Dioxins--- from the Risk Assessment Perspectives

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Abstract

The estimation of exposure levels of and human health risks from dioxins are attempted for four receptor groups in Japan: two groups of general population, local residents living near municipal garbage incinerator and heavy fish eaters. Among the four receptor groups, heavy fish eaters are most highly exposed. The estimated risks for the heavy fish eaters are as follows; cancer risk estimated using linearized multistage model based on the values of TEQs is 7×10^{-4}, the MOE value for cancer calculated on the basis of the AUC TCDD is 9.0, and the MOE value for endometriosis calculated using 1996 Proposed Guidelines is 5.3.

1. Introduction

In Japan, chemical regulation policies tend to be extensively influenced by panic reactions or topical issues. To be more specific, the regulation of hazardous chemical policy emphasizes methods of identifying a limited number of extremely toxic chemicals and their strict regulation. The government as well as the public are interested in the nature of chemicals, irrespective of the risk posed by or the social benefits of the chemicals. This method is, however, ineffective for maximizing the risk reduction with limited resources, because the most hazardous chemical does not always pose the greatest risk and this risk may not necessarily be easily reduced.

Emission control of polychlorinated -dibenzo dioxins (PCDDs) and polychlorinated -dibenzo furans (PCDFs), to the family of which the word “dioxins” is used as a shorthand rference, has not been undertaken till recently and data of dioxins emitted from municipal garbage incinerators were sealed until 1997, when the government released this data and issued a directive to regulate dioxins levels in the stack gas of the incinerators from the year. Due to the sudden release of this data and a lack of understanding of the extent of the risks posed by dioxins, the public has reached in a panic caused by a fear of possible broad spectrum of adverse effects that can result from exposure to dioxins such as deformed babies, cancer and decreased immune capability. In particular, mothers who breast feed their babies and local

residents living near the incinerators are in great fear of the possible risks associated with dioxins. To overcome such a panic reactions, it is essential for the government to formulate a policy to reduce dioxin emission based on scientific analysis. This is necessary not only to use rational countermeasures from the technological and economic perspective , but also to reach an agreement between the government and the public on the countermeasures proposed by the government.

2. Exposure pathways and levels

In assessing human health risks posed by dioxins, the following six receptor groups must be considered: 1) the general population, 2) local residents living near garbage incinerator (LRs), 3) heavy fish eaters (HFEs) , 4) breast-fed infants, 5) fetuses and 6) workers believed to be exposed to high dioxin levels at their workplaces such as garbage incinerators or in pesticides production plants. In this study, the first five receptor groups are considered. In Table 1, major dioxin exposure routes and exposure levels estimated in terms of the 2,3,7,8-tetrachlorodibenzo-p-dioxin toxic equivalents (TEQs) are shown for each group of receptor.

Table 1. Dioxin Exposure Levels in Terms of TEQs by Receptor

Receptor		Exposure routes							
		Daily exposure (pg/day)							One time(pg)
		inhalation	fish	green vegetables	other foods	breast milk	others	total	
General (1)	G(1)	10	105	11	47	0	2	175*	0
General (2)	G(2)	10	32	9	22	0	2	75**	0
Local residents	LR	31	105	53	47	0	2	238***	0
Heavy fish eaters	HFE	10	382	11	9	0	2	419	0
Breast-fed infants	—	0	0	0	0	305	0	305	0
Fetuses	—	0	0	0	0	0	0	0	NA
Workers	—	beyond the scope of our study							

* Takayama et al., 1991 ** EA, 1997 *** LADD

Here, the exposure is estimated mainly on the basis of measured data in Japan and supplementarily simulated data. To evaluate human health risk from dioxin exposure, not only daily intake amounts but also tissue levels due to long-term exposure are needed, because the half-life of dioxins in humans is long and most of the dioxins ingested are retained in the human body. Assuming a half-life time of dioxins in the human body of 6. 5 years, the total body burden dioxins and tissue levels due to long-term exposure are predicted for the five receptor groups and shown in Table 2.

Table 2. Dioxin Tissue Levels Estimates in Terms of TEQs.

Receptor	Total burden (ng)	Adipose (pg/g of fat)	Liver (pg/g)
G(1)	598	48.3	12.0
G(1)	256	20.7	5.1
LR	813	65.7	16.3
HFE	1,432	115.7	28.6
Infants	53	—	—

Assumptions and parameters:

1) Half-life of dioxins in human body is 6.5 years.
2) Human body weight is 60 kg.
3) Fraction of dioxins in liver and fat is 0.03 and 0.97, respectively.
4) Relative tissue weight to the whole body weight of liver and fat is 0.025 and 0.2, respectively.

2.1 *General population*

The general population is further divided into two subgroups , G(1) and G(2), because of the scarcity and diversity of data regarding dioxin levels in fish. Regarding TEQs from foods, G(1) is based on the data by Takayama et al. (1991) and G(2) is based on the data provided by the Environment Agency (EA) (1997). Using the monitoring data provided by the EA, average urban air level of 0.6 pg/Nm^3 for dioxins is assumed . The dioxin tissue levels are predicted for G(1) and G(2) and compared with the observed dioxin tissue levels in Table 3. The observed values lie between the predicted values for G(1) and G(2), which validates the estimated exposure levels for the general population.

Table 3. Predicted vs. Observed TEQs Tissue Levels

Tissue	Predicted		Observed
	G (1)	G(2)	
Adipose (pg/g of fat)	48.3	20.7	31.0(7)*, 24.6(13)**, 24.5(13)**, 15.4(13)**
Blood (pg/g of fat)	48.3	20.7	23.9(7)*
Milk (pg/g of fat)	48.3	20.7	15.0(15)***, 10.9(7)****, 11.4(7)****, 18.3(3)****, 28.1(6)****, 13.1(9)*****
Liver (pg/g of tissue)	12.0	5.1	7.7(7)*

*Hirakawa (1992), **Wakimoto (1989), ***Hirakawa (1995), ****Morita (1996), *****Matsueda(1992): (n), number of samples

2.2 *Local residents living near incinerator*

The possibility of a high level of exposure to dioxins is likely to occur in situations where individuals live near garbage incinerator and consume green vegetables harvested from farmlands contaminated with dioxins. Local residents (LRs) are defined as those who live within 1000 m from the garbage incinerator emitting the highest level of dioxins and are exposed to air and consume the green vegetables affected by emissions from the incinerator for thirty years. A yearly average of the dioxin levels in air on the downwind side of the incinerator is estimated by simulating the past state of the Shirotori garbage incinerator managed by several municipalities in Ibaraki Prefecture, one of the worst garbage incinerators in Japan. It is assumed that the dioxin level in the stack gas is 3600 ng/Nm^3 in terms of TEQs. Using ISCLT3 (Industrial source complex, long-term model 3) and a soil fugacity model developed by the European Centre for Ecotoxicology and Toxicology of Chemicals, we attempt to choose some parameter values so that the estimated dioxins levels in soil with a mixing depth of 2 cm could match dioxin levels measured in soil samples collected near the Shirotori incinerator (Miyata et al., 1997). However, on comparing the measured levels, it is found that the models underestimated the dioxin levels in soils very close to the incinerator site comparing the measured levels. Possible explanations as to why the models underestimate the dioxin levels in soil near the emission source include: 1) irregular operations were conducted at the incinerator, 2) wet deposition is not considered, and 3) all dioxins are postulated to behave in a manner similar to 2,3,7,8-TCDD. To overcome the shortcomings of the simulations, the partition coefficient between air dioxin levels and soil dioxin levels is calculated, using which the dioxin levels in the atmosphere in the proximity to the incinerator are revised. Thus, average dioxin levels in the air and in the soil within 1000 m from the incinerator site is 4.9 pg/Nm^3 and 144pg/g, respectively. In addition, the LRs' daily intake of green vegetables harvested in the farmlands contaminated with dioxins is 77.2 g , although the daily intake of dioxins from other foodstuff is similar to that for G(1). Although the duration of exposure to dioxins from the incinerator is assumed to be thirty years, the lifetime average daily dose adjusted to the lifetime duration (lifetime average daily dose, LADD) is indicated in Table 1.

2.3 *Heavy fish eaters*

The possibility of a high level of exposure to dioxins as a result of the consumption of a large quantity of fish must be considered in Japan. We, the Japanese, consume daily, on an average, about 95 g of fish. Also, a certain portion of the people in fish related businesses such as fishermen, fish mongers and sushi-cooks, referred to as heavy fish eaters (HFEs) reportedly consume much more than the daily average. In this study, each HFEs' average daily consumption is assumed to be 320 g, based on the survey of Minamata Disease patients (Futatsuka, 1979). In addition, the fish that they consume is of the same quality as that consumed by G(1). The duration of exposure is as long as the lifetime. It is probable that there is a subgroup of HFEs who consume limited varieties of fish , the dioxin levels of which are higher than the average values. The exposure levels to dioxins of this subgroup must be higher than the levels estimated here. However, such a subgroup is not considered in this study.

2.4 *Others*

One group of potentially highly exposed receptors is breast-fed infants. An average TEQ level of 20 pg/g of fat in breast milk obtained from observed data (Table 3) is used for the estimation of the daily dioxin intake by breast-fed infants. A body weight of 6 kg and breast feeding duration of 6 months, which represents the average over the breast feeding time period, are assumed. The body burden of dioxins six months after birth is shown in Table 2.

Fetuses are a group which might be highly exposed to dioxins. No information is available for the estimated amount of dioxins transferred from the mother to fetus through the placenta. The estimation of the exposure level and risk evaluation for fetuses remain to be studied.

Problems faced by workers are beyond the scope of this study.

3. Risk estimation

Accepted and established methodologies for characterizing the risks from dioxin exposure are not yet available. However, we don't wait for the methodology to be established for risk characterization of dioxins. Although the available information and knowledge needed for risk evaluation are limited, evaluation of the extent of human health risks from dioxin exposure for the five receptor groups is attempted. In performing the risk assessment of persistent organic pollutants (POPs) such as dioxins, it is noteworthy that dosimetry of the POPs in the dose-response relationship may not be as simple as that of nonpersistent chemicals. The slow elimination of dioxins indicates the body's burden retention of dioxins over many years than the administered dose is important for the accurate assessment of their chronic effects. However, at the same time we must be careful of using the body burden as a dosimetric across species, because of various possible differences in the metabolic mechanism between species. Considering the persistent nature of dioxins, some dosimetrics in the dose-response relationship have been proposed; body burdens, tissue levels and the product of exposure levels and duration of exposure which is referred to as the area under the curve (AUC). In this study, some of them are used as trial basis.

It is known that 2,3,7,8-tetrachlorodibenzo-p-dioxin(2,3,7,8-TCDD) is a carcinogen in laboratory animals. In addition, recently, WHO identified 2,3,7,8-TCDD as a human carcinogen. On the other hand, the evidence that 2,3,7,8-TCDD is not an initiator but a promoter is increasing.

3.1 *Linearized multistage model*

Here, a typical and established method for the estimation of cancer risk, thought suitable for carcinogens with genotoxicity, is applied to evaluate the cancer risk from dioxin exposure, although this method is not suitable for the cancer promoter. The excess lifetime cancer risk from dioxins is calculated from the average daily dioxin exposure level in terms of TEQs multiplied by the oral slope factor of 2,3,7,8-TCDD. For this procedure, the following two assumptions are made; dioxins other than 2,3,7,8-TCDD in terms of TEQs have the same cancer causing capability as 2,3,7,8-TCDD , and dose via pathways other than the oral pathway is

equivalent to the oral dose in terms of toxicity.

The oral slope factor of 2,3,7,8-TCDD of 10^{-4}(pg/kg/day)$^{-1}$is used (EPA, 1994). The results for G(1), G(2), LRs and HFEs are shown in Table 4. The excess lifetime cancer risk from dioxin exposures ranges from one to ten in a thousand for all four receptor groups.

Table 4. Cancer Risk Estimates (Linearized Multistage Model)

Receptor	Lifetime cancer risk
G(1)	2.9×10^{-4}
G(2)	1.3×10^{-4}
LR	4.0×10^{-4}
HFE	7.0×10^{-4}

3.2 *Dioxin liver levels*

Scheuplein and Bowers (1995) proposed an equation to calculate human cancer risk; (Human cancer risk) = (Animal cancer risk) × (the relative dioxin tissue level), where the relative dioxin tissue level indicates the ratio of dioxin levels in human tissues to that in rat tissues. They address a key reason for recommending this method; in the absence of " differences in intrinsic species sensitivities, the toxicological response across species from a chemical is expected to be proportional to the corresponding target organ concentrations." They derived the relationship between the 2,3,7,8-TCDD liver levels and the incidence of cancer on the basis of Kochiba's results and assumed linearity at lower doses. Thus the cancer risks are calculated on the basis of TEQ liver levels for the four receptor groups and the results are the same as those calculated in 3.1.

3.3 *AUC*

Aylward reports that measures of internal dose such as lifetime AUC, lifetime peak or average body burden, and peak or average blood levels, should be used to describe the dose-response relationship in cancer risk assessments of 2,3,7,8-TCDD, because both the tissue level and duration of maintenance at a certain tissue level are almost certainly the key factors in predicting the magnitude of the cancer risk due to a persistent chemical such as TCDD. In addition, they emphasize that the use of LADD as a dosimetric can be misleading.

The cancer risks for the four receptor groups are estimated, using the lifetime AUC as a dosimetric. Since the study of the National Institute of Safety and Health (NIOSH) cohort in the United States is used as a reference, the daily intake of 2,3,7,8-TCDD is estimated for the four receptor groups, on the basis of which AUC adipose 2,3,7,8-TCDD levels are calculated. The results are shown in Table 5. According to the analysis by Aylward et al., the AUC serum lipid TCDD levels of 6059 ppt・year (196～136,823) is an average for an apparent "no-effect level" group in the NIOSH cohort. Based on the AUC value of 6059, the MOE (margin of exposure) values for the four receptor groups, defined as the ratio of the no-effect level to the exposure

level, are 23, 60, 22 and 9 for G(1), G(2), LR and HFE, respectively.

Table 5. AUC 2,3,7,8-TCDD Levels and Corresponding Cancer Risks

Receptor	TCDD daily intake (pg/day)	TCDD total body burden (ng)	TCDD adipose (pg/g)	AUC TCDD adipose (ppt.year)	MOE for cancer
G(1)	15.8	54.0	4.4	265	23
G(2)	6.0	20.5	1.7	101	60
LR	17.7	60.6	4.9	279	22
HFE	40.2	137.4	11.1	675	9

1) $AUC = \int_0^{t'} C dt = \frac{D}{k} \int_0^{t'} \{1 - \exp(-kt)\} dt,$
where k = 0.1066 (1/year) = overall elimination rate constant, t'=70 years,
D = yearly dose (1/year)

2) TCDD = 2,3,7,8-TCDD. Portions of TCDD in TEQs are postulated as follows: 0.04 for air, 0.00 for green vegetables and 0.01 for others.

Here AUC 2.3,7,8-TCDD levels rather than the AUC TEQs levels but are used as a dosimetric for the estimation of cancer risk, because only 2,3,7,8-TCDD serum levels are measured for the workers in the NIOSH cohort, although they are likely to be exposed to mixtures of dioxins. If we use the data on laboratory animals as a reference, the use of TEQ levels is appropriate , because laboratory animals are exposed only to 2,3,7,8-TCDD. However, TEQ data for the NIOSH cohort is needed for more precise risk estimation.

Although the method proposed by Aylward is challenging and has future prospects, the underlying NIOSH data involves some problems, as Aylward herself pointed out; 1) a limited number of serum sampling for TCDD measurement, 2) the classification of workers for the calculation of group SMRs may not necessarily be appropriate and 3) the NIOSH cohort consists of only male workers.

3.4 *1996 Proposed Guidelines by EPA*

The USEPA issued "Proposed Guidelines for Carcinogen Risk Assessment" (1996 Proposed Guidelines) in 1996. This includes the following procedures for the estimation of risks as a default:1) A human equivalent dose for oral exposure is estimated from data on test animal species by the adjustment of the animal oral dose, by a scaling factor, to a power of 0.75. 2) LED_{10}, the lower 95% confidence limit on a dose associated with 10% excess response, is used as a standard point, on the basis of which the responses in the low doses range are extrapolated. 3) In extrapolating to low doses, a linear or nonlinear dose response relationship is assumed. For linear extrapolation, the risk is extrapolated as a probability of an effect at low doses, while, for nonlinear extrapolation, the risk is represented as MOE.

According to current studies, it is shown that the NOEL is the same as an LED_5 or LED_{10},

or ED_4 is close to an upper bound of NOEL.

According to the EPA's 1996 Proposed Guidelines, risks associated with dioxins in terms of TEQs for the four receptor groups are estimated for three endpoints. The results and the underlying data are shown in Table 6.

For cancer and reproductive dysfunction endpoints, the values of MOE lie in the range of 40.8 to 228 for the four receptor groups. On the other hand, the MOE values are much smaller for endometriosis endpoint and range from 5 to 30.

Table 6. MOE Values for Three Endpoints

	Receptor \ Endpoint	Cncer	Reproductive capability	Endometriosis
MOE	G(1)	98	98	13
	G(2)	228	228	30
	LR	72	72	9
	HFE	41	41	5
Toxicity	Test Animal	SD rat	SD rat	rhesus monkey
	NOEL (pg/kg/day)	1,000	1,000	63*
	LED_{10} (pg/kg/day)	285	285	37

* Estimated from LOEL value.

4. Risk Characterization

4.1 *Exposure estimation*

The population of breast-fed infants and fetuses are thought to be potential highly exposed. However, the risk assessment for these two populations is not undertaken in this study. The difficulty in conducting this assessment arises from the availability of limited data pertaining to dioxin levels in breast milk in Japan and insufficient knowledge for the estimation of the extent of the adverse effects resulting from high levels of exposure for comparatively short duration.

As a result, risk assessment from dioxin exposure is performed for the four receptor groups. G(1) and G(2) are adopted as representatives of the general Japanese population. The difference in the two stems primarily from the difference in dioxin levels in fish and shellfish measured. Since extensive studies on the dioxin levels in food are being conducted throughout Japan, this problem will be solved in the near future. For the time being, the two groups are considered as representatives of the general Japanese population. The estimation of the exposure levels for LRs is not yet firmly rooted in reliable monitoring data, although they are likely to be overestimated rather than underestimated.

The following conclusions are drawn from the exposure estimation study:

1) For all the four receptor groups, fish ingestion is the dominant route for dioxin exposure. The ratio of exposure from fish consumption to exposure via all routes is 60 % for G(1)

and 91% for HFE.

2) Among the four groups, the most highly exposed group is HFE.

3) For LR , ingestion of green vegetables harvested in the proximity (within 1000 m) of the incinerator is the second dominant exposure route.

4.2 *Risks evaluated*

Due to the lack of an accepted methodology for the estimation of risks from highly persistent chemicals such as dioxins, several methods are attempted in this study. Therefore, the results attained are insufficient to draw distinct conclusions from, for the time being. However, the following are observed.

(1) Assuming the linear dose response relationship at low doses, the excess lifetime cancer risk evaluated on the basis of TEQs is in the range of less than 10^{-3} and more than10^{-4} for all the four receptor groups. In Japan, drinking water quality criteria for carcinogens with genotoxicity and ambient air quality criteria for benzene are established at levels for a lifetime cancer risk of
10^{-5} . The evaluated risks from dioxin are approximately ten to one hundred times the level of 10^{-5}. However, the risks from dioxins are the risks for a mixtures of congeners and are therefore obtained by applying the additivity rule to individual congeners. Although the cancer risk level from individual carcinogens in drinking water is less than 10^{-5} , the sum of the cancer risks from a mixture of chlorination byproducts in water supplied in Tokyo was 1.2×10^{-4} in the latter 1980 and that in the United States on average was in 1.1×10^{-4} (Bull, 1990). Furthermore, generally speaking , risks from food is harder to control than that arising from drinking water.

The cancer risks associated with dioxins estimated here are not exceptionally high, though it is sure that risks from dioxins should certainly be reduced. Furthermore, it is noteworthy that larger values are proposed for cancer potency of 2,3,7,8-TCDD and that there may exist more sensitive subpopulations.

(2) Recently the belief that 2,3,7,8-TCDD may exhibit thresholds for its toxic effects have been prevailing in the scientific community. If this belief is correct, the MOE approach is more appropriate than the approach employed in (1). As shown in Table 6, the MOE values for cancer and reproductive dysfunction are large enough to guarantee safety but those for endometriosis are on the borderline.

(3) Considering the persistency of dioxins, risks should be evaluated on the basis of the AUC rather than the LADD. The analysis based on the AUC shows that the MOE values lie in the range of 9 to 60. In this analysis, risks are estimated in terms of 2378TCDD. The results show that risks estimated in terms of TEQs are not parallel to those in terms of 2378TCDD. The risk for HFEs are much greater than those for other groups and the risks for G(1) are close to that for LR. Although this method is promising, there are many problems unsolved which are described in section 3.3.

The objective of our research project is not only to estimate the risk for each endpoint, but also to weigh importance of respective endpoints, which may be translated into severity of

respective endpoints, and finally to represent all risks in terms of LLE. However, as of now, we are far from realizing the final objective. This subject needs to be studied further. In this analysis, uncertainty analysis is not yet performed . These will be examined the next year.

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