Report on Tolerable Daily Intake (TDI) of Dioxins and Related Compounds (Japan)

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Environmental Health Committee of the Central Environment Council
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Living Environment Council and Food Sanitation Investigation Council
Ministry of Health and Welfare

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1. Introduction

The tolerable daily intake (TDI) of dioxins and related compounds is an important index established by the World Health Organization (WHO) and individual countries, based on scientific knowledge, to help design sound measures to prevent the effects of dioxins on human health.

In Japan, the Environment Agency and the Ministry of Health and Welfare have established a TDI index and a Health Risk Assessment Index for Dioxins. These have been applied as indices to evaluate the effects of pollution on human health and for policies relating to dioxins and related compounds.

In context of this background, in May 1998 a re-evaluation of the TDI of dioxins was conducted during the WHO Consultation of experts, organized by the WHO European Centre for Environment and Health (WHO-ECEH) and the International Programme on Chemical Safety (IPCS).

Similar moves have been taken in Japan. The Environment Agency and the Ministry of Health and Welfare have established expert committees (the Dioxin Risk Assessment Subcommittee, Environmental Health Committee, Central Environment Council; the Living Environment Council; and the Special Dioxin Health Effects Evaluation Committee, Food Sanitation Investigation Council) and it was decided at a joint consultation earlier this year that the TDI should be re-evaluated in Japan. On 30 March 1999 a Cabinet Meeting adopted the "Basic Guidelines of Japan for the Promotion of the Measures Against Dioxins" which required a review of the TDI within three months.

This report discusses the TDI of dioxins and related compounds by analyzing and assessing the discussions of the 1998 WHO Consultation and contributing new information.

2. Outline of the History of TDI

(1) 1990 WHO Consultation

A WHO meeting held in 1990 (Bilthoven, the Netherlands) proposed a TDI of 10 pg/kg for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic dioxin congener, based on information available at the time. This proposal was based on a study (Kociba et al., 1978) in which the inhibition of body weight gain and liver damage were observed when low doses of 2,3,7,8-TCDD were administered to rats over 2 years. The study found that doses of 1 ng/kg/day led to no manifestation of toxicity (NOAEL, the no observed adverse effect level, or "non-toxic dose"). Applying an uncertainty factor of 100 resulted in the TDI noted above.[1]

While some changes were later made regarding the selection of data, this method used by WHO to set the TDI was adopted by relevant administrative agencies of individual countries (with the exception of the US) as the basic method for setting standards. (The US Environmental Protection Agency (EPA) took the approach of evaluating the health effects of dioxins using the virtually safe dose (VSD), which differs from the concept used by WHO.)[2]

(2) Establishment of TDI in Japan

The Dioxin Risk Assessment Study Group of the Japanese Ministry of Health and Welfare proposed in 1996 a provisional TDI of 10 pg/kg/day for 2,3,7,8-TCDD. This figure was reached based on the WHO estimation formula and consideration of new scientific data, resulting from a 3-generation reproduction test using rats, in addition to the 2-year Kociba study noted above. Evaluation of *in utero* deaths, decrease in litter size, and inhibition of postnatal body weight gain led to the conclusion of a non-toxic dose of 1 ng/kg/day, to which an uncertainty factor of 100 was applied to produce the TDI noted.[3]

In 1997 the Environment Agency's "Dioxin Risk Evaluation Committee", while also adopting the WHO estimation formula using the data by Kociba et al. as the basis for discussion, took into consideration experimental data on rhesus monkeys, and adopted 5 pg/kg/day as the Health Risk Assessment Index for Dioxins (a value that serves as a guideline for environmental protection measures and also for human exposure assessment, but not for the tolerable limit for maintaining human health).[4]

(3) Re-evaluation by 1998 WHO Consultation

A variety of studies on the health effects of dioxins and related compounds have been conducted internationally since 1990. For this reason, WHO-ECEH and IPCS held an expert consultation in Geneva, Switzerland in May 1998 to review the TDI based on new scientific data accumulated after 1990 to discuss the health risks for infants, cancer and non-cancer endpoints in humans and animals, mechanistic aspects, toxicokinetics, modeling, exposure, the applicability of the TEQ concept, and risk assessment approaches for dioxins in various countries.

As a result, the approach of using 'body burden', rather than the exposure dose, in extrapolating the results of toxicity data from animal studies to human was introduced. In this approach, the lowest adverse effect level for human was determined by the lowest body burden at which adverse effects were observed in animals, then the dose was multiplied by the uncertainty factor of 10, giving the value of 1-4 pg TEQ/kg/day for TDI.

The Executive Summary of the WHO final report concludes that this value for TDI is considered to be the provisional tolerable value, in view of the fact that the current exposure conditions in industrialized countries are said to be 2-6 pg TEQ/kg/day. Although subtle effects may occur at these exposure levels, no confirmed manifestations of toxic effects have yet been reported. In addition, the influence of other chemical substances cannot be ruled out in regard to the effects that have been observed. Finally, while the consultation considered the upper range of 4 pg TEQ/kg/day to be the “maximal tolerable intake on a provisional basis”, it stressed that the ultimate goal should be to reduce human intake levels to less than 1 pg TEQ/kg/day.

3. Exposure Conditions

(1) Background Exposure Levels

① Europe and America

In general, more than 90% of exposure to dioxins in daily life in Europe and America comes from the diet, with animal food products such as meat and dairy products being the principal source of intake. According to studies in major industrialized countries, the level of exposure to dioxins is 1-3 pg TEQ/kg/day, and reportedly 2-6 pg TEQ/kg/day when co-planar polychlorinated biphenyls (co-planar PCBs) are added.[5]

② Japan

The average exposure level in Japan is about the same as, or lower than, exposure levels in Europe and America.

In a food survey by the Ministry of Health and Welfare (1997, market-basket method), the level of exposure to dioxins was 0.96 pg TEQ/kg/day, rising to 2.41 pg TEQ/kg/day if 3 co-planar PCB congeners were included.[6] There is so little exposure via drinking water that it can practically be ignored.

The level of exposure to dioxins in ambient air was calculated to be 0.17 pg TEQ/kg/day according to the estimate in the 1997 Dioxin Risk Assessment Committee Report,[4] based on the average value of 0.55 pg TEQ/m^3 in the results of monitoring surveys[7] conducted by the Environment Agency and local governments. Current data on co-planar PCBs are limited, however an estimate in an Environment Agency report for 1997 gave the range 0.044-0.026 pg TEQ/m^3. Because this is considerably lower than the concentration of dioxins in ambient air noted above, the total exposure level remained at 0.17 pg TEQ/kg/day even after 12 co-planar PCBs were added.[8]

With regard to exposure levels via soil, it is difficult to make accurate estimates because the required information is not always adequate, such as current nationwide concentrations in soil, soil intake levels, and absorption rates of dioxins in soil. However, based on an Environment Agency study (1997)[9] if the concentration of dioxins in soil is assumed to be 20 pg TEQ/g and the concentration of co-planar PCBs to be 2.2 pg TEQ/g, then the exposure level of dioxins is estimated to be approximately 0.0022-0.019 pg TEQ/kg/day, and after adding 12 co-planar PCBs it would be about 0.0024-0.021 pg TEQ/kg/day.

When the sum of the exposure levels arising from each of these routes is calculated, the exposure to dioxins is 1.15 pg TEQ/kg/day, and after adding co-planar PCBs, the average exposure of Japanese people is thought to be 2.60 pg TEQ/kg/day (Figure 1).

The residual level in the adipose tissue in the human body as a result of this exposure is thought to be 10-30 pg TEQ/g lipid (corresponding to 2-6 ng TEQ/kg in terms of body weight).[5] This level is approximately the same as in other major industrialized countries.

③ Dioxins and related compounds in breast milk

According to data from other countries, the daily intake of dioxins and related compounds by nursing infants is greater than in adults on a body weight basis, and the results of the latest survey in Japan show that their mean dioxin intake is generally 60 pg TEQ/kg/day.[10]

On the other hand, there are reports from several countries that the dioxin concentration in breast milk has decreased over the past 20 years, and the results of a study sponsored by the Ministry of Health and Welfare of breast milk samples stored in Osaka Prefecture also showed a more than 50% decrease in dioxins and 3 co-planar PCBs between 1973 and 1996 in Japan (Figure 2).

(2) Accidental and Occupational Exposure

Accidental and occupational exposures are sometimes far greater than ordinary levels of exposure.

①Accidental exposure

Pollution at Times Beach in the United States and an accidental explosion at a chemical plant in Seveso, Italy are known examples of localized accidental pollution. The peak serum level of 2,3,7,8-TCDD at Seveso was 56,000 pg TEQ/g lipid, and the median values in Zone A (high pollution region) and Zone B (moderate pollution region) were 450 pg TEQ/g lipid and 126 pg TEQ/g lipid, respectively.[12]

Poisoning as a result of PCB food contamination occurred in Japan (1968) and Taiwan (1978). Both cases are said to have been caused by PCB used as a heat transfer medium contaminated with very small amounts of dioxins being mixed in cooking oil.[13, 14]

② Occupational exposure

Known examples of occupational exposure include cases of poisoning by exposure to 2,3,7,8-TCDD in a chemical factory involved in the synthesis and use of 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) and its derivatives. Estimates in an epidemiological survey of these incidents of the blood 2,3,7,8-TCDD levels of the workers exposed to high concentrations ranged from 140 to 2,000 pg TEQ/g lipid,[15] levels that are 10 to 100 times greater than the estimated blood levels of ordinary human populations.

No studies on severe examples of excessive exposure of workers to dioxins associated with waste incineration are available from other industrialized countries, but a survey related to waste incineration facilities in the town of Nose in Japan's Osaka Prefecture revealed relatively high levels.[16]

Note: While dioxin toxic equivalents are slightly different because of the differences in toxicity equivalency factors used in the I-TEF (1988), WHO-TEF (1993) and WHO-TEF (1998), the toxic equivalents in this paper are quoted directly from the literature.

4. Effects on Humans

(1) Effects of Accidental and Occupational Exposure

Data on the effects on humans come from actual cases of accidental and occupational exposure. Representative examples are described below.

① Effect of exposure of workers engaged in the production of 2,4,5-T

Exposure of workers to agricultural chemicals such as 2,4,5-T which contains dioxins has mainly occurred in factory accidents during manufacturing processes. Chloracne is a common non-cancerous condition that has occurred after such accidents.[17-22] While various other non-cancerous conditions have been recorded,[19, 23-36] besides chloracne, common symptoms have rarely been described in the cases of factory accidents. Increases in total cancer death rates have been reported in factory accidents or in populations that have been exposed in association with spraying operations.[37-42] Increases in rates of occurrence have been observed for respiratory cancer,[40-42] non-Hodgkin's lymphoma,[40-42] soft tissue sarcoma,[39, 40, 43, 44] and others.

② Effects of exposure in Seveso factory accident

Chloracne was the most prominent non-cancerous manifestation observed among the residents of Seveso, where exposure to dioxins caused by a 1976 factory accident affected ordinary residents, particularly children.[45-50] The rate of occurrence of chloracne in 0 to 14 year old children corresponded to the 2,3,7,8-TCDD pollution levels observed in each region.[48, 49] The follow-up survey conducted from the year of the accident until 1991 found that 10 years or more after the accident there was an increase in the occurrence in cancer-related deaths in males (rectal cancer, lymphopoietic system cancer, leukemia) and females (digestive system cancer, stomach cancer, lymphopoietic system cancer, multiple myeloma) who had been exposed in Zone B. [51, 52] In Zone B, pollution levels had been slightly lower than in Zone A, however the number of exposed was greater. In addition, among the 74 cases of childbirth by the residents of Zone A during the 12-month period from April 1977 (9 months after the accident) until December of the following year, the sex of newborn infants was biased toward girls.[53]

③Effect of exposure on Vietnam War veterans

A survey on US veterans engaged in the spraying of Agent Orange (principal component: 2,4,5-T) during the Vietnam War, indicated a correlation between carbohydrate metabolism disorders, such as diabetes, and exposure to 2,3,7,8-TCDD.[54] Increased numbers of motor vehicle accidents, suicides, and other incidents during the first year after return to the US were pointed out as causes of death, but the mortality pattern since then has not been different from the overall population.[55-57]

④ Effect of exposure of *Yusho* patients

In the *Yusho* outbreak which occurred mostly in Fukuoka and Nagasaki prefectures in Japan in 1968, PCBs and very small amounts of dioxins were detected in the contaminated rice bran oil, and in the blood and adipose tissue of victims.[58]

The manifestations of *Yusho* included comedo, increased prominence of the pores,

increased conjunctival secretion, pigment deposition in the skin, nail deformity and pigmentation, and chloracne.

In a study from 1968 to 1990, a significant increase in deaths from liver cancer was observed in the males, but additional research is necessary in order to verify the findings scientifically.[59]

(2) Exposure to Background Levels

No clear evidence of health effects has been reported resulting from background exposure such as from food

Research on the immune system and thyroid function has been under way in several countries in regard to background exposure, especially in relation to health effects on infants due to dioxin exposure via breast milk and *in utero* exposure.

Breast-feeding has been shown to have beneficial effects on the physical and neurological development of infants. While discussions of the WHO Consultation emphasized the necessity of efforts to decrease dioxin concentrations in breast milk, there was no change in the WHO policy of promoting breast-feeding.

5. Effects on Experimental Animals

Among many dioxin congeners, 2,3,7,8-TCDD, which is considered the most toxic congener, has mostly been used as the test substance in toxicity tests.

(1) Carcinogenicity

Kociba et al. investigated the carcinogenicity of 2,3,7,8-TCDD in experimental animals, and reported the occurrence of hepatocellular carcinoma when a dose of 100 ng/kg/day was administered to rats (continuous dosage for two years; Table 1, No. 23).[60] They reported induction of thyroid follicular adenoma, palatal, nasal concha, lingual, and pulmonary squamous cell carcinoma, and lymphoma when doses of 71 ng/kg/day were administered in long-term experiments on mice and rats (continuous dosage for 2 years; Table 1, No. 22).[61]

In attempts to identify the carcinogenic mechanism, results were negative in several series of experiments designed to detect genotoxicity. A promotion effect was demonstrated in a series of two-stage carcinogenicity experiments using mice and rats.[15]

(2) Liver Toxicity

Liver toxicity was observed biochemically as elevation of glutamate-oxaloacetate transaminase and glutamate-pyruvate transaminase, porphyria and hyperlipidemia. In addition, the toxicity was also observed pathologically as hepatocyte hypertrophy and abnormalities of lipid metabolism.

(3) Immunotoxicity

In immunotoxicity experiments, 2,3,7,8-TCDD caused thymic atrophy, abnormalities of cellular and humoral immunity, inhibition of host resistance to viral infections and inhibition of antibody formation (Table 1, No. 15).[64] In addition, when administered to female rats, inhibition of delayed-type hypersensitivity [65] and inhibition of antibody formation capacity [66] were observed in the offspring (Table 1, No. 12). When 2,3,7,8-TCDD was administered at a single dose, these effects were manifested at as low as 100 ng/kg and over in a clearly dose-dependent manner.

There is a report of increased viral infections after a single 10 ng/kg dose to mice, but no dose-dependency was observed (Table 1, No. 3).[63]

(4) Reproductive and Developmental Toxicity

In reproductive and developmental toxicity tests the effects of 2,3,7,8-TCDD were manifested in the fetuses and newborn animals even at the low doses that caused no effect in the dams. The data described below are concerned with the dosages given during pregnancy and lactation and their effects.

① Cleft palate, hydronephrosis and other effects in offspring

In developmental toxicity tests, administration of continuous high doses of 2,3,7,8-TCDD (starting at 500 ng/kg/day) during pregnancy was reported to cause kidney anomalies in rats [67] and cleft palate and hydronephrosis in mice [67, 68] (Table 1, Nos. 19, 25). In the case of conception rate decrease observed in F_1 and F_2 generations in rats, effects in descendant generations were observed at lower doses that caused no apparent effect in the dams.[69]

② Effects on the reproductive system of female offspring

When 2,3,7,8-TCDD was administered at a single dose to rat dams on gestational day 15, starting at a 200 ng/kg dose, genital anomalies were observed in their female offspring (Table 1, No. 13).[70]

③ Effects on the reproductive system of male offspring

A decrease in daily sperm production by the testes, and a decrease in sperm number in the cauda epididymis and reduced ejaculated sperm counts were observed in the male offspring when 2,3,7,8-TCDD was administered to pregnant rat dams.

When maternal rats were subcutaneously injected with 2,3,7,8-TCDD starting from 2 weeks before mating until weaning in an experiment conducted by Faqi et al. (1998), a dose-dependent decrease in daily sperm production by the testes in male offspring was observed starting in the low-dose group (after an initial dose of 25 ng/kg, and then 5 ng/kg/week) (Table 1, No. 7). In addition, a decrease in serum testosterone concentration, histological changes in the testes, and so on were observed in the high-dose group.[71]

Mably et al. (1992c) conducted a study in which maternal rats were given 2,3,7,8-TCDD on 15 gestational day. They found in the offspring in the low-dose group (64 ng/kg), decreases in daily sperm production by the testes, in the sperm counts in the cauda epididymis, and in the weight of the epididymis and the cauda epididymis (Table 1, No. 11).[72] No significant differences were observed with fertility between the offspring and the control group.

Gray et al. (1997a) observed a decrease in sperm count in the epididymis, and the cauda epididymis, a decrease in weight of the glans penis, and delayed preputial separation, at the 200 ng/kg dose (single dose to rat dams on gestational day 15), and a decrease in ejaculated sperm counts at the 800 ng/kg dose (Table 1, No. 14).[73]

④ Others

When 2,3,7,8-TCDD was administered to rhesus monkeys at an estimated daily dose of 0.15 ng/kg/day for 4 years, the incidence and severity of endometriosis were significantly higher 10 years after the start of administration (Table 1, No. 9).[74] However, inadequacies in the technical aspects of this experiment have been pointed out, including the rearing conditions.[75]

Data from the same research institution showed a decrease in the outcome of learning behavior tests in the offspring of dams administered 2,3,7,8-TCDD (0.15 ng/kg/day from 7 months before pregnancy until weaning) (Table 1, No. 8).[76]

(5) Other Effects

Induction of drug-metabolizing enzymes (ex. CYP1A1) was observed in rats at 1 ng/kg.[77] A similar effect was found in mouse liver at 1.5 ng/kg (Table 1, Nos. 1 and 5).[78]

In addition, alterations of lymphocyte subsets were observed in marmosets at 0.3 ng/kg and 10 ng/kg (Table 1, Nos. 2 and 4).[79, 80]

Chloracne was observed in rabbits at a dose of 4.0 ng/kg (Table 1, No. 6).[81]

6. Pharmacokinetics

(1) Oral Intake and Absorption

Dioxins are absorbed through the gastrointestinal tract, skin, and lungs. The degree of absorption varies with the congener, the route of absorption, and the medium. The oral route accounts for more than 90% of the total intake of dioxins in daily life for humans, although dioxins may be absorbed through all three routes in some exposure cases such as in explosion accidents.

The rate of absorption of orally ingested 2,3,7,8-TCDD is close to 90% when dissolved in plant oil,[82, 83] and about 50-60% when mixed with the diet.[82] Absorption via contaminated soil varies with the type of soil, however it is about half, or less than half the amount absorbed when administered dissolved in plant oil.[84-86]

No large differences in gastrointestinal absorption were observed among animal species.

(2) Distribution in the Body

When dioxins are orally administered to experimental animals they are principally distributed to the blood, liver, muscles, skin, and adipose tissue. Bioaccumulation is particularly prominent in the liver and adipose tissue.[87, 88] Their distribution also varies with the congener and the dose.

Although species differences have been found in the ratio of distribution of 2,3,7,8-TCDD in the liver and adipose tissue, no other major species or strain differences have been observed.

The amount of TCDD in the serum closely parallels its concentration in adipose tissue over a broad range of concentrations.[89]

(3) Metabolism/Excretion

Dioxins are generally difficult to be metabolized,[90-93] and are slowly metabolized into polar substances by drug-metabolizing enzymes in the liver microsomes. There are large species differences in the metabolism of dioxins.[94] Hydroxylated metabolites and sulfur-containing metabolites have been detected,[95] and many of the metabolites are conjugated and excreted in the urine or bile.[94] Nearly no covalent bindings have been found between 2,3,7,8-TCDD or its metabolites with proteins or nucleic acids.[96]

Dioxins are mainly excreted in feces,[97] with only small amounts being excreted into the urine, and there are large species differences in the rate of excretion. Their half-life in rats and hamsters is 12-24 days, in contrast to 94 days in guinea pigs, and about a year in monkeys. A half-life of 5.8 years and 9.7 years was found when 2,3,7,8-TCDD was orally administered to human volunteers, and serum half-life values of 7.1 years, 8.7 years, and 11.3 years were measured in veterans of the Vietnam War.[4]

(4) Transfer from Mother to Offspring

Dioxins are transferred from mother to fetus, but there have been no reports of higher concentrations in a fetus than its mother.[98] Moreover, since dioxins are secreted into breast milk, they are transferred to newborn infants via milk.[99]

(5) Body Burden

Toxic manifestations of chemical substances generally depend more on their blood concentrations and the amounts present in the body, i.e. body burden, than on the daily exposure level.

Therefore, it is not always appropriate to directly apply the results of animal toxicity experiments to predict effects on humans, when evaluating the toxicity to humans of chemicals such as dioxins that have been found to have high bioaccumulation rates and large species differences in the half life through elimination from the body.

7. Mechanisms of Toxicity

The mechanisms of the toxicity of dioxins have not yet been fully understood. However, it has been suggested that binding with the arylhydrocarbon receptor (Ah receptor) is a common mechanism in the toxic manifestations of a variety of dioxins.[100]

(1) Toxicity Mediated by the Ah Receptor

The principal toxicities of dioxins, i.e., liver toxicity, thymus toxicity, and embryotoxicity, are not observed in the mouse line that lacks Ah receptors (Ahr-/- mice),[101, 102] and thus manifestation of these toxicities appears to be mediated by the intracellular Ah receptor. Moreover, it has been shown that when dioxins bind to the Ah receptor, they alter gene expression in conjunction with several other receptors, which gives rise to a variety of toxicities.[103]

The affinity of dioxins for the Ah receptor varies among animal species and strains.[104] At the WHO Consultation it was argued that this affinity for human Ah receptors is similar to that of a strain of mice that has low sensitivity to dioxins. This provides the basis for regarding humans as a species that has low sensitivity to the toxicity of dioxins.[105, 106]

The carcinogenicity of dioxins is not caused by direct damage to DNA molecules, but rather is thought to be due to their promotional activities on the initiation of other carcinogens. It will be necessary to await further research to explain the mechanism of involvement of the Ah receptor in the carcinogenic and endocrine-disrupting actions of dioxins, but already it is clear that the binding of dioxins to the Ah receptor is important in relation to toxic manifestations of dioxins.

(2) Toxicity not Mediated by the Ah Receptor

Some toxicity elicited by dioxins has also been observed that does not appear to be mediated by the Ah receptor,[107] and the manifestations are said to occur at higher doses than those mediated by the Ah receptor.

8. Toxic Equivalency Factors (TEF) and Toxic Equivalents (TEQ)

(1) Dioxins and Dioxin-like Compounds

The term "dioxins" refers to the general name for 210 different polychlorinated dibenzo-*p*-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) congeners. In addition, some PCBs possess a planar-type molecular structure and toxicity similar to that of dioxins, and are referred to as "co-planar PCBs".

(2) Toxic Equivalency Factors (TEF)

The toxic manifestations of the above substances appear to share a common mechanism of action mediated by the Ah receptor. The method used to express the degree of the toxicity of the individual congeners is based on utilization of toxic equivalency factors (TEF), with the toxicity of 2,3,7,8-TCDD set equal to "1."

TEF has been established by WHO committee and others by comparing test results on long-term toxicity, short-term toxicity, and *in vivo* and *in vitro* biochemical reactions for different congeners. The TEF figures have been revised from their previous values, and they are expected to improve as new scientific data are acquired in the future.

(3) Toxic Equivalents (TEQ)

Since dioxins and related compounds are usually present in the environment in the form of a mixture of congeners, the degree of toxicity of the dioxins and related compounds ingested can be expressed as the toxic equivalents (TEQ) by multiplying the amount of each congener by its TEF, and adding up the products. Dioxin toxicity is evaluated internationally on the basis of the TEQ expressed as numerical values.

(4) Calculation of TEQ according to New TEF

Having been corroborated to be generally appropriate by numerous studies, it is now considered valid to calculate TEQ based on the new TEF[108] re-evaluated by the WHO in 1997, and to use them in evaluations of exposure to dioxins and co-planar PCBs. As shown in Table 2, the dioxin congeners which have given TEF values as toxic substances at present include 7 PCDDs, 10 PCDFs, and 12 co-planar PCBs.

9. Estimation of TDI

(1) Basic Approach

Tolerable daily intake (TDI) is the amount of intake per kg body weight per day of a chemical substance suspected of causing harmful health effects as a result of long-term incorporation by the body, that is judged not to give rise to manifestations of adverse health effects even if humans take in as much as that amount throughout their entire lifetimes.

In view of the pharmacokinetic and toxic mechanisms of dioxins and related compounds, it is considered appropriate to base TDI estimates on concepts ① to ④ below. These concepts are the same as the policy adopted by the WHO expert consultation.

① Judgment of no genotoxicity

Since 2,3,7,8-TCDD is not thought to have direct genotoxicity, methods that apply the no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL) are used to calculate the TDI.

Note: If a substance has genotoxicity, the possibility that it will produce health effects is theoretically never zero, no matter how small the dose is. For this reason, it is impossible to set an intake level below which the substance cannot produce health effects. In other words, it is not considered to have any threshold value regarding the risk of health effects. Accordingly, the approach used for risk assessment is different from the threshold approach: a substance may be considered virtually safe based on a theoretical calculation of the number of persons per million who will develop cancer if that number is extremely small for a given amount of intake.

In contrast, if a substance does not possess genotoxicity, the method widely used internationally to establish the intake (or exposure) levels that do not result in health effects on humans includes the NOAEL and LOAEL as mentioned above.

② Body burden

Body burden is a more appropriate measure than daily intake when discussing the relationship between substances and their effects, for substances known to bioaccumulate, and to exhibit large differences among species in the degree of bioaccumulation.

Note: For a given amount of continuous intake of a highly bioaccumulative substance over a long period, the amount that accumulates initially increases because more is absorbed than is metabolized and excreted However, as the amount that bioaccumulates continues to increase, metabolism and excretion also increase, and eventually the amount present in the body (body burden) reaches a state of equilibrium at a certain level that corresponds to the amount of intake.

Toxic manifestations caused by chemicals generally depend on the amount present in the body. An important factor to assess toxicity of a highly bioaccumulative substance is the amount of continuous intake that will lead to the level at which the body burden will manifest toxicity.

Moreover, because animals have large species differences in the half-life of elimination of dioxin congeners from the body, the dosage is not the relevant factor to apply the results of toxicity tests to humans. Rather, it is more appropriate to calculate the body burden from the dosage at which health effects develop in animal tests, to obtain the amount that if taken continuously would reach that body burden in the case of humans.

③ Evaluation of toxicity test data

TDI is estimated based on the lowest body burden in toxicity tests in which toxic reactions are observed, after taking into consideration the toxicological significance of the reaction that was used as an endpoint, its dose-dependency, and the reliability and reproducibility of the tests.

Note: Careful consideration is necessary when selecting test results to use as the basis of TDI calculations for dioxins and related compounds. While the results of numerous toxicity tests have been reported, some results are not appropriate as a basis for quantitative evaluations of toxicity because some of the reactions observed in animals were judged not to be of toxicological significance and because the reliability and reproducibility of some tests have been inadequate.

④ Establishing uncertainty factors

A considerable influence would be observed on the estimation of TDI values for humans based on results of toxicity tests including species differences between humans and animals regarding sensitivity to the test substance, individual differences between humans, and the reliability and validity of the toxicity tests. A way to compensate for the uncertainties caused by these issues is to establish an “uncertainty factor” after carefully assessing the various issues involved.

The significance of uncertainty factors is especially important when evaluating the toxicity of substances such as dioxins and related compounds, whose effects on the body are highly diverse and for which large species and strain differences have been observed in the manifestations of their effects.

Note: Uncertainty factors for species differences and individual differences are usually set on the basis of findings related to pharmacokinetics and mechanisms of action. Furthermore, important elements to consider for the reliability and validity of toxicity tests include the test conditions, dose-dependency, and the toxicological significance of the endpoints used in the evaluation.

(2) Body Burden in Individual Toxicity Tests

Many dioxin toxicity examinations are conducted by utilizing mainly the most toxic congener, 2,3,7,8-TCDD. Body burdens calculated from data on very low doses that caused effects based on toxicity tests reported since 1990 are shown in Table 1.

Table 1 also incorporates tests reported in new literature published after the WHO

Consultation, but both are basically compatible since the table includes all of the toxicity tests used for assessment in the WHO Consultation.

Because very little appropriate data relating to the NOAEL were available from the various tests surveyed for this memorandum, the LOAEL data were used to calculate the TDI estimates. In addition, calculations to estimate body burden were based upon either actual experimental data that were considered reliable or findings in literature.

NOTE: The experimental results for estimating body burden obtained by workers such as Gray et al. were presented in the Executive Summary Document by the WHO Consultation, but the estimation method was not clearly described. Accordingly, several committee members visited investigators at the US Environmental Protection Agency (EPA) who had submitted the figures, and confirmed that the values were derived from actually determined data.

In addition, it was confirmed that some of the body burden values presented at the WHO Consultation were based on conditions that differed from the dosage conditions when the toxic reactions were investigated. Accordingly, this paper utilizes newly calculated values instead of the noted body burden values.

(3) Animal Body Burden Levels that Served as the Basis for Estimating TDI

The results of the various toxicity tests described above, especially those in which an effect was observed at low body burden levels, were carefully assessed in regard to their validity as data for the basis of TDI estimates after considering toxicological significance, dose-dependency, and the reliability and reproducibility of the tests.

① Results of tests that caused enzyme induction

Induction of drug-metabolizing enzymes (ex. CYP1A1) was observed in rats at a body burden level of 0.86 ng/kg,[65] and a similar effect was observed in mouse liver at 20 ng/kg.[78] However, it is more valid to regard these findings as an adaptive reaction of the body than a toxic reaction to 2,3,7,8-TCDD (Table 1, Nos. 1 and 5) (See 5 (5)).

② Results of tests that caused changes in lymphocyte composition

Alterations in lymphocyte composition were observed in marmosets at body burden levels of 9 ng/kg and 10 ng/kg (Table 1, Nos. 2 and 4), but because the effect on T-lymphocyte subset composition ratios observed was the opposite of that seen at high doses, it is inappropriate to directly apply the effect observed at low doses to humans (see 5 (5)).

③ Results of tests that produced chloracne

Chloracne was reported to be found in rabbits at a dose (topical application to the skin) of 4.0 ng/kg,[81] but since this result may be the effect of local exposure, it does not appear appropriate to use this observation as a basis for calculating body burden (Table 1, No. 6) (See 5 (5)). Moreover, since human findings have been obtained in regard to chloracne, the human data take priority in calculating the TDI. The minimal body burden level at which chloracne has been

observed in humans is said to be 95 ng/kg (see 4 (1)).[11]

④ Results of tests that produced immunotoxicity

Immunotoxicity, for which delayed hypersensitivity was used as an index, was observed in the offspring of rats at a body burden of 86 ng/kg (Table 1, No. 12) (Gehrs et al., 1997).[65] Immunotoxicity in the adult mice, in which inhibition of antibody formation was used as the index, was observed at 100 ng/kg (Table 1, No. 15).[64] Since these findings also showed dose-dependency, they may be considered to be the effects of 2,3,7,8-TCDD.

By contrast, Burleson et al. (1996) stated that viral infections increased at 10 ng/kg in an immunotoxicity experiment (Table 1, No. 3),[63] but no dose-dependency was observed, making this data inappropriate for assessment as a dioxin effect (see 5 (3)).

Since the immune system is an extremely complex network that is composed of various cell populations and soluble factors, effects of dioxins and related compounds on the immune system will need detailed studies using multiple indices.

⑤ Results of tests related to effects on the male reproductive system

Results on spermatogenesis, which were affected by low body burdens, have been reported by Faqi et al., (1998), Mably et al. (1992c), Gray et al. (1997a) and others. Decreased changes in daily sperm production by the testes and sperms in the cauda epididymis have been noted at body burdens of 27 ng/kg and above (Faqi et al., 1998), 55 ng/kg and above (Mably et al., 1992c), and 86 ng/kg and above (Gray et al. (1997a) (Table 1, Nos. 7, 11, 14). [71, 73]

These changes could be regarded as toxic effects. However, consistency has not been adequately observed with results of other tests related to effects on the male reproductive system, in terms of associations between body burden levels and manifestation of the effects. More specifically, no effects have been observed in the ejaculated sperm counts at these body burden levels but the effects have been reported at 425 ng/kg,[73] and a statistically significant difference in fertility of the offspring from the control group have not even been observed at 860 ng/kg.[72] Moreover, experiments conducted at the National Institute for Environmental Studies under the same conditions as those by Mably et al. did not demonstrate any effect on the daily sperm production by the testes or sperm numbers in the cauda epididymis even at a body burden of 688 ng/kg, although anogenital distance was observed to be shorter at the 43 ng/kg level (Table 1, No. 10) (see 5 (4) ③). [62]

As described above, the relationship between the manifestation of effects on the male reproductive system and body burden levels differ among the endpoints, the test parameters, or the institution that conducted the tests. Accordingly, the minimal body burden that caused the effects should be determined on the basis of comprehensive assessment of multiple related examinations, not on the basis of a particular single experiment.

⑥ Effect of tests related to endometriosis and reduced learning ability of offspring

Technical flaws have been pointed out relating to animal care conditions and other factors in tests which manifested an increased incidence of endometriosis in rhesus monkeys at a body burden of 40 ng/kg (Table 1, No. 9).[74] Accordingly, the reliability of the tests is considered

inadequate as a starting point for directly estimating TDI.

Moreover, although a decrease in scores on a learning ability test was observed in the offspring of the rhesus monkeys at a body burden of 29-38 ng/kg at the same research institution,[76] it appeared to be a mild decrease from which the animals could recover by training (Table 1, No. 8). In this case evaluation was made based on behavioral tests alone; neurochemical, anatomical, or histological examinations were not performed (see 5 (4) ④).

⑦ Results of tests that produced female genital anomalies

Genital anomalies that were observed in the female offspring of rats (Table 1, No. 13)[70] are thought to be significant as toxic endpoints. The test was judged to be valid in terms of dose-dependency and the reliability of the test.

In this test, rats were given 2,3,7,8-TCDD on gestational day 15. Measurements of body burden yielded 97 ng/kg on day 16 and 76 ng/kg on day 21. Since the embryological critical period is thought to be between gestational day 16 and day 21, the value midway between these measurements, 86 ng/kg, is calculated and used as the body burden in the critical period (5 (4) ②).

(4) Human Body Burden

There have been no reports of systematic studies on the relationship between body burden and species differences with regard to toxic manifestations of dioxins and related compounds. However, when results of existing toxicity tests and epidemiological surveys are integrated, it is considered that major differences do not emerge between humans and animals for body burden values that cause toxic effects. A similar argument was made at the 1998 WHO Consultation. In view of the above, this memorandum assumes that the minimal body burden level that produces a certain toxic effect in animal toxicity tests is the minimal body burden level that exerts a toxic effect in humans as well.

(5) Estimation of Human Daily Intake

This memorandum uses the following formula, the same adopted at the WHO Consultation, to estimate the daily intake necessary for humans to reach a certain body burden as a result of life-long exposure:

$$\text{human daily intake} = \frac{\text{body burden} \times \ln 2^*}{\text{7.5-yr half-life} \times \text{50\% absorption rate}}$$

*ln2 = 0.693

(6) Determination of Uncertainty Factors

In order to compensate for uncertainties when calculating the human TDI based on the LOAEL for humans inferred from toxicity test data, it is necessary to apply uncertainty factors.

This memorandum uses an uncertainty factor of 10, after taking the following points into consideration. This is the same value used by the WHO Consultation.

A. This memorandum has been using the LOAEL instead of the NOAEL as the value for the basis of TDI calculations.
B. Since this memorandum uses the body burden when calculating the minimal toxic level in humans, based on section (4) above, species difference elements that arise from pharmacokinetics need not be considered.
C. There are no clear data showing that humans are more sensitive to dioxins and related compounds than experimental animals. In fact, there are data from studies on affinity for the Ah receptor that suggest that humans are less sensitive.
D. Data related to individual differences in toxic manifestations in humans are insufficient.
E. Data are inadequate on the half-life of each of the dioxin congeners.

(7) Derivation of TDI

① Selection of body burden as the basis for calculating TDI

The relation between body burden and manifestation of effects in each of the toxicity experiments is shown in Figure 3. A level of approximately 86 ng/kg is the lowest body burden value just below or above that at which effects are manifested, including female genital anomalies. This is evident by examination of the tests in which effects regarded as clearly toxic are used as endpoints, as discussed in section (3) above. In some toxicity experiments effects have been observed at lower body burden values, but when dose-dependency, reliability, reproducibility, and the toxicological significance of the tests are comprehensively taken into consideration, because the values in each of these tests have relatively low reliability, they are considered inadequate to use as indices for human health effects.

For these reasons, in our judgement it is generally appropriate to use 86 ng/kg as the budy burden for estimating TDI. This view is based on the perspective that body burden as a basis for estimating TDI should be decided after carrying out a comprehensive evaluation of test results, rather than specific numerical values from specific tests, as discussed in section (3) above.

② Report of the WHO Consultation

Based on the results of various toxicity tests, the WHO Consultation set 1-4 pg TEQ/kg/day as the range of TDI values. The daily intake in industrialized countries is 2-6 pg TEQ/kg/day, and subtle effects may be manifested in people of these countries. However, the subtle effects that have been reported do not appear to be overtly adverse effects and other chemical substances may be involved in the effects. Accordingly the WHO Consultation considered the current exposure levels to be tolerable, setting 4 pg TEQ/kg/day as the maximal tolerable intake, while stating that the ultimate goal should be to reduce the human intake levels to less than 1 pg TEQ/kg/day.

The memorandum accepts the conclusions of the WHO Consultation, and it is thought that for the present, the existing exposure conditions in Japan are within the tolerable range.

③ Conclusion on TDI

While some aspects of the human health effects of dioxins and related compounds remain unresolved, it is reasonable to set the provisional TDI for dioxins and related compounds, including co-planar PCBs, at 4 pg TEQ/kg/day (Figure 4). This conclusion is based on current scientific knowledge and an uncertainty factor of 10 applied to the human daily intake of 43.6 pg TEQ/kg/day, which corresponds to a body burden of 86 ng/kg of 2,3,7,8-TCDD.

Since subtle effects have been observed at body burden levels below 86 ng/kg in some toxicity tests, further research is necessary including studies on the toxicological significance of these effects.

(8) Differences from Earlier Methods of Estimating TDI

In both the WHO report of 1990 and Ministry of Health and Welfare report of 1996, the human TDI was calculated by directly applying uncertainty factors to the non-toxic doses in toxicity tests. However, in the WHO report of 1998 and the present memorandum, body burden values are used instead as the basis for calculating the TDI.

When the TDI was calculated from the results of toxicity tests in the past, uncertainty factors were applied empirically, using a standard value of 100. However, this has changed in recent years due to more appropriate methods to estimate risk assessment for humans, with uncertainty factors that recognize species and individual differences, taking into account scientific findings related to the pharmacokinetics and mechanisms of action of test substances. This memorandum also sets the uncertainty factor at 10, after taking new research findings into account.

When making assessments in the past, the results of long-term continuous dosing tests were used as basis for studies. However, in the present assessment, based on the assumption that the manifestation of the principal toxicity of dioxins and related compounds is mediated by binding to the Ah receptor, by using body burden it has become possible to apply the results of single and short-term dosage tests to long-term human exposure to small amounts of dioxins and related compounds. As a result, it is now possible to use body burden as a dose-response index to consider many types of highly sensitive health effect indices in reproductive toxicity tests.

10. Conclusions

(1) Significance of TDI and Points to Bear in Mind

① TDI is an index of life-long exposure.

It should be remembered that the general significance of TDI lies in the fact that it is a value calculated as an index of effects on health when daily intake continues throughout life.

This means that there will be no damage to health even if intake temporarily slightly exceeds the TDI during the course of a person's lifetime, as long as the average intake over the long term is within the TDI.

② TDI is an index of toxicity at times when sensitivity is greatest.

It is important to remember that effects due to exposure in what is considered the most sensitive period, the fetal period, were used as the indices in the dioxin toxicity tests to calculate the TDI shown in this memorandum. Thus, it can be regarded as being on the safe side for use in evaluation of the human population as a whole.

In this connection, manifestation of effects such as carcinogenicity, for example, would occur as a result of higher exposure.

③ TDI uses an uncertainty factor.

Uncertainty factors in the results of the toxicity tests have been applied to the TDI in this memorandum, and allowances have also been made for differences in sensitivity between humans and animals as well as for individual differences.

④ Meals and breast milk

The dioxin exposure is mostly through the diet, and contamination varies according to the type of food. However, it is important to maintain a balanced diet, keeping in mind the nutritional value of each type of food and its beneficial effects on the body.

In addition, while it is necessary to continue research on the effects of the intake by infants of dioxins in breast milk, breast-feeding should continue to be encouraged, judging from its beneficial effects on infants. A similar conclusion was also reached at the WHO Consultation. The results of studies in Japan have shown that the dioxin concentration in breast milk has decreased to less than half of what it was about 20 years ago.

⑤ Decreases in the concentration of dioxin pollution

The mean daily dioxin intake of the Japanese population is currently approximately 2.6 pg TEQ/kg/day, and the decreasing concentration of dioxins and related compounds in breast milk indicates that the exposure level is also decreasing.

Moreover, according to the Basic Guidelines of Japan for the Promotion of the Measures Against Dioxins, the promotion of measures to cut emissions from waste incineration facilities and other efforts will cut dioxin emissions by approximately 90% within the next 4 years compared to 1997 levels. As a result dioxin concentrations in the environment can be expected to decrease considerably.

(2) Promotion of Measures against Dioxins and Related Compounds in the Near Future

① Promotion of measures against dioxins and related compounds

Because the human exposure to dioxins and related compounds in Japan is currently not sufficiently below the new TDI, it is necessary to decrease emissions into the environment in order to decrease dioxins and related compounds in the food chain and reduce the human body burden. Furthermore, since dioxins and related compounds are not chemical substances produced for any useful purpose, but rather are toxic to living organisms and provide no benefits, it is desirable to minimize their intake as much as possible.

It is most important that people who are concerned or dealt with dioxin issues, including national and regional governments, businesses, and the public, promote efforts to reduce dioxin emissions into the environment.

② The need for further research

The current TDI is a provisional estimate calculated on the basis of existing major scientific findings related to dioxins and related compounds.

Many aspects of the effects of dioxins and related compounds on humans remain unknown, and it is important to promote various types of research and studies, including toxicity tests and surveys of effects on humans.

The report of the WHO Consultation states an intention to re-evaluate the TDI in about 5 years. In Japan it will also be appropriate to conduct a re-evaluation on the basis of progress in research and in WHO discussions.

Table 1. Summary of Experimental Results on Low Level Effects of 2,3,7,8-TCDD

No.	Species	Biological Effects	Exposure (LOEL or LOAEL)*		Body Burden ng/kg	Exposure Level for Humans** pg/kg/day	References	***
1	rat	Induction of P450 enzymes	1	Single administration (po)	0.86	0.44	Van den Heuvel et al. (1994)	1
2	marmoset	Altered lymphocyte subsets	0.3	1 administration/week (sc) for 24 weeks, thereafter 1.5 ng/kg/week(sc) for 12 weeks	9	4.56	Neubert et al. (1992)	1
3	mouse	Enhanced viral susceptibility	10	Single administration (po), infection 7days after TCDD administration	9	4.56	Burleson et al. (1996)	1
4	marmoset	Altered lymphocyte subsets	10	Single administration (sc)	10	5.06	Neubert et al. (1990)	1
5	mouse	Induction of P450 enzymes	1.5	5 administrations/week (po) for 13 weeks	20	10.13	DeVito et al. (1994)	1
6	rabbit	Chloracne	4.0	Spread on skin 5 administrations/week for 4 weeks	22	11.14	Schwetz et al. (1973)	1
7	rat	Decreased daily sperm production by testes	25	Single administration (maternal sc), thereafter 5 ng/kg/week (maternal sc) till weaned Start mating 2 weeks after the first administration	27	13.67	Faqi et al. (1998)	1
8	monkey	Object learning	0.151	In mothers diet for20.2 months (po)	29	14.69	Schantz & Bowman (1989)	1
9	monkey	Endometriosis	0.15	In the diet for 4 years (po)	40	20.26	Rier et al. (1993)	1
10	rat	Decreased anogenital distance	50.0	Single administration (maternal po), dissolved in corn oil	43	21.77	Ohsako et al. (1999)	1
11	rat	Decreased daily sperm production by testes	64	Single administration (maternal po), dissolved in corn oil	55	27.85	Mably et al. (1992)	1
12	rat	Immunotoxicity	100	Single administration (maternal po), dissolved in corn oil	86	43.55	Gehrs et al. (1997)	1
13	rat	Anomalis of female genitalia	200	Single administration (maternal po), dissolved in corn oil	86	43.55	Gray et al. (1997)	2
14	rat	Decreased sperm count in cauda epididymis	200	Single administration (maternal po), dissolved in corn oil	86	43.55	Gray et al. (1997)	2
15	mouse	Immunotoxicity	100	Single administration (ip), dissolved in corn oil	100	50.64	Narashimhan et al. (1994)	1
16	monkey	Increased offspring death rate (Decreased offspring viability)	0.76	In the diet for 4 years (po)	202	102.3	Bowman et al. (1989)	1
17	rat	Decreased birth weight	400	Single administration (maternal po), dissolved in corn oil	344	174.2	Mably et al. (1992)	1
18	monkey	Chloracne	1,000	9 administrations in the diet in 4 animals (po), or single administration in 12 animals (po)	500	253.2	McNulty et al. (1985)	1
19	rat	Kidney abnormalities	500	Single administration (sc)	500	253.2	Courtney et al. (1971)	1
20	rat	Increased offspring death rate (Decreased offspring viability)	1,000	Single administration (po)	860	435.5	Gray et al. (1997)	1
21	rat	Delayed pubertal development	1,000	Single administration (po), dissolved in corn oil	860	435.5	Bjerke&Peterson et al. (1994)	1
22	mouse	Cancer	71.4	2 administrations/week (po) for 104 weeks	979	495.7	NTPNo.209(1982)	1
23	rat	Cancer	100	In the diet for 2 years (po)	1710	865.8	Kociba et al. (1978)	1
24	hamster	Decreased birth weight	2,000	Single administration (maternal po), (unidentified)	1720	870.8	Schueplein et al. (1991)	1
25	mouse	Hydronephrosis	3,000	(po) dissolved in corn oil for 30 weeks	2580	1306	Couture et al. (1990)	1
26	rat	Down regulation of EGFR	125	(po) dissolved in corn oil for 30 weeks	3669	1858	Sewall (1993)	1
27	rat	Cancer promotion	125	(po) dissolved in corn oil for 30 weeks	3669	1858	Maronpot et al. (1993)	1

*: po: peroral administration, sc: subcutaneous administration, ip: intraperitoneal administration,

**: Human daily intake on normal condition was calculated on the assumption that a half-life for elimination of 7.5 years and absorption of 50%.
Human daily intake = (body burden *ln2)/(T1/2*absorption rate)

***: 1: Calculated from the exposure condition of original report (assuming the gastrointestinal absorption of dioxins as 50 % for from diet, and 86% for from peroral treatment with corn oil.)
2: Body burden was calculated based on results at gestational day 16 and 21 (Hurst et al., personal communication).

Table 2. Toxic Equivalency Factors (TEF) of Dioxins and Dioxin-like Compounds
Based on the Re-evaluation in 1997 by the WHO Meeting[108]

	Congener	TEF value
PCDD (Polychlorinated dibenzo-*p*-dioxin)	2,3,7,8-TCDD	1
	1,2,3,7,8-PeCDD	1
	1,2,3,4,7,8,-HxCDD	0.1
	1,2,3,6,7,8-HxCDD	0.1
	1,2,3,7,8,9-HxCDD	0.1
	1,2,3,4,6,7,8-HpCDD	0.01
	OCDD	0.0001
PCDF (Polychlorinated dibenzofuran)	2,3,7,8-TCDF	0.1
	1,2,3,7,8-PeCDF	0.05
	2,3,4,7,8-PeCDF	0.5
	1,2,3,4,7,8-HxCDF	0.1
	1,2,3,6,7,8-HxCDF	0.1
	1,2,3,7,8,9-HxCDF	0.1
	2,3,4,6,7,8-HxCDF	0.1
	1,2,3,4,6,7,8-HpCDF	0.01
	1,2,3,4,7,8,9-HpCDF	0.01
	OCDF	0.0001
Co-planer PCB	3,4,4',5-TCB	0.0001
	3,3',4,4',-TCB	0.0001
	3,3',4,4',5-PeCB	0.1
	3,3',4,4',5,5'-HxCB	0.01
	2,3,3',4,4'-PeCB	0.0001
	2,3,4,4',5-PeCB	0.0005
	2,3',4,4',5-PeCB	0.0001
	2',3,4,4',5-PeCB	0.0001
	2,3,3',4,4',5-HxCB	0.0005
	2,3,3',4,4',5'-HxCB	0.0005
	2,3',4,4',5,5'-HxCB	0.00001
	2,3,3',4,4',5,5'-HpCB	0.0001

TEF value: Dioxins and dioxin-like compounds consist of many congeners and the levels of toxicity vary among congeners. Thus the degree of the toxicity of the individual congeners is expressed relative to the toxicity of 2,3,7,8-TCDD, which is assigned a TEF of 1.

Food (Survey on the State of Food Contamination by Dioxins and Related Compounds, by the Ministry of Health and Welfare, 1997)

Food Group	Daily Consumption (National Nutrition Survey) A (g)	Dioxin Concentration B (pg/g)		Dioxin Intake C (pg)		Dioxin Daily Intake per kg Body Weight (pg/kg)
Fish and shellfish	97.0	0.776		75.28		1.506
Meat and eggs	120.0	0.174		20.87		0.417
Milk and dairy products	133.9	0.070		9.42		0.188
Green vegetables	98.9	0.050		4.94		0.099
Cereals, potatoes	166.2	0.025		4.21		0.084
Nonessential foods	182.4	0.007	A X B	1.31	C / 50 kg	0.026
Other vegetables, seaweeds	205.0	0.006		1.23		0.025
Rice	166.5	0.007		1.18		0.024
Sugar and sweets	34.2	0.020	→	0.70	→	0.014
Oils and fats	16.9	0.031		0.53		0.011
Processed foodstuffs	5.5	0.073		0.40		0.008
Beans and processed beans	72.3	0.006		0.40		0.008
Fruits	118.6	0.002		0.21		0.004
Water	600.0	0.00003		0.02		0.0004
Total	2,017.4			120.7		**2.41**

Environment

			Dioxin Daily Intake per kg Body Weight (pg/kg)
Atmosphere	・Atmosphere concentration: 0.55 pgTEQ/m^3 "Monitoring of Hazardous Air Pollutants by Local Governments in 1997" ・Daily intake by respiration: 15 m^3	→	0.17
Soil	・Soil concentration: 22 pgTEQ/g "Comprehensive Pilot Study on Dioxins in 1997" ・Oral daily intake of soil: (Children / Adults) : (150/50) to (200/100) mg/day ・Additional exposures via lungs and skin are also considered.	→	0.0024-0.021
			0.19

Total Dioxin Intake	**2.60 pg/kg/day**

Fig. 1 Daily Intake of Dioxins and Related Compounds in Japan

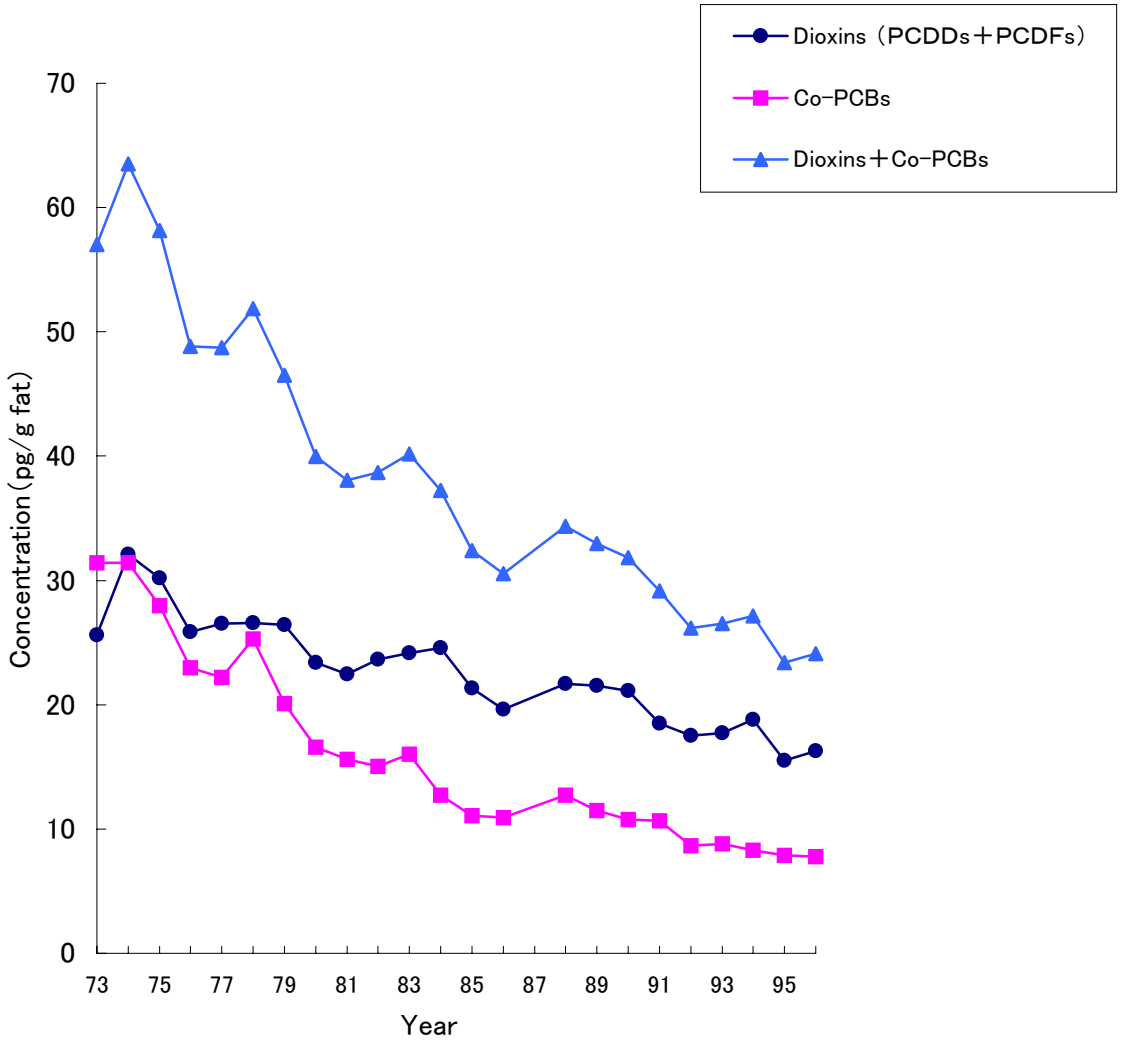
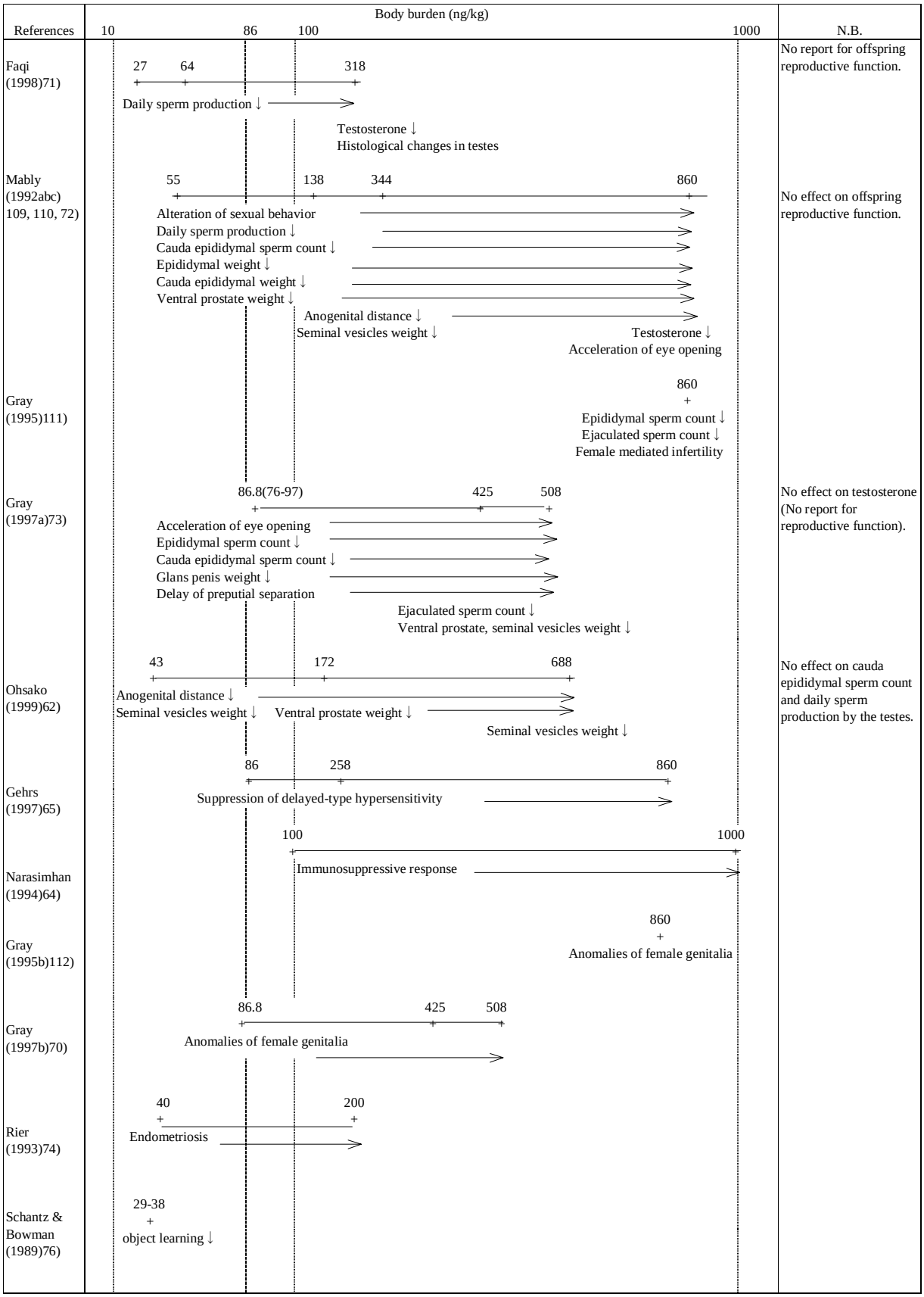


Fig.2 Dioxin Concentration in Breast Milk

Source: Health and Welfare Scientific Study Project in Fiscal Year 1997 Studies on Dioxins in Breast Milk[10] (Ministry of Health and Welfare)



N.B. The effects were observed in offspring of dams exposed to 2,3,7,8-TCDD, except for those reported by Rier (1993) and Narasimhan (1994). The dose dependent effects observed in each experiment are presented in this table.

Fig. 3 Relationships between Body Burden and Effects Observed at Low Levels of Dioxin Body Burden

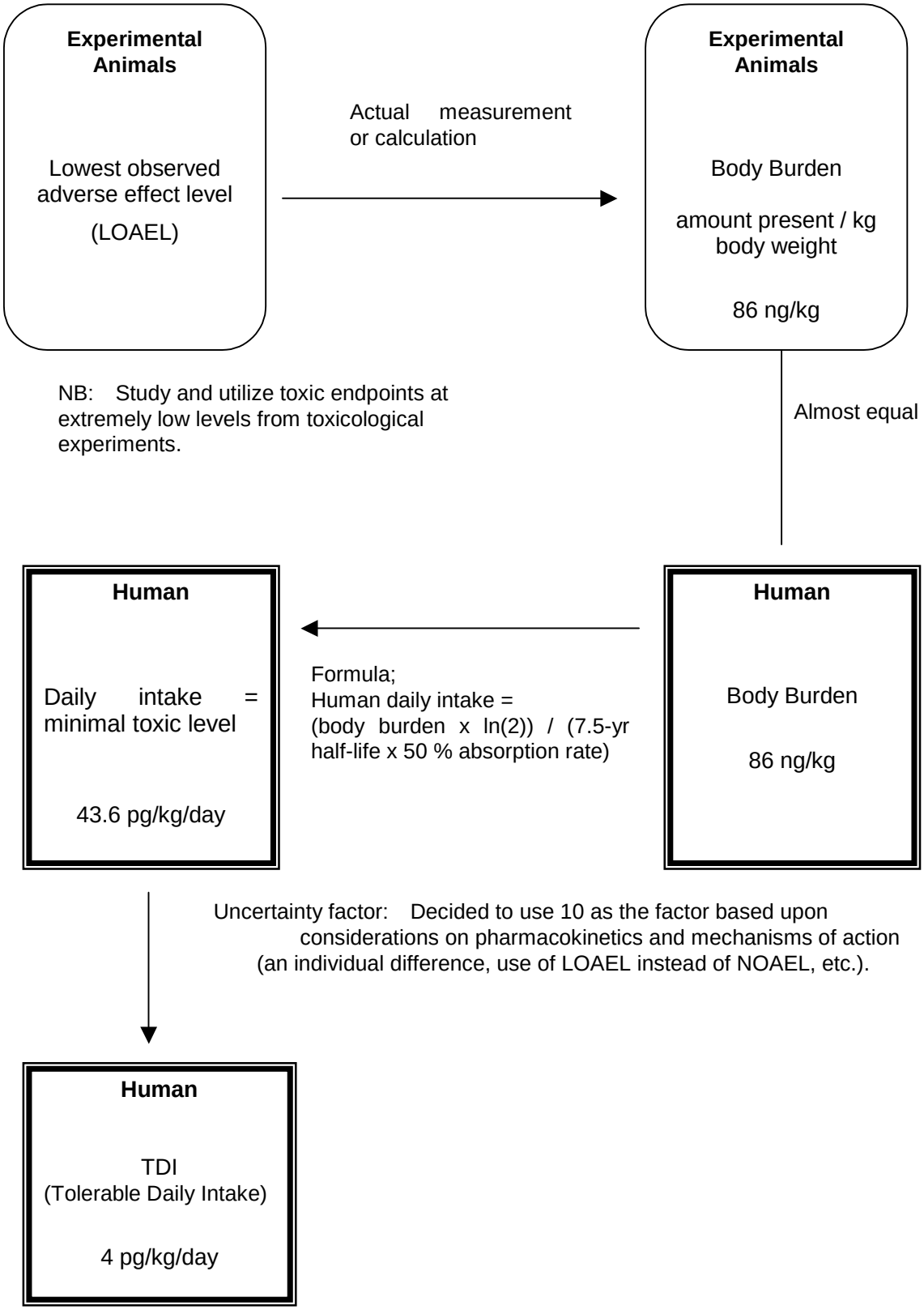


Fig. 4 Establishment of Dioxin TDI by Using Body Burden

Abbreviations

TDI: Tolerable Daily Intake

PCDDs: Polychlorinated dibenzo-*p*-dioxins

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

PeCDD: Pentachlorodibenzo-*p*-dioxin

HxCDD: Hexachlorodibenzo-*p*-dioxin

HpCDD: Heptachlorodibenzo-*p*-dioxin

OCDD: Octachlorodibenzo-*p*-dioxin

PCDFs: Polychlorinated dibenzofurans

TCDF: Tetrachlorodibenzofuran

PeCDF: Pentachlorodibenzofuran

HxCDF: Hexachlorodibenzofuran

HpCDF: Heptachlorodibenzofuran

OCDF: Octachlorodibenzofuran

Co-PCBs: Coplanar polychlorinated biphenyls

EPA: United States Environmental Protection Agency

VSD: Virtually Safe Dose

TEQ: Toxic Equivalents

* The degree of toxicity of the dioxins which are usually present in the form of a mixture of congeners is expressed as the toxic equivalents (TEQ) by multiplying the amount of each congener by its TEF, and adding up the products.

2,4,5-T: 2,4,5-Trichlorophenoxyacetic acid

I-TEF: International Toxic Equivalency Factor

Ah Receptor: Arylhydrocarbon Receptor

* Intracellular receptors with which aromatic hydrocarbons such as dioxins specifically bind, which result in manifestation of toxic effects.

NOAEL: No Observed Adverse Effect Level

*The maximum dose that led to no manifestation of toxicity

LOAEL: Lowest Observed Adverse Effect Level

*The minimal dose that led to manifestation of toxicity

LOEL: Lowest Observed Effect Level

*The minimal dose that led to non-adverse effects

ng: nano gram (billionth of a gram = 10^{-9}g)

pg: pico gram (trillionth of a gram = 10^{-12}g)

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Chronology of Discussions on Tolerable Daily Intake (TDI) of Dioxins

(Living Environment Council and Food Sanitation Investigation Council of Ministry of Health and Welfare, and Central Environment Council of Environment Agency)

1998

(May Dioxin TDI was re-evaluated at the WHO Consultation.)

June 29 In order to re-evaluate the TDI in Japan, the Ministry of Health and Welfare established the Special Committee on Health Impact Assessment of Dioxins under the Living Environment Council and Food Sanitation Investigation Council, and held the first meeting.

November 16 The meeting of the Environmental Health Committee of the Central Environment Council was held and thereupon establishment of the Dioxin Risk Assessment Sub-Committee was decided.

1999

January 28 First Joint Meeting
(The Environment Agency and the Ministry of Health and Welfare previously decided to hold joint meetings of the two Committees noted above in order to discuss re-evaluation of the TDI.)
- Past initiatives of the Environment Agency and the Ministry of Health and Welfare
- WHO Consultation's re-evaluation of the TDI
- Directions of future tasks (Establishment of a Working Group)

February 24 First Working Group Meeting
March 12 Second Working Group Meeting
March 28 Third Working Group Meeting
- Detailed discussions on known scientific literature

March 30 Meeting of Cabinet Ministers on Dioxin Responses adopted the Basic Guidelines of Japan for the Promotion of the Measures Against Dioxins, which required that a conclusion be reached on re-evaluation of the TDI within three months.

April 7 Fourth Working Group Meeting
- Discussions on approaches to calculation of the TDI, etc.

April 14 Second Joint Meeting

・Discussions on approaches to calculation of the TDI, etc.

May 12 Fifth Working Group Meeting

May 24 Sixth Working Group Meeting

・Discussions on assessments of the results of toxicity tests and on the calculation of the TDI.

June 4 Seventh Working Group Meeting

・Discussions on the draft report

June 21 Third Joint Meeting

・Discussions on the draft report

The meetings of the Environmental Health Committee of the Central Environment Council and the Standing Committee of the Food Sanitation Investigation Council followed.

Appendix I

List of Members
Dioxin Risk Assessment Sub-Committee, Environmental Health Committee,
Central Environment Council

Name	Affiliation
Akihiro Igata	Executive Director, Aichi Prefecture Health Promotion Foundation
Masayuki Ikeda	Professor Emeritus, Kyoto University
Iwao Uchiyama	Director, Labor Health Department, National College of Public Health
Masaru Kitano	Professor, The College of Cross-Cultural Communication and Business, Shukutoku University
Masaomi Kondo	Professor Emeritus, Osaka University
Haruhiko Sakurai	Director, Industrial Health Institute, Ministry of Labor
Makoto Shimizu	Professor Emeritus, Tokyo University
Tsuguyoshi Suzuki	Former Director General, National Institute for Environmental Studies
Nobuo Takeda	Professor, Graduate School of Engineering, Kyoto University
Chiharu Tohyama	Director, Environmental Health Sciences Division, National Institute for Environmental Studies
Yuzo Hayashi	Visiting Professor, Department of Pharmacology, Kitazato University
Yoshito Masuda	Professor, Daiichi College of Pharmaceutical Science
Hideaki Miyata	Professor, Faculty of Pharmaceutical Sciences, Setsunan University
Masatoshi Morita	Senior Research Coordinator, Global Environment Research Group, National Institute for Environmental Studies
Mineo Yasuda	Professor, Department of Anatomy, Hiroshima University School of Medicine
Hidetoshi Yoshimura	Professor Emeritus, Kyushu University

Appendix II

List of Members
Special Dioxin Health Effects Evaluation Committee
(Living Environment Council, and Food Sanitation Investigation Council)

Name	Affiliation
Nobuyuki Itoh	President, Nagoya City University
Makoto Ema	Chief of Second Section, Division of Biological Evaluation, National Institute of Health Sciences, Osaka Branch
Gen Ohi	Director General, National Institute for Environmental Studies
Yasuo Ohno	Chief, Pharmacology Department, Biological Safety Testing Center, National Institute of Pharmacy and Food Hygiene
Masuo Ogawa	Technical Advisor, Japan Food Research Laboratories
Yuji Kurokawa	Director, Biological Safety Research Center, National Institute of Health Sciences
Shinichi Sakai	Associate Professor, Environment Preservation Center, Kyoto University
Yuji Taketani	Professor, Medical Department, Tokyo University
Hiroshi Tada	Professor, Medical Department, Toho University
Toshiro Tango	Director of Theoretical Epidemiology, Department of Epidemiology, National Institute of Public Health (Director of Library)
Mitsuo Terao	Director General, National Institute of Health Sciences
Masaaki Terada	President, National Cancer Center
Masatake Toyoda	Director, Food Department, National Institute of Health Sciences
Katsuya Nagata	Professor, Science and Engineering Department, Waseda University
Masataka Hanashima	Professor, Engineering Department, Fukuoka University
Yuzo Hayashi	Visiting Professor, Department of Pharmacology, Kitazato University
Kenji Fujita	Professor, Science and Engineering Department, Saitama University
Yasumoto Magara	Professor, Engineering Department, Hokkaido University
Nobuo Matsuura	Professor, Medical Department, Kitazato University
Hideaki Miyata	Professor, Faculty of Pharmaceutical Sciences, Setsunan University
Mineo Yasuda	Professor, Department of Anatomy, Hiroshima University School of Medicine
Hisashi Yamada	Chief, Environmental Conservation Division, National Research Institute of Fisheries and Environment of Inland sea
Shaw Watanabe	Professor, Tokyo Agricultural University

Appendix III

List of Joint Working Group Members
Dioxin Risk Assessment Sub-committee
the Environmental Health Committee of the Central Environment Council
and
Special Committee on Health Impact Assessment of Dioxins
the Living Environment Council and Food Sanitation Investigation Council

Name	Affiliation
Masayuki Ikeda	Professor Emeritus, Kyoto University
Makoto Ema	Chief of Second Section, Division of Biological Evaluation, National Institute of Health Sciences, Osaka Branch
Yasuo Ohno	Chief, Pharmacology Department, Biological Safety Testing Center, National Institute of Health Sciences
Yuji Kurokawa	Director, Biological Safety Research Center, National Institute of Health Sciences
Chiharu Tohyama	Director, Environmental Health Sciences Division, National Institute for Environmental Studies
Yuzo Hayashi	Visiting Professor, Department of Pharmacology, Kitazato University
Masatoshi Morita	Senior Research Coordinator, Global Environment Research Group, National Institute for Environmental Studies
Mineo Yasuda	Professor, Department of Anatomy, Hiroshima University School of Medicine

Tolerable Daily Intake (TDI) of Dioxins (Summary)

(Summary of the Report by Environmental Health Committee of the Central Environment Council of the Environment Agency, and the Food Sanitation Investigation Council and Living Environment Council of the Ministry of Health and Welfare on June, 1999)

1. Introduction

The Tolerable Daily Intake (TDI) is an important index for establishing sound measures to prevent the effects of dioxins on human health. This report discusses the TDI for dioxins based on the latest available information.

* Dioxin
  - Dioxins
    - Polychlorinated dibenzo-*p*-dioxins (PCDDs)
    - Polychlorinated dibenzofurans (PCDFs)
  - Dioxin-like compounds
    - Co-planar polychlorinated biphenyls (Co-planar PCBs)

2. Outline of the History of TDI

1990	Report of the WHO Consultation at the WHO European Centre for Environment and Health	TDI: 10 pg/kg/day
1996	The Dioxin Risk Assessment Study Group of the Japanese Ministry of Health and Welfare	TDI: 10 pg/kg/day
1997	Dioxin Risk Evaluation Committee of the Environment Agency	Health Risk Assessment Index: 5 pg/kg/day
1998	WHO Consultation held by WHO European Centre for Environment and Health and International Programme on Chemical Safety (IPCS)	TDI: 1 - 4 pgTEQ/kg/day. Maximum tolerable intake level, on a provisional basis, at 4 pgTEQ/kg/day; ultimately less than 1 pg TEQ/kg/day.

3. Exposure Conditions　4. Effects on Humans

	Exposure Conditions	Effects on Humans
General exposure levels	European countries: 2 to 6 pgTEQ/kg/day Japan: 2.6 pg/TEQ/kg/day (both including coplanar PCBs) * Dioxin concentrations in breast milk have dropped to half the level of 20 years ago.	No confirmed manifestations of toxic effects have been reported.
Accidental high exposure levels	* Times Beach (USA), Seveso (Italy), etc. * Occupational exposure in chemical factories	High-level exposures resulted in increased total cancer death rates, chloracne, etc.

5. Effects on Experimental Animals

① Carcinogenicity
② Liver toxicity
③ Immunotoxicity
④ Reproductive toxicity (deformities, effects on reproductive organs, etc.)
⑤ Other effects

6. Pharmacokinetics

① Oral intake and absorption	Absorbed via the gastrointestinal tract, skin, and lungs.
② Distribution in the body	Distributed in blood, liver, muscles, skin, and fat. Accumulated predominantly in liver and fat.
③ Metabolism/Excretion	Difficult to metabolize. Excreted mainly via feces. Large species differences in the rate of excretion.
④ Transfer from mother to offspring	Dioxins transfer from mother to fetus, but concentrations in the fetus are not higher than those in the mother. Transferred to newborns via breast milk.

7. Mechanisms of Toxicity

・Dioxin toxicity is manifested **through binding with Ah receptor that is present in the cell**.
・Humans are regarded as an animal species that has low sensitivity to the toxicity of dioxins.
・The carcinogenicity of dioxins is not caused by direct damage to genes, but rather is thought to be due to their promotional activities on the initiated cells by other possible carcinogens.
・Toxicities not mediated by the Ah receptor exist, but are observed at a higher level of exposure.

8. Toxic Equivalency Factors (TEF) and Toxic Equivalents (TEQ)

① Toxic Equivalency Factors (TEF):

- The degree of the toxicity of the individual congeners is expressed as a factor relative to the most toxic congener, 2,3,7,8-TCDD, the factor of which is set at "1".

② Toxic Equivalents (TEQ)

- The degree of toxicity of the dioxins which are usually present in the form of a mixture of congeners is expressed as the toxic equivalents (TEQ) by multiplying the amount of each congener by its TEF, and adding up the products.

③ It is now considered valid to calculate TEQ based on **the latest TEF re-evaluated by the WHO** in 1997[108].

- The dioxin congeners which are thought to have toxicities and have been given TEF values at present consist of 7 PCDDs, 10 PCDFs, and 12 co-planar PCBs.

9. Estimation of TDI

① Basic Approach (Same as Adopted by the WHO)

(a) Since dioxins are **not thought to have direct genotoxicity**, methods that apply the no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL) are used to calculate the TDI, and an uncertainty factor is applied.

(b) When discussing the relationship between chemicals and their effects, when the chemicals are known to bioaccumulate and to exhibit large differences among animal species in the degree of bioaccumulation, **body burden is a more appropriate measure** than daily intake.

(c) TDI is estimated from toxicity tests, in which toxic responses are observed by the lowest body burden, after **taking into consideration the endpoints in terms of toxicological significance, dose-dependency, and the reliability and reproducibility of the various tests.**

(d) When estimating TDI values for humans based on results of toxicity tests on animals, an "uncertainty factor" was adopted to compensate for the uncertainties caused by various factors.

② Body Burden in Various Toxicity Tests

Effects	Body burden levels in animal tests	Evaluation
① Induction of drug-metabolizing enzymes	0.86 ng/kg (rat) 20 ng/kg (mouse)	Regarded as an adaptive reaction of the body.
② Changes in lymphocyte composition	9 ng/kg (marmoset) 10 ng/kg (marmoset)	Composition ratios at low doses were reversed at high doses.
③ Chloracne	4.0 ng/kg (rabbit)	Effects of topical exposure are not appropriate to calculate body burden level. Human data available to date have priority.
④ Immunotoxicity	86 ng/kg (rat) 100 ng/kg (mouse)	Seen as toxic effects. Since the immune system is complex, detailed studies using multiple indices are needed.
⑤ Effects on the male reproductive system	Changes such as decreased spermatid or sperm counts have been reported at body burden levels equal or more than 27 ng/kg, 55 ng/kg, and 86 ng/kg. However, there is a report that failed to find the effect at 688 ng/kg. Decreased ejaculated sperm counts in semen were reported at 425 ng/kg. Statistically significant difference in fertility was not seen at even 860 ng/kg. (rat)	The relationships between the manifestation of effects on the male reproductive system and body burden levels differ among endpoints, among test parameters, or among institutions that conducted the tests. Accordingly, the lowest body burden level that caused the effects should be determined on the basis of comprehensive assessment of multiple related examinations, not on the basis of a particular single experiment.
⑥ Endometriosis	40 ng/kg (rhesus monkey)	Reliability of tests is not sufficient.
⑦ Lower cognitive and behavior test scores	29-38 ng/kg (rhesus monkey)	Subtle decrease, and recoverable by training. Evaluation made based on behavioral tests alone.
⑧ Female genital anomalies	86 ng/kg (rats)	Thought to be a toxic effect. Dose-dependency and the test reliability judged valid.

③ Estimation of Human Daily Intake

The daily intake necessary for humans to reach a certain body burden as a result of life-long exposure was estimated using the same formula as the one adopted by the WHO.

④ Determination of Uncertainty Factor

After consideration of various factors, an uncertainty factor of 10 was adopted, which is the same as the one used by the WHO.

⑤ Derivation of TDI

- **After a comprehensive evaluation of test results, it was judged generally appropriate to use 86 ng/kg as the body burden for the basis for estimating TDI.**

・The WHO Consultation set 1-4 pg TEQ/kg/day as the TDI values. The Consultation, judging that the current exposure levels in industrialized countries are tolerable, set the TDI at 4 pg TEQ/kg/day, on a provisional basis, as the maximal tolerable intake, while stating that the ultimate goal should be to reduce it to less than 1 pg TEQ/kg/day. It is thought that for the time-being, **the existing exposure conditions in Japan are within the tolerable range.**

・Taken together, **it is reasonable to set the provisional TDI for dioxins at 4 pgTEQ/kg/day, based on the calculation of the daily intake for humans using the body burden of 86 ng/kg and the uncertainty factor of 10.**

・Since **subtle effects have been observed at body burden levels below 86 ng/kg in some toxicity tests, research should be conducted further**.

10. Conclusions

(1) Significance of TDI and Points to Bear in Mind

① **TDI is a value calculated as an index of health effects when daily intake continues throughout life.**

→Accordingly, temporary slight excess of intake over TDI does not necessarily mean damage to health.

② For setting up this TDI, endpoints due to exposure during **the fetal period, which is thought to be the most sensitive period, were used**.

→Thus, it is thought that the TDI is based on the safe side for the human populations as a whole. In this connection, manifestation of effects such as carcinogenicity, for example, would occur as a result of higher exposure.

③ **An uncertainty factor is incorporated for the TDI.**

→The uncertainty factor used here takes account of the differences in sensitivity among individuals.

④The dioxin exposure is mostly through the diet and **it is important to maintain a balanced diet**, keeping in mind the nutritional value of each food item.

In addition, breast-feeding should be encouraged due to its beneficial effects on newborns, while it is necessary to continue research on the effects of the intake by infants of dioxins in breast milk.

⑤It is considered that **the exposure level to dioxins has decreased in Japan, as** indicated by the decreasing concentration of dioxins in breast milk to less than half the level of about 20 years ago.

Moreover, since the government plans to reduce dioxin emissions by approximately 90% within the next 4 years, the dioxin concentrations in the environment **can be expected to decrease considerably**.

(2) Future Measures

① Promotion of measures against dioxins

・Because **the current exposure level to dioxins in Japan is not sufficiently below the new TDI** , it is necessary to decrease emissions of dioxins into the environment.

・Furthermore, since dioxins are harmful and not beneficial to living organisms, it is **desirable to minimize the intake level as much as possible**.

・It is important for people who are concerned or deal with dioxin issues to promote efforts to reduce dioxin emissions into the environment,

② The need for further research

・The new TDI level is a provisional estimate calculated on the basis of existing scientific findings.

・Since there are so many unclear matters about the effects of dioxins on humans, it is important to promote research and investigations on various aspects.

・ It will be appropriate to review these conclusions again according to progress in research and investigations, and the situation of WHO re-evaluations.

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