Dermal	Chloracne (children)	2357	Mocarelli et al 1991
Not specified	Dermal	Chloracne	80.5 18	Schecter et al 1993
11 year	Dermal	Chloracne	646	Jansing et al 1994
6.5 year	Immunplogic	Immuno-suppression	156-176	Tonn et al 1996
> 15 year	Reproductive	High LH and low testosterone	31	Egeland et al 1994
> 1 year	Cancer	Increased cancer mortality risk	124-459	Fingerhut et al 1991
> 20 year	Cancer	Increased cancer mortality risk	69-461	Manz et al 1991

Health effects of TCDD in human infans (ATSDR 1997)

1) Late-type hemorrhage disease of newborn
2) Decreased vitamin K1 and decarboxylated prothrombin levels in infants
3) Higer plasma levels of TSH in infants
4) Reduced neonatal neurologic optimality
5) Increase in total T cells and lower monocyte and granulocyte counts
6) Alteration of plasma ALT and AST activities
7) Increased thyroxine levels
8) Alteration of the human sex ratio in their offspring ?