「The 19th International Symposium on Halogenated Environmenal Organic Pollutants and POPs-DIOXIN '99 」要旨

Uncertainty analysis of dioxin toxicity - its implication to human risk assessment

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Aim: Complex toxicity profile and wide margin of variation in toxicity among inter- and intra-species are one of the conspicuous features of dioxins toxicity. Available evidences suggest that aryl hydrocarbon (Ah) receptor mediated effects to homeostasis and cellular regulation are involved in divergent toxicities. Most intriguing concern is how toxic dioxins are to humans, and what is the level of variations of toxicity among humans, and if a potential exposure level will pose any significant risk to humans. We examined the source of uncertainties in estimating human risk from dioxins, and propose to present it in an explicit way in risk assessment.

Analysis: Fat content in the body was suggested as a major determinant in distribution and elimination of dioxins. Humans have relatively high fat-content compared to experimental animals and show extremely longer half-life for dioxin elimination of 5.8 years (Poiger & Schlatter, 1986), compared to that of 10-30 days in rodents. Human half-life of elimination is predicted to increase almost linearly from about 4 months in newborn to 5-6 years at the age when the ratio of body fat reaches plateau (Kreuzer et al., 1997). Humans have similar Ah receptor as other animal species, however its binding affinity to TCDD is somewhat lower (dissociation-constant range: 3-15 nM), and show saturation and CYP1A1-induction at one-order higher concentration than rodents with sigmoidal response curves (Okey et al., 1994). Expression of Ah receptor and induction of CYP1A1-dependent enzyme varied widely among individuals (Clark et al., 1992), which may reflect polymorphism in CYP1A1 gene (Kawajiri et al, 1990). Ethnic variation in CYP1A1 polymorphism is also known (Puga et al., 1997). These factors will contribute to variation in toxicity and risk estimation based on dioxin body-burden in humans. The variation in human sensitivity to the chloracnegnic effects ranges two-order of magnitude in body burden (Beck et al., 1979). Body burdens of dioxins appear to be log-normally distributed in humans (Sielken et al., 1977), and there are subgroups, such as fish-eaters who are likely to have much greater body-burdens. Recently, disturbance of signal transduction via tyrosine phosphorylation by TCDD was suggested as another mechanism than gene-transcription level (Enan & Matsumura, 1995).

Proposal: From current knowledge of wide range of variations in toxicity with huge unsolved uncertainty in significance of low-dose exposure of fetus and infant, we propose to select different critical endpoints with different critical-effect doses which may be relevant to each subpopulation. Presentation of pertinent guidance values showing the range of uncertainty in protecting different human subpopulations, such as fetus, infant, pregnant woman and adult, will be desirable.

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References:

Beck et al. (1979) Chemosphere, 18, 507-516; Clark et al (1992) Environmental Health Perspectives, 98, 125-132; Enan & Matsumura (1995) Biochemical Pharmacology, 49, 249-261 Kawajiri et al (1990) FEBS Letters, 263, 131-133; Kreuzer et al. (1997) Archives of Toxicology, 71, 383-400; Okey et al (1994) Toxicology Letters, 70, 1-22; Poiger & Schlatter (1986) Chemosphere, 15, 1489-1494; Sielken et al. (1977) Chemosphere, 16, 2135-2140

「 日本内分泌撹乱化学物質学会第２回研究発表会 」要旨

BENCHMARK DOSE ESTIMATION FOR REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF DIOXINS

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Introduction Dioxins show complex toxicity profile to various organisms and in some cases, with wide interspecies-difference in toxic potencies. These attributes together with insufficient knowledge on mechanism of toxicity give uncertainties and variations to risk assessment on dioxins. Benchmark dose (BMD) approach is introduced to make better use of available data in reflecting the nature of dose-response relationship and estimate the dose quantitatively for any proportion of the potentially affected organisms, as compared to the current methods of determining NOAEL (No-Observed-Adverse-Effect Level) or LOAEL (Lowest-Observed-Adverse-Effect Level) which is an arbitrarily chosen single dose in a toxicological study.

Methods WHO/IPCS (1998) and MHW/EA (1999), Japan have established Tolerable Daily Intake (TDI) for dioxins as 1 - 4 and 4 pg/kg bw/day, respectively, through observations that reproductive and developmental effects in several studies as critical to choose LOAEL to derive TDI by applying a safety (uncertainty) factor of 10 to this LOAEL. BMD was estimated in this study applying US-EPA BMDS beta version 1.1b to original data of the above studies and other human data on the reproductive effect (Sekizawa et al 1999). BMD estimates derived as such were compared with current human blood levels of dioxins.

Results and Discussion BMDs for 1% and 10% responses of permanent vaginal thread in female offspring of rats in Gray et al (1997) which was considered to be one of the critical effects, were estimated as 49 and 131 ng TCDD/kg bw in administered dose (corresponding to blood levels of 116 and 309 pg TCDD*/g, fat basis) of the rats, respectively. Benchmark level for 10% response was estimated for the case of unbalanced gender-ratio found in Seveso residents (Mocarelli et al 1996) to be 60-121 pg TCDD/g blood (fat basis), although there is wide margin of uncertainty due to few numbers of population under study and lack of detailed information. These estimates can be compared to the dioxin levels in blood of various populations (eg. 16-40 pg TEQ**/g fat basis for ordinary citizens) to examine risk. Although BMD approach improves the assessment as described above, lack of information on background mechanism and others for the events found in animals and humans preclude us from assessing risk more appropriately.

* TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin ** TEQ: Toxic Equivalent

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References Gray et al (1997) Toxicol.Appl.Phamacol,146,237; MHW/EA (1999) Memorandum on Tolerable Daily Intake of Dioxin and related compounds (Japan) 1999; Mocarelli et al (1996) Lancet, 348, 409; Sekizawa et al (1999) 19th Int Symp. Halogen. Environ. Org. Poll. POPs, Vol.44, 497; WHO/IPCS (1998) Report of the WHO/IPCS Consultation on Assessment of the Health Risk of Dioxins

表1　ベンチマーク法を用いた母親の血中ダイオキシンレベルによる子供の性比の変化の可能性の推定

イタリア・セベソでダイオキシンに高濃度曝露された両親から生まれた子供の性

母親の血中ダイオキシン濃度 (pg/g脂肪)	子供の性 *1
14 *2	男 *2
16 *2	女 *2
18 *2	男 *2
20 *2	女 *2
22 *2	男 *2
24 *2	女 *2
26.6	男
27.7	男
36.5	男
126	女, 女#1
238	女
245	女
257	女
434	女
463	女
485	女, 女
960	女
1650	女, 女

*1　事故後10ヶ月(妊娠期間)から7.5年(ダイオキシンの半減期に相当)後までの間に生まれた子供のみ

ー>*2　統計処理の必要からダミーとして背景曝露のデータを導入

ベンチマーク法による影響の現れる血中濃度の統計的推定

仮定	発生割合 %	血中濃度 (pg/g 脂肪) 最頻確率濃度	95%信頼限界
A	5	58.5	7.4
	10	59.6	9.9
B#1	5	118	6.0
	10	121	9.5

#1: 観察された最低濃度における子供の性が女でなく、実際には男であったと仮定した場合(このレベルが影響が起こらない濃度ならば真実かも知れない)

説明

ベンチマーク法では、観察された生物現象にふさわしい統計モデル(この場合はログロジスティックモデル)を適用して、観察された事象が対象集団にある確率(たとえばここでは5%と10%)で起こる時の影響因子(ダイオキシン)の血中濃度がどの程度なら起こるといえるかを推定する。

つまり従来行われているように無毒性量(NOAEL)という実験データのうちの1点のみを使うのでなくデータ全体と分布のあり方を基に推定すると同時に、事象が起こる割合を指定してその時の濃度をも推定する。

ー> 同じ時期に同地区で生まれた子供全体では女48人、男26人の割合だった(カイ二乗検定; $p<0.001$)。さらにその後、9年間のフォローアップによると子供の性比は女64人、男60人に戻ったとされている。
なお同地区では敬虔なカトリック信者がほとんどのために中絶はほとんど行われていなかった。

表２　ドイツ、米国、ベトナム、日本人の組織中ダイオキシン濃度

数値は 脂肪あたりの毒性等量（TEQ pg/g）で表示。 括弧内に組織の脂肪含量を％で、Nは対象の人数を表す。
化合物＃：PCDD=ダイオキシン、PCDF=ジベンゾフラン、 *1 数値はPCDD/PCDFのように左に示した化合物（の組み合わせに対応して表示

国と地域など：文献番号	化合物＃	血液 *1	子宮 *1	胎児 *1	脂肪組織 *1
一般人の体内レベル					
ドイツ：1	PCDD+PCDF	16.0 (男性, N=113) 範囲: 9.1-26.9*2 16.8 (女性, N=29) 範囲: 10.3-26.7*2			
米国女性：2	PCDD/PCDF	30/11 (N=100)	7.2/2.9 (0.85%, N=14)	4.0/1.3 (0.65%, N=10)	
ベトナム(ハノイ)：3	PCDD/PCDF	6/6 (N=32)			
大阪能勢・住民：5	PCDD	25.3			
事故などによる曝露の体内レベル					
台湾(油症患者)：4	PCDD/PCDF		5.8-72.7/604-8940 (0.5-2.17%)		
ベトナム(ダナン)：3	PCDD/PCDF	46/31 (N=50)			
大阪能勢・焼却場作業員：5	PCDD	39.7 (男性, N=94) 範囲: 13.3 - 831			
日本(油症患者)：6	2,3,4,7,8-PCDF				20,000 - 30,000 *3

文献　1: Papke (1998)　2: Schecter et al. (1994, 1996)　3: Schecter et al. (1994)　4: Schecter (1996)
5: Watanabe et al. (1999)　6: Masuda (1999)
*2　5th%値-95th%値　*3 推定値

表３　ラットに１，１０，５０％　発現確率で Vaginal thread を残させる用量の推定値

Benchmark Dose and Blood Level Estimation for Permanent Vaginal "Thread" in Female Offsprings*1

BMR*2	BMD*3	Blood level*4	
%	ng/kg bw	pg/g blood	pg/g fat*5
1	48.8	0.58	116
10	131	1.55	309
50	333	3.95	790

*1 Data of vaginal thread taken from Gray et al (1997)

*2 Benchmark Response

*3 Benchmark dose calculated using US EPA BenchMark Dose Software beta version 1.1b

*4 Blood levels were estimated using data from Hurst et al (1998) which was published by the same group as Gray et al with assumptions and the data shown below.

(1) Concentrations of TCDD in blood is assumed to pararell with the doses of 0.05 - 1.15 μg/kg bw.

(2) Pregnant rats received a single oral dose of 1.15 μg [H3]TCDD/kg bw on gestation day 8 (GD8).

(3) TCDD levels on GD9, GD16 and GD21 were as follows.
- Blood of dams : 15, 18 & 8 ng/g (Average: 13.7 ng/g)
- Whole embryo/fetus: 39.6, 18.1 & 22.1 pg/g tissue
- Placenta: Not assayed, 32.2 & 23.2 pg/g tissue

*5 Estimated assuming fat content of 0.5%.