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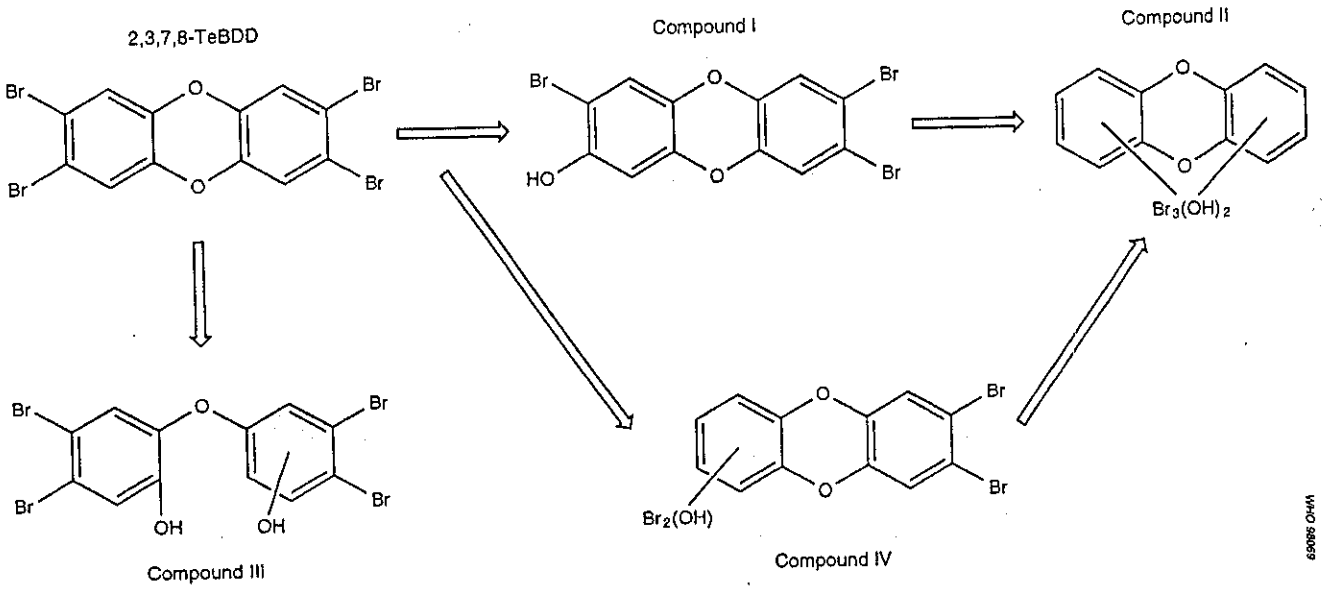

Fig. 1 Proposed biotransformation routes of 2,3,7,8-TeBDD in rat.
(From: De Jongh et al., 1993)

Table 1. Absorption of 2,3,7,8-TeBDD in rats

Strain (sex)	Route (vehicle)	Dosing regimen	Absorption,[a] time	Method	References
Wistar (female, male) (n = 4)	oral (arachis oil with 5% toluene)	single dose 100 µg/kg body weight (= 0.2 µmol/kg body weight)	80% (male), 48 h 83% (female), 48 h	faeces analysis [TBDD]	Ivens et al. (1992)
Fischer 344 (male) (n = 3–4)	oral (water : ethanol : Emulphor® = 3 : 1 : 1)	single dose		faeces and tissue analysis [^{3}H-TBDD]	Diliberto et al. (1990a,b, 1993); Kedderis et al. (1992a)
		0.5 µg/kg body weight (= 0.001 µmol/kg body weight)	78%, 72 h		
		5 µg/kg body weight (= 0.01 µmol/kg body weight)	82%, 72 h		
		50 µg/kg body weight (= 0.1 µmol/kg body weight)	60%, 72 h		
		250 µg/kg body weight (= 0.5 µmol/kg body weight)	47%, 72 h		
Fischer 344 (male) (n = 3–4)	intratracheal (water : ethanol : Emulphor® = 3 : 1 : 1)	single dose 0.5 µg/kg body weight (= 0.001 µmol/kg body weight)	80%, 72 h	faeces and tissue analysis [^{3}H-TBDD]	Diliberto et al. (1991, 1993); Kedderis et al. (1992a)
Fischer 344 (male) (n = 3–4)	dermal (acetone)	single dose 0.5 µg/kg body weight (= 0.001 µmol/kg body weight) (= 0.2 nmol/1.8 cm^2)	12%, 72 h	faeces and tissue analysis [^{3}H-TBDD]	Jackson et al. (1991); Kedderis et al. (1992a); Diliberto et al. (1993)

[a] Values based on concentration of 2,3,7,8-TeBDD [TBDD] or on ^{3}H activity ([^{3}H-TBDD]).

Table 2. Distribution of TBDD-derived radioactivity in Fischer 344 rats 3 days after oral, dermal, or intratracheal administration of 1 nmol [^{3}H]TBDD/kg body weight[a,b]

Tissue	% administered dose[c,d]			% absorbed dose/g tissue[d,e]		
	Oral	Dermal	Intratracheal	Oral	Dermal	Intratracheal
Liver	20.3	2.4	19.5	2.4	2.4	0.3
Adipose tissue	19.6	3.8	24.7	0.8	1.6	1.2
Skin	10.9	1.8	8.3	0.3	0.5	0.3
Muscle	3.5	0.8	3.0	0.04	0.07	0.04
Blood	0.4	0.06	0.2	0.03	0.03	0.01
Thymus	0.03[f]	0.03	0.08	0.2	1.1	0.4
Adrenals	0.4[f]	0.01	0.02	0.5	1.2	0.4
Kidneys	–	0.05	0.1	–	0.2	0.1
Spleen	–	0.01	0.02	–	0.2	0.06
Lungs	–	0.06	0.1	–	0.5	0.2
Heart	–	0.02	0.03	–	0.2	0.06
Testes	–	0.02	0.05	–	0.06	0.03
Brain	–	0.01	0.02	–	0.05	0.02
Stomach	–	0.03	0.1	–	0.3	0.2
Small intestines	–	0.04	0.2	–	0.2	0.1
Large intestines	–	0.04	0.2	–	0.3	0.1

[a] Adapted from Diliberto et al. (1993); oral absorption = 79%; dermal absorption = 12%; intratracheal absorption = 78%.
[b] Mean values; n = 3–4; standard deviation and statistical details omitted.
[c] Percentage of the administered dose normalized to 100% recovery.
[d] – = not analysed.
[e] Percentage adjusted to 100% absorption.
[f] n = 1.

Table 3. Partition of [^{3}H]TBDD-derived radioactivity between liver and adipose tissue of rats[a,b]

Route of exposure	Dose[c] (nmol/kg body weight)	Observation period (days)	TBDD concentration (pmol/g)		Liver : fat concentration ratio
			Liver	Fat	
Intravenous	1	3	8.1	2.4	3.4
	1	56	0.2	1.1	0.2
	100	56	117.2	45.3	2.6
Oral	1	3	4.9	1.7	2.9
	10	3	79.9	13.6	5.9
	100	3	518.3	93.4	5.6
	500	3	2216.3	340.1	6.5
Intratracheal	1	3	4.1	2.1	2.0
Dermal	1	3	0.6	0.4	1.5

[a] Adapted from Kedderis et al. (1992a); Diliberto et al. (1993).
[b] Male Fischer 344 rats; n = 3–4; single doses; vehicle: ethanol : Emulphor® : water = 1 : 1 : 3 (oral, intravenous, intratracheal exposure), acetone (dermal exposure).
[c] 1 nmol/kg body weight corresponds to 0.5 µg/kg body weight.

Table 4. Comparison of tissue concentration and of liver : adipose tissue concentration ratio after a single subcutaneous injection of 2,3,7,8-TeBDD or 2,3,7,8-TeCDD in rats[a,b]

Dose (ng/kg body weight)	Liver tissue			Adipose tissue			Liver : adipose tissue concentration ratio	
	TCDD (ng/g)	TBDD (ng/g)	TCDD : TBDD concentration ratio	TCDD (ng/g)	TBDD (ng/g)	TCDD : TBDD concentration ratio	TCDD	TBDD
30	0.16	0.08	2.1	0.14	0.6	0.2	1.2	0.2
300	3.38	3.60	0.9	0.82	2.7	0.3	4.1	1.4
3000	27.9	20.5	1.4	3.7	12.5	0.3	7.7	1.9
Increase: 30–3000	174 x	256 x		26 x	21 x			

[a] Adapted from Nagao et al. (1995/96).
[b] Female Wistar rats; n = 3 or 6; single subcutaneous doses; vehicle: toluene/DMSO (dimethyl sulfoxide); observation: day 7 after treatment.

Table 5. Elimination of 2,3,7,8-TeBDD in rats after single radiolabelled and unlabelled doses[a]

Strain (sex)	Route (vehicle)	Dose		Observation period (days)	Test	Elimination[b] (% of administered dose)		Reference
		nmol/kg body weight	µg/kg body weight			Faeces	Urine	
Fischer 344 (male) (n = 3–4)	intravenous (water : ethanol : Emulphor® = 3 : 1 : 1)	1	0.5	1	R	8–10	n.sp.	Kedderis et al. (1991a)
		1	0.5	56		50	4.5	
		100	50	56		70	7.6	
Fischer 344 (male) (n = 3–4)	oral (water : ethanol : Emulphor® =3 : 1 : 1)	1	0.5	3	R	42 ± 2	0.3	Diliberto et al. (1993)
		10	5	3		39 ± 1	0.3	
		100	50	3		58 ± 5	0.2	
		500	250	3		72 ± 5	0.2	
Fischer 344 (male) (n = 3–4)	intratracheal (water : ethanol : Emulphor® = 3 : 1 : 1)	1	0.5	3	R	41 ± 2	1	Diliberto et al. (1993)
Fischer 344 (male) (n = 3–4)	dermal (acetone)	1	0.5	3	R	2	0.2	Diliberto et al. (1993)
Wistar (female, male) (n = 5)	oral (arachis oil with 5% toluene)	200	100	2	U	20 (male) 17 (female)	n.sp.	Ivens et al. (1992)
				3–7		1	n.sp.	

[a] R = administration of [1,6-^{3}H]-2,3,7,8-TeBDD (purity = >98%); elimination refers to eliminated radioactivity. U = administration of unlabelled 2,3,7,8-TeBDD (purity = 98%); elimination refers to recovery of TBDD.
[b] n.sp. = not specified.

Table 6. Percent administered dose of parent [^{3}H]TBDD recovered in faeces of rats[a,b]

Route	Dose (nmol/kg body weight)	% administered dose excreted in faeces characterized as parent [^{3}H]TBDD[c]			
		Day 1 after dosing	Day 2 after dosing	Day 3 after dosing	Cumulative (days 1–3)
Oral	1	11.7 ± 3.6	7.9 ± 2.1	2.5 ± 1.6	22.2 ± 2.1
	10	6.9 ± 4.9	12.5 ± 3.8	2.0 ± 1.2	21.4 ± 1.8
	100	16.1 ± 9.6	16.7 ± 9.0	2.6 ± 1.6	35.4 ± 1.8[d]
	500	26.4 ± 11.2	18.3 ± 9.7	3.6 ± 3.4	48.3 ± 3.0[d]
Intratracheal	1	12.4 ± 1.7	4.6 ± 0.7	0.6 ± 0.02	17.6[d]
Intravenous[e]	1	1.6 ± 0.3	0.7 ± 0.3	0.5 ± 0.3	2.8[d]

[a] Adapted from Diliberto et al. (1993).
[b] Fischer 344 rats.
[c] Mean ± SD; n = 3 or 4; faecal extraction with hexane followed by HPLC characterization of the extract.
[d] Statistically different from 1 nmol/kg oral dose group ($p < 0.05$).
[e] Kedderis et al. (1991a).

Table 7. Contents of parent [^{3}H]TBDD in faeces of rats[a]

Route	Dose (nmol/kg body weight)	% total radioactivity in faeces characterized as parent [^{3}H]TBDD (cumulative percentages days 1–3)	Reference
Oral	1	53[b]	Diliberto et al. (1993)
	10	55	
	100	60	
	500	67	
Intratracheal	1	43	
Intravenous	1 and 100	10–20	Kedderis et al. (1991a)

[a] Group size: n = 3–4.
[b] Percentage represents the amount of parent TBDD that was excreted via faeces (days 1–3) as a result of unabsorbed TBDD and/or gastrointestinal transluminal excretion of TBDD.

Table 8. Body burden of [^{3}H]TBDD-derived radioactivity in rats[a] 3 days after administration of a single dose

Route (vehicle)	Dose (nmol/kg body weight)	% body burden		Reference
		Administered dose	Absorbed dose	
Oral (water : ethanol : Emulphor® = 3 : 1 : 1)	1	58	73	Diliberto et al. (1993)
	10	61	75	
	100	41	67	
	500	28	59	
Intratracheal (water : ethanol : Emulphor® = 3 : 1 : 1)	1	59 ± 2	76 ± 2	Diliberto et al. (1993)
Dermal (acetone)	1	10 ± 1	82 ± 18	Diliberto et al. (1993)
Intravenous (water : ethanol : Emulphor® = 3 : 1 : 1)	1	82 ± 2	–	Diliberto et al. (1993); Kedderis et al. (1991a)

[a] Fischer 344 rats, n = 3–4.

Table 9 Biological half-lives of several PBDD/PBDF congeners in rats after single doses

Strain (sex)	Congener[a] (solvent)	Route (observation period)	Dose	Elimination from	Calculated half-life (days) (kinetic phase)	Reference
Dibenzo-*p*-dioxins						
Fischer 344 (female) (n = 3–4)	[^{3}H]TBDD (water : ethanol : Emulphor® = 3 : 1 : 1)	intravenous (56 days)	1 nmol/kg body weight	whole body	0.7 (1st phase) 2.9 (2nd phase) 17.8 (3rd phase)	Kedderis et al. (1991a)
			100 nmol/kg body weight	whole body	0.6 (1st phase) 17.8 (2nd phase)	
			1 nmol/kg body weight	liver	4.5 (1st phase) 16.5 (2nd phase)	
				adipose tissue	57.8	
				skin	2.5 (1st phase) 57.8 (2nd phase)	
				muscle	1.6 (1st phase) 26.7 (2nd phase)	
				blood	18.2	
Wistar (female) (n = 3–10)	TBDD (toluene/DMSO = 1+2; v/v)	subcutaneous (78 days)	60 ng/kg body weight (1.2 nmol/kg body weight)	liver	13.3 (12.0–14.9)[b]	Nagao et al. (1995/96)
				adipose tissue	39.4 (26–82)[b]	
Wistar (female) (n = n.sp.)	1,2,3,7,8-PeBDD (toluene/DMSO = 1+2; v/v)	subcutaneous (35–95 days)	2.2 nmol/kg body weight[c]	liver	21 (17–27)[b]	Golor et al. (1993)
				adipose tissue	55 (39–97)[b]	
Wistar (female) (n = 3)	2,3,7-TrBDD (<5% toluene in peanut oil/0.9% NaCl, 1+9, v/v)	intravenous 14 days	50 µg/kg body weight[c] (119 nmol/kg body weight)	liver	2 (3rd phase) (47 h)	Golor et al. (1995)
				adipose tissue	2–3 (3rd phase) (43 h)	
				thymus	3–4 (3rd phase) (91 h)	
	2,3-Cl_2,7-Br_1DD (<5% toluene in peanut oil/0.9% NaCl, 1+9, v/v)	intravenous 14 days	50 µg/kg body weight[c] (151 nmol/kg body weight)	liver	3–4 (3rd phase) (72 h)	
				adipose tissue	1.5 (3rd phase) (36 h)	
				thymus	3–4 (3rd phase) (92 h)	
Dibenzofurans						
Wistar (female) (n = n.sp.)	TBDF (toluene/DMSO = 1+2; v/v)	subcutaneous (35–95 days)	1.7 nmol/kg body weight[c]	liver	20 (17–25)[b]	Golor et al. (1993)
				adipose tissue	30 (26–36)[b]	
Wistar (female) (n = n.sp.)	2,3,4,7,8-PeBDF (toluene/DMSO = 1+2; v/v)	subcutaneous (35–95 days)	1.1 nmol/kg body weight[c]	liver	99 (59–302)[b]	Golor et al. (1993)
				adipose tissue	80 (49–220)[b]	
Fischer 344 (male) (n = 3–4)	[^{3}H]1,2,7,8-TeBDF (water : ethanol : Emulphor® = 3 : 1 : 1)	intravenous (24 h)	1 nmol/kg body weight	body	1	Kedderis et al. (1994)

[a] n.sp. = not specified.
[b] 95% confidence interval in days.
[c] Given in a mixture together with other brominated and chlorinated PHDD/PHDF congeners.

Table-10　PBDDs/PBDFs の経口投与に関連する死亡率

PBDDs/PBDFs	動物種	性（数）	用量 (μg/kg)	試験法	観察期間	死亡率	死亡時間
2,3,7,8-TeBDD	ﾗｯﾄ	♀♂（5）	10,33	単回	28 日	死亡ナシ	—
			100	単回	28 日	♀:3/5	11-19
			300	単回	28 日	♀:5/5	
						♂:3/5	16-22
2,3,7,8-TeBDD	ﾗｯﾄ	♀♂ (10)	0.01	反復(90 日)	90 日	♀:1/10	
			0.1	反復(90 日)	90 日	♀:1/10	
			1	反復(90 日)	90 日	♀:1/10	
						♂:2/10	
			3	反復(90 日)	90 日	♀♂:5/10	
			10	反復(90 日)	90 日	♀♂:10/10	
2,3,7,8-TeBDF	ﾗｯﾄ	♀♂ (5)	1,10,50	反復 (5 日/週, 4 週)	4 週	死亡ナシ	
			150	反復 (5 日/週, 4 週)	4 週	♀:4/5 ♂:3/5	
			500	反復 (5 日/週, 4 週)	4 週	♀♂:5/5	
2,3,7,8-TeBDF	ﾓﾙﾓｯﾄ	♂ (6)	0.47	単回	30 日	死亡ナシ	
			1.58	単回	30 日	死亡ナシ	
			4.74	単回	30 日	1/6	
			15.84	単回	30 日	6/6	

Table-11. PBDD の Ah レセプターへの結合強度およびミクロゾーム酵素活性誘導の相対強度

	レセプター結合強度	AHH 活性誘導(in vitro)	AHH 活性誘導(in vivo)	EROD 活性誘導(in vitro)	EROD 活性誘導(in vivo)
Rat hepatoma cell cytosol					
2,3,7,8-Cl_4-DD	100	100	100	100	100
2,3,7,8-Br_4-DD	66(43)	14	1570	35	<100<
2,3,7-Br_3-8-Cl-DD					>100
2,3-Br_2-7,8-Cl_2-DD	68	180	2430	140	<100
2,8-Br_2-3,7-Cl_2-DD	200	>10		14	
2-Br-3,7,8-Cl_3-DD	10	<10	480	10	50
non-2,3,7,8- Br_4-DD		>1	<<1	<<1	
2,4,6,8-Br_4-DD	1				
1,3,7,8-Br_4-DD	50				
1,2,3,7,8-Br_5-DD	15	10	50	>10	
1,2,4,7,8-Br_5-DD	5	2	6	1	
2,3,7-Br_3-DD	80			2	
Br_2-DD	7			<<1	
BrDD	<1			0	

＊括弧内は mouse liver cytosol での値、それ以外は rat liver(in vivo), rat hepatoma cell での値

Table-12 A comparative survey of several biological parameters for 2,3,7,8-TeBDD and 2,3,7,8-TeCDD (tested in parallel-running experiments)

Parameter	Details	TBDD	TCDDa	Reference
Receptor binding (EC50)	incubation of cytosolic receptor protein	1.5 x 10^{-9} mol/litre	1.0 x 10^{-9}mol/litre	Mason et al. (1987b)
Microsomal enzyme induction				
Binding affinity of CYP1A2	rat liver	9.0 nmol	6.5 nmol	Kedderis et al. (1993)
AHH induction (pED50)*	rat liver	9.12	8.41	Mason et al. (1987b)
EROD induction (pED50)	rat liver	9.45	8.16	Mason et al. (1987b)
EROD induction (molar basis)	rat liver -after 7 days - after 98 days	6740 pmol resorufin/mg protein per min 410 pmol resorufin/mg protein per min	5210 pmol resorufin/mg protein per min 162 pmol resorufin/mg protein per min	Schulz-Schalge et al. (1991a,b)**
EROD induction (relative potency, molar basis)	rat liver	identical dose-effect	enzyme concentration and curves	Nagao et al. (1995/96)
EROD induction(ED50)	chick embryo liver	9.4 pmol/egg	11.1 pmol/egg	Ramalingam et al. (1986)
EROD induction(relative potency, molar basis)	mouse liver (subchronic exposure)	0.2	1	Birnbaum et al. (1993); Birnbaum & DeVito (1995)
ACOH*** induction(relative potency, molar basis)	mouse liver (subchronic exposure)	0.2	1	Birnbaum & DeVito(1995)
EROD induction(relative potency, molar basis)	mouse lung (subchronic exposure)	0.1	1	Birnbaum & DeVito(1995)
EROD induction(relative potency, molar basis)	mouse skin (subchronic exposure)	0.04	1	Birnbaum et al. (1993); Birnbaum & DeVito (1995)
EROD induction(relative potency)	mouse liver (subchronic exposure)	0.31	1	Van Birgelen et al. (1996)
ACOH induction(relative potency)	mouse liver(subchronic exposure)	0.11	1	Van Birgelen et al. (1996)
Hepatic porphyrin accumulation(relative potency)	mouse liver(subchronic exposure)	0.4	1	Van Birgelen et al. (1996)
Body weight loss(pED50)	rat	7.17	7.28	Mason et al. (1987b)

*: pED50 = -log ED50 (molar basis).

**: Data in agreement with results of Abraham et al. (1988) and Nagao et al. (1990b).

*** : ACOH = acetanilide-4-hydroxylase.

厚生科学研究費補助金分担研究報告書

（ダイオキシン類の健康影響に関する総合的評価研究）

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ダイオキシン類の一般毒性・発がん性に関する評価に関する研究

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研究要旨

実験動物に対する 2,3,7,8-TCDD の発がん性については、Kociba ら(1978)が、ラットの実験により肝細胞がんの発生を観察、報告しているが、その他に、マウス・ラットを用いた長期試験で甲状腺濾胞腺腫、口蓋・鼻甲介・舌および肺の扁平上皮がん、リンパ腫の誘発が認められている。発がんメカニズムについては、遺伝子障害性を検出するための複数の実験系で陰性の結果が得られ、マウス・ラットを用いる二段階発がんの試験系でプロモーション作用が証明されている。

肝毒性としては、肝細胞肥大や脂質代謝異常が適切な指標になる。

免疫毒性としては、胸腺萎縮や細胞性および体液性免疫異常を引き起こし,ウイルス感染に対する宿主抵抗性や抗体産生能の抑制が認められる。また、母ラットへ投与すると、仔動物における遅延型過敏反応の抑制や抗体産生能の抑制がみられる。これらの影響は、体内負荷量 86ng/kg 以上で明瞭に発現すると考えられる。

その他に、肝臓の薬物代謝酵素誘導や T リンパ球の分化への影響が上記より低い体内負荷量低用量（23ng/kg 以下）で認められる。これらの変化は各 adverse effects を引き起こす因子に属するものであると捉えることはできるが、生体の恒常性の観点からこれらの体内負荷量によって adverse effects を引き起こすとは考えにくい。

A．研究目的

ダイオキシン類は、特定の使用目的をもって生産される化学物質ではなく、各種有機化学物質の生産工程や廃棄物の処理過程等で生成する非意図的な化学物質で、動物を用いた試験で強い毒性を有することが明らかにされている。しかし、人への健康影響等科学的に未解明な部分が多く残されており、国際的にも種々の調査研究が行われている。

国際がん研究機関（ＩＡＲＣ）においては、ダイオキシンの発がん性について、最も毒性が強い 2,3,7,8-ﾃﾄﾗｸﾛﾛｼﾞﾍﾞﾝｿﾞ-ﾊﾟﾗ-ｼﾞｵｷｼﾝに関して、平成９年２月に、グループ１（人に発がん性あり）と判断されたところである。さらに、平成９年には、ＷＨＯ欧州事務局においてダイオキシン類の毒性評価に用いられる毒性等価係数（ＴＥＦ）の見直し、平成１０年には、ＷＨＯ欧州事務局においてダイオキシンの耐容一日摂取量（ＴＤＩ）が再評価された。我が国においても、各省庁が連携してダイオキシン類に対する総合的な調査研究を実施するとともに、厚生省と環境庁が合同で、我が国のダイオキシンのＴＤＩの見直しに関する検討を行ったところである。本研究では、ダイオキシン類のダイオキシン類の一般毒性・発がん性に関する情報を収集し、評価する事を目的としている。

B．研究方法

本年度は、ダイオキシン類のダイオキシン類の一般毒性・免疫毒性、発がん性に関する最新

の情報を収集し、整理すると共に最も体内負荷量が低いと考えられる実験動物への影響を示す知見に関して有害影響の観点から評価を行った。

C．研究結果と考察

(1) 発がん性影響

マウス・ラットへの経口投与で肝細胞がん、甲状腺濾胞腺腫、口蓋・鼻甲介・舌および肺の扁平上皮がん、リンパ種と多部位にがんの誘発が観察される。経皮投与ではマウスで外皮系線維肉腫、腹腔及び皮下投与でハムスターに皮膚の扁平上皮がんも観察されている。経口投与では、これらの器官での発がん又は前がん病変が、10～360 ng/kg/day の投与量で発現している。これらの実験における最低の毒性発現量は、Kociba らの報告による 10 ng/kg/day（2 年間）であり、この場合の体内負荷量は 294 ng/kg と算出される。また、これより高い投与量（360ng/kg/day 以上）において、HCDD の 2 種類の異性体混合物がラットおよびマウスに、また、2,7-DCDD がマウスに肝がんを誘発したという報告がある。

発がん性のメカニズムに関して、TCDD は、遺伝子毒性を検出する復帰突然変異試験（Ames 試験）やその他多くの試験で、変異原性陰性の結果が得られている。一部の陽性の結果も、非遺伝子毒性的メカニズムによる間接的な作用の結果であると考えられ、TCDD は DNA と直接相互作用せず、イニシエーション作用はないものと思われる(WHO/IARC, 1997)。TCDD の発がんプロモーション作用については、マウスやラットを用いた二段階発がんモデル実験で実証されている。また、2,3,7,8-TCDF、2,3,4,7,8- PeCDF や 1,2,3,4,7,8-HCDF においても、ラットで肝腫瘍のプロモーション作用のあることが報告されている。以上のことから、ダイオキシン類による発がん性は、遺伝子傷害性というよりは、腫瘍のプロモーション作用に起因するものであると考えられる。

一方、Kociba らのラットを用いた TCDD の発がん性試験では下垂体、子宮、乳腺、膵臓及び副腎の腫瘍発生率が減少した。また、卵巣摘出したラットで diethylnitrosamine をイニシエーターとして使用し、TCDD を投与した実験では、肝臓の前がん病変の発生程度が著しく低くなることが認められているが、肺がんに関する二段階発がん実験では、腫瘍の発生は卵巣の存在でむしろ抑制されていることが示唆されている。これらの知見は、TCDD の内分泌かく乱作用による影響が、発がんの促進又は抑制に深く関わっていることを示唆している。

(2) 非発がん性影響

TCDD の致死投与量は、動物種・系統により著しく異なる。たとえば、経口投与における半数致死量（LD50 値）では，動物種差が雄のモルモットの 0.6 μg/kg から雄のハムスターの 5051 μg/kg まで約 8000 倍の大きな開きがある。また同じラットでも 2 系統 (Long-Evans、Han/Wistar) 間で LD50 値は約 300 倍の差が認められている。致死量の TCDD 投与により，ほとんどの動物で急激な体重減少（消耗症候群）が生じ、暴露数週間後に死亡する。LD50 値は、マウスでは Ah レセプターの発現量に依存した結果が出ているが、ラットでは依存性は認められておらず、単に Ah レセプターの発現量だけで決定付けられてはいないようである。単回または反復投与による毒発現感受性の高い器官は、肝臓、胸腺とリンパ組織及び生殖器官であると考えられる。また、ヒトにおいて認められる塩素ざ瘡は、実験動物では、ウサギ、サル、ヌードマウスにおいてのみ観察されている。

肝毒性は主にラットでよく研究されており、血清 ALT，AST の上昇や、ポルフィリン症、高脂血症等の生化学的変化に加え、組織病理学的には肝細胞の肥大や、脂肪の蓄積などが観察される。

免疫毒性としては、胸腺萎縮が TCDD 暴露により認められる顕著な兆候の一つであり、さらに、細胞性および体液性免疫異常を引き起こす。最も低用量では、ウイルス感染に対する宿

主抵抗性や抗体産生能の抑制が認められる(Burleson ら, 1996、Narasimhan ら, 1994)。また、成熟動物への投与に比べ、胎児や新生児は TCDD の免疫毒性に対する感受性が高いと考えられる。母ラットへ投与すると、仔動物における遅延型過敏反応の抑制 (Gehrs ら, 1997 、Gehrs, B.C.& Smialowics, R.J. 1999) や抗体産生能の抑制(Badesha ら, 1995)がみられる。その中でも最も低濃度で認められる影響としては、妊娠 14 日目のラットに 0.1 μg/kg を単回投与したときの児動物にウシ血清アルブミン (BSA) に対する遅延型過敏反応 (DTH) の抑制が観察されている。この場合の母動物における体内負荷量 (body burden) は 86 ng/kg と算出される (文献評価シート (1) ～ (4))。

また、TCDD はほとんどすべてのホルモンに影響を与える内分泌かく乱化学物質であると考えられている。TCDD による様々な酵素誘導の結果、ホルモン合成量の変化やホルモンの代謝亢進、ホルモンレセプター発現量のダウンレギュレーションを引き起こすことにより、特にステロイドホルモン系に様々な影響を与える。そのメカニズムの解析のひとつとして、抗エストロゲン作用においては、TCDD･Ah レセプター複合体がエストロゲンレセプターを介した遺伝子発現を直接阻害しているという報告がある。一方、ダイオキシン類は UDP-グルクロニルトランスフェラーゼ (UDP-GT) 活性の誘導などにより、血漿中の T4 レベルを減少させると考えられている。この T4 レベルの減少は、ラットでは、約 30～50 ng/kg/day の投与量から観察されていると共に、妊娠 10～16 日目の母動物へ 0.1 μg/kg/day の TCDD を投与したときの児動物においても、UDP-GT の増加と共に観察された。この報告は、アカゲザルで認められた児動物における脳の発生分化過程への影響と考えられる神経学的障害 (学習障害) と関連しているという可能性が示唆される。以上のような多岐にわたるホルモン系への影響が、発生異常や発がん性などの毒性発現に複雑に関わりあっているものと思われる。

その他に、TCDD の生体への影響として、CYP1A1、CYP1A2 等の薬物代謝酵素の誘導、T リンパ球のサブセット比率の変化が、1～20 ng/kg という体内負荷量で認められており、この負荷量は、上記の adverse effects が認められる量よりも低いものであった。2,3,7,8-TCDD による酵素誘導は発がんのプローモーションや内分泌かく乱作用の原因となるかもしれないが、実際にはこれらのような低い体内負荷量でプロモーション作用や内分泌系への影響は認められておらず、有害作用とは考えにくい。T リンパ球の分化への影響に関しては、高用量では T リンパ球サブセットの構成比に逆の影響が認められ、低用量への外挿に用いるのは不適当であると共に、その変化が宿主の免疫状態にどのような有害作用をもたらすかは不明である。

D．参照文献

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