VALIDATION OF CONGENER PROFILES OF DIOXINS IN HUMANS USING THE CONGENER-SPECIFIC BIOAVAILABILITY FACTOR

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Introduction

A revised range of the tolerable daily intake (TDI) of 1 to 4 pg TEQs/kg body weight for dioxin-like compounds was presented by the WHO in 1998, where TEQ refers to the 2,3,7,8-TCDD toxic equivalents proposed by the WHO in 1997. The TDI was established based on the understanding that the most sensitive adverse effects are hormonal, reproductive and developmental ones and that the body burden is the most appropriate dose metric. This implies that the magnitude of adverse effects from dioxin congener is controlled by not only its toxic equivalent factor (TEF) but also its bioavailability. The most important characteristics for determining the bioavailability of a dioxin congener are gastrointestinal absorption and biological half-life in humans, because 95 % of dioxins exposed are thought to be through the diet in Japan. Thus, an indicator that represents the relative bioavailability of a congener which is named Yoshida-Nakanishi factor (YNF) here, was estimated for 17 2,3,7,8-substituted dioxin congeners based on published data of the half-life of dioxins in the human body and the gastrointestinal absorption ratio. Furthermore, the validity of YNF was examined by comparing the congener profiles of dioxins in the diets for the last two decades with those of dioxins accumulated in humans, in Japan, where the word "dioxins", in this paper, refers to the family of polychlorinated dibenzo-p-dioxins and of polychlorinated dibenzofurans.

Proposed value for the YNF

The data on the half-life of 17 2,3,7,8-substituted dioxin congeners in the human body were chosen and are shown in the Table, based on mainly the results by Liem et al[1]. and partially on those by Flesch-Jenys et al[2]. The relative absorption ratio of a dioxin congener in the gastrointestinal tract for adults was assumed to be equal to that of the dioxin congener in breast milk in nursing infants[1]. The product of the half- life and the absorption ratio of congener relative to 2,3,7,8-TCDD is defined as YNF and is shown in the Table.

Congener profiles of dioxins in humans

Based on the congener profiles of dioxins in breast milk from 420 mothers who are nursing their first child, which were monitored nationwide in 1998[3], the average dioxin congener profile of fat in Japanese mothers was estimated in terms of TEQ and is shown as "observed" in the Table, where the congener profile is expressed as the ratio of the congener in terms of TEQ to the total TEQ.

Next, the temporal trends of dioxins ingested through the diet were estimated based on the results of a total diet study conducted by M. Toyoda et al[4]. In that study, diet samples consisting of 13 food categories that were taken in 1977, 1982, 1988, 1992, 1995, 1995, 1997 and 1998 and archived, were submitted for determination of dioxin congeners in 1998. Using these data, the levels of dioxin congeners for respective food categories in the diet from 1977 to 1998 were extrapolated. Furthermore, assuming that dioxins were ingested from 1979 to 1998 according to the above extrapolated results, and assuming a one-compartment model, the congener profiles of dioxins in the human body in 1998 were estimated in the two cases with and without consideration of YNF and the results are shown as "estimated" in the Table. The two estimated congener profiles in the human body were compared with those observed in breast milk. The slopes and intercepts of linear regression curves for the both cases are statistically equivalent to 1 and 0, respectively (P=0.05), although 95 % confidence intervals of the slope and intercept for the case with consideration of YNF were narrower than those for case without consideration of YNF. First of all, the level of TCDF in human body cannot be explained without the YNF.

A 27-year-old female model

To examine the dioxin levels in the human body, a 27-year-old female model was used with the following considerations; 1) she continued to ingest dioxins from birth, i.e., for 27 years from 1971 to 1998; 2) the dioxin levels in her diet from 1977 to 1998 were the same as those estimated in the previous section; 3) the dioxin levels in her diet from 1971 to 1976 were the same as those in 1978; 4) her diet and body weight changed with age; 5) her body weight at her adulthood was 50 kg; 6) the half-life of 2,3,7,8-TCDD is 6.2 years and those of other congeners are 6.2 times the YNF; 7) 97 % dioxins ingested is distributed in fat; and 8) the fat weight relative to the entire body weight is 0.25.

The dioxin levels of 17 congeners in the female model were estimated and are shown in the Figure. The estimation of the contribution of dioxins ingested during childhood is unreliable, due to lack of information of the dioxin levels in the diet before 1977 and due to not taking into consideration the presumably more active metabolism during childhood. However, this is not a major drawback, because the contribution of the dioxin ingestion from birth to five years of age to her present body burden is minimal. As shown in the Figure, the pattern of the values estimated with consideration of YNF is similar to that of the observed ones. However, the levels estimated of all congeners are larger than those observed. The total dioxin level is 23.2 (36.3 - 16.8, 95% confidence limit) pg TEQ/g fat in the 27 year-old female model and 15.1 (27.9-2.5) pg TEQ/g fat for the observed results. These may imply that the absorption ratio of dioxins should be revised to 65 % of the value shown in the Table, although, considering that the data used were limited, the YNF values were not revised.

In conclusion, considering that YNF represents the bioavailability of a congener, the congener profiles of dioxins in the human body can be well related to that of the diet. Hereafter, YNF should be considered in evaluating human health risks due to dioxins.

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Table Validation of congener profiles of dioxins using the YNF

Congener	YNF	Absorption ratio	Half-life (years)	Ratio of congener (%)		
				Estimated		Observed
				Without YNF	With YNF	
TCDD	1.00	0.97	6.2	11.8	9.5	8.9
PeCDD	1.41	0.99	8.6	28.0	31.6	38.0
123478HxCDD	3.09	0.98	19.0	0.9	2.2	1.3
123678HxCDD	2.11	0.97	13.1	5.5	9.3	14.4
123789HxCDD	1.36	0.96	8.5	1.9	2.0	2.5
1234678HpCDD	0.95	0.86	6.6	2.7	2.1	0.7
OCDD	0.71	0.76	5.6	0.1	0.0	0.1
TCDF	0.06	0.97	0.4	9.9	0.5	0.5
12378PeCDF	0.14	0.99	0.9	1.3	0.1	0.1
23478PeCDF	1.61	0.98	9.9	28.8	37.3	27.5
123478HxCDF	0.92	0.97	5.7	2.6	1.9	2.1
123678HxCDF	1.00	0.97	6.2	2.0	1.9	2.3
123789HxCDF	ND	0.95	-	0.0	0.0	0.0
234678HxCDF	0.38	0.96	2.4	3.3	1.0	1.4
1234678HpCDF	0.37	0.87	2.6	1.2	0.5	0.1
1234789HpCDF	0.54	1.00	3.2	0.0	0.0	0.0
OCDF	0.03	0.95	0.2	0.0	0.0	0.0

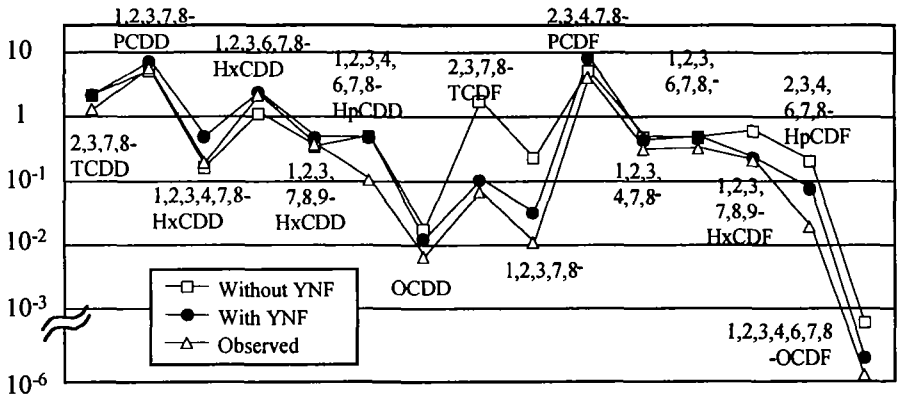

Figure The results of a 27-year-old female model (TEQ-pg/g fat)