

Dioxins: Recommendation for a Tolerable Monthly Intake for Australians

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FOREWORD

Dioxins are a group of chemicals that are highly persistent in the environment, and can become absorbed into the body fat of animals. If exposure to dioxins is sufficiently extensive, these chemicals can cause a range of toxic effects in animals and humans, including skin lesions, reproductive disorders and cancer.

In the 2001-2002 Federal Budget, the Commonwealth Government announced funding for a National Dioxins Program (NDP) to be conducted over four years by the Department of the Environment and Heritage (Environment Australia). The NDP will be implemented in three phases. In the first phase, relevant federal government agencies are undertaking monitoring programs to determine whether dioxins and related compounds are present in the environment and in certain agricultural commodities. Phase Two of the NDP will use the findings of Phase One to assess the potential risks to human health and the environment arising from exposure to dioxins. Finally, the third phase will use the Phase Two risk assessment to develop national management strategies to reduce, and where feasible to eliminate, the release of dioxins in Australia.

As part of the Phase One monitoring programs and their reporting, Environment Australia (EA) and Agriculture, Fisheries and Forestry – Australia (AFFA) sought advice from the Department of Health and Ageing on establishing a tolerable intake for dioxins and related compounds. The Therapeutic Goods Administration (TGA)¹ prepared a draft report which was forwarded to NHMRC for consideration. It was agreed that an Australian guideline value established through the NHMRC process would ensure national acceptability.

The report underwent public consultation processes under the auspices of NHMRC and, following minor revisions, was subject to external review before finalisation. The authors and working party took into consideration the reviewers' comments and the document was edited accordingly.

The proposal for a tolerable intake made in this report is based on the deliberations of:

- (i) the consultation between technical experts representing the World Health Organization European Centre for Environmental Health (WHO-ECEH) and the International Programme on Chemical Safety (IPCS) in May 1998;
- (ii) the outcome of the meeting of the European Community Scientific Committee on Food (EC-SCF) on the risk assessment of dioxins and dioxin-like polychlorinated biphenyls (PCBs) in food, in May 2001; and
- (iii) the outcome of the Food and Agriculture Organization of the United Nations (FAO)/WHO Joint Expert Committee on Food Additives (JECFA) evaluation of dioxins, at its 57th meeting in June 2001.

¹ The TGA is a business unit of the Department of Health and Ageing.

The proposed tolerable intake is a human health reference value based on the toxicological effects of dioxins and related compounds in animals and humans, following known exposures. Establishing a tolerable intake for dioxins is part of a continuing risk assessment process in Australia. The tolerable intake value is not a measure of human exposure to dioxins, and it should not be used as an action level for dioxins in food or the environment. Rather, it is a level of tolerable intake, against which estimated human exposure from all sources combined should be compared.

The recommendations made in this paper will contribute to the development of national management strategies that, subject to the outcomes of the risk assessment, could include standards or guidelines for emission of dioxins and for acceptable levels of dioxins in the environment. Other risk management measures may be implemented, such as use of appropriate waste disposal or remediation technologies and introduction of economic instruments to effect reductions in dioxin emission. When considering the adoption of management strategies, the government will take due account of the costs and benefits associated with these measures. Hence, this paper does not include an analysis of whether any economic impact will arise from promulgation of the proposed tolerable intake level, as this issue will be addressed in Phase Three of the National Dioxins Program.

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I INTRODUCTION

What are dioxins?

The term 'dioxins' is used to describe a group of environmentally persistent halogenated aromatic hydrocarbon chemicals that includes polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polybrominated dibenzodioxins (PBDDs), polybrominated dibenzofurans (PBDFs) and polychlorinated biphenyls (PCBs). PCDDs, PBDDs, PBDFs and PCDFs are not manufactured intentionally but are byproducts of combustion. They are formed naturally by volcanoes and forest fires, as well as by industrial processes such as waste incineration and the synthesis of certain chemicals. PCBs, on the other hand, were manufactured for approximately 50 years for use as components of insulating fluids in transformers and other electrical equipment.

The potential toxicity of dioxins began to be recognised some 40 years ago. Concern over the potential adverse effects of dioxins has been amplified by evidence that they are resistant to metabolism and tend to remain in the body fat of animals and humans for a long time. The different structurally related chemicals (referred to as congeners) that make up the dioxins have half-lives that vary from 3.7 years for the least persistent type to 50 years for the most persistent, with an average half-life of approximately 7 years.

Toxic equivalency factors

When found in the environment, biological tissues and industrial sources, dioxins are usually present as complex mixtures; this complicates risk assessment because the different congeners vary significantly in their toxicity. However, the potency of different dioxins can be ranked relative to 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD), the most toxic member of the dioxin class. These rankings are known as toxic equivalency factors (TEFs). To be included in the TEF scheme, a compound must be structurally related to PCDDs and PCDFs, bind to the cellular aryl hydrocarbon (*Ah*) receptor, elicit *Ah* receptor-mediated biochemical and toxic responses, must be persistent, and accumulate in the food chain (WHO 1998).

The most recent review of TEFs was that of the WHO in 1998 (Van den Berg et al 1998). This review has subsequently been recognised by the United States Environmental Protection Agency (US EPA) as being the most appropriate scheme for estimating the toxicity of dioxin mixtures (EPA 2000). Under the WHO TEF scheme shown in Table 1, TCDD is assigned a TEF of 1.0, and other PCDDs, PCDFs and PCBs have TEF values ranging from 1.0 down to 0.00001. To estimate the toxic potency of a given dioxin mixture, the mass concentration of each individual component is multiplied by its respective TEF, and the products are summed to represent the TCDD toxic equivalence (TEQ) of the mixture. Throughout this document, the intake of dioxins will be expressed in units of TEQs, applying the 1998 WHO TEFs, unless they were derived using the previous international TEF scheme (EPA 1989), which is abbreviated as I-TEQ.

The database on many of the polybrominated compounds has been less extensively evaluated, and these compounds have not been assigned TEFs by the WHO. Consequently, polybrominated compounds have not been explicitly considered in this assessment, which focuses on PCDDs, PCDFs and PCBs. Evaluation of the most common chlorinated congeners is generally considered to be sufficient to characterise environmental dioxins. PBDDs and PBDFs could be included in future assessments if sufficient information becomes available and inclusion is considered desirable on toxicological grounds.

Recently, it has been recognised that in addition to synthetic halogenated aromatic hydrocarbons, there are a number of quite potent natural compounds that can interact with the *Ah* receptor. These include indole-3-carbinol (IC3) and related compounds from cruciferous vegetables. Polycyclic aromatic hydrocarbons (PAHs) and other aromatic amines formed during cooking can also interact with the *Ah* receptor, and may further complicate risk assessment (Safe 1998). However, it is still unknown whether these compounds exert a significant influence on the toxicity of dioxins, and their possible effects cannot be assessed at present.

Table 1 WHO TEFs for human risk assessment

Congener	TEF value	Congener	TEF value
<i>Dibenzo-p-dioxins</i>		<i>Non-ortho PCBs</i>	
2,3,7,8-TCDD	1	PCB 77	0.0001
1,2,3,7,8-PnCDD	1	PCB 81	0.0001
1,2,3,4,7,8-HxCDD	0.1	PCB 126	0.1
1,2,3,6,7,8-HxCDD	0.1	PCB 169	0.01
1,2,3,7,8,9-HxCDD	0.1		
1,2,3,4,6,7,8-HpCDD	0.01		
OCDD	0.0001		
<i>Dibenzofurans</i>		<i>Mono-ortho PCBs</i>	
2,3,7,8-TCDF	0.1	PCB 105	0.0001
1,2,3,7,8-PnCDF	0.05	PCB 114	0.0005
2,3,4,7,8-PnCDF	0.5	PCB 118	0.0001
1,2,3,4,7,8-HxCDF	0.1	PCB 123	0.0001
1,2,3,6,7,8-HxCDF	0.1	PCB 156	0.0005
1,2,3,7,8,9-HxCDF	0.1	PCB 157	0.0005
2,3,4,6,7,8-HxCDF	0.1	PCB 167	0.00001
1,2,3,4,6,7,8-HpCDF	0.01	PCB 189	0.0001
1,2,3,4,7,8,9-HpCDF	0.01		
OCDF	0.0001		

Note: TEFs are based on the conclusions of the WHO meeting in Stockholm, Sweden, 15-18 June 1997 (Van den Berg et al, 1998).

2. EXPOSURE STANDARDS AND MAXIMUM LEVELS FOR DIOXINS

A number of national regulatory agencies have established human exposure standards for dioxins, generally referred to as tolerable daily or weekly intakes. Current or proposed tolerable daily intakes (TDIs) range from 1 pg TCDD/kg bodyweight (bw) (the Netherlands and Germany), through 4 pg/kg bw (Japan), 5 pg TCDD/kg bw (Sweden, Norway, Finland and Denmark), to 10 pg TCDD or TEQs/kg bw (UK, New Zealand and Canada) (Larsen et al 2000).

In 1990, a WHO expert meeting recommended that the TDI for TCDD be set at 10 pg/kg bw on the basis of a no-observable-effect level (NOEL) of 1 ng/kg bw/day for the appearance of precancerous liver lesions, reproductive effects and immunotoxic effects in experimental animals (WHO 1991). The meeting decided not to apply the commonly used safety factor approach to determine the TDI. Instead, it calculated the level of daily intake of TCDD that would lead to a concentration of TCDD in the human liver, after 70 years of exposure, of 540 parts per trillion (ppt) or 540 ng/kg tissue. This figure was the amount of TCDD measured in the liver of rats fed 1 ng/kg bw/day for two years (Kociba et al 1978). The intake was estimated to be 110 pg TCDD/kg bw/day, assuming steady state conditions, an elimination half-life of 7 years in humans and a liver-to-adipose tissue ratio of 0.15. Thus, in humans, the same liver tissue concentration would be reached after a lifetime daily dose of about 1/10 the daily dose for rats. This method gave the same result as using a safety factor of 10 to extrapolate from rats to humans. An additional safety factor of 10 was applied to account for potential differences in the susceptibility of the target organs and the inadequate database on reproductive effects in humans. (WHO 1991, Larsen et al 2000).

The then NHMRC Standing Committee on Toxicology contracted the production of a national assessment on dioxins in 1992. The report was reviewed in draft form by the Environmental Health and Nutrition Standing Committee in 1994–95. The report proposed a limit of 10 pg TCDD/kg bw/day. However, this TDI value was never promulgated for a number of reasons, including the fact that the US EPA published a draft report in 1994 (EPA 1994) recommending a considerably lower limit.

Some national governments have set maximum levels (MLs) for dioxins in certain food commodities. These are summarised in Table 2, over page.

Table 2 Maximum levels for dioxins in food commodities

Country	Maximum or provisional maximum levels (pg WHO-TEQ/g fat)
Austria	2 (pork), 3 (milk), 5 (poultry/eggs) and 6 (beef)
Belgium	3 (pork and derived products) and 5 (milk, bovine, poultry, animal fats and oils, eggs and derived products (if >2 per cent fat))
France	5 (milk and dairy products)
Germany	<0.9 (milk and dairy products) ^{a, b}
Luxembourg	2 (pork), 3 (milk), 5 (poultry/eggs) and 6 (beef)
The Netherlands	6 (dairy products and foods with milk or dairy products as ingredients)
Spain	>5 (dairy products)

Source: CAC 2001

^a This is a proposed desirable target level. At levels exceeding 3 pg I-TEQ/g fat, measures to reduce exposure would be undertaken, and at levels above 5 pg I-TEQ/g fat, trade would be prohibited.

^b pg I-TEQ/g fat for PCDDs and PCDFs

The United Kingdom has a guideline level of 0.66 ng WHO-TEQ dioxins and PCBs/kg whole milk (16.6 ng WHO-TEQ/kg fat) for cow's milk. In Sweden, the National Food Agency has advised that women of a fertile age should not consume fatty fish from the Baltic Sea more than twice a month because of contamination with dioxins (Larsen et al 2000).

3. RECENT INTERNATIONAL DEVELOPMENTS IN THE RISK ASSESSMENT OF DIOXINS

Comprehensive risk assessments of dioxins have been performed during the last several years by the International Agency for Research on Cancer (IARC), US EPA, EC-SCF, WHO-ECEH and JECFA. These assessments incorporate the latest advances in research on molecular biology, animal toxicity and epidemiology in exposed human populations.

Assessment by the IARC

In 1997, the IARC classified TCDD as ‘carcinogenic to humans’ (Group 1). The IARC’s decision was based primarily on evidence in four groups of highly-exposed industrial workers. IARC also took into consideration the following supporting evidence:

- there was ‘sufficient evidence’² that TCDD was carcinogenic at several sites in experimental animals (acting via the cellular aryl hydrocarbon (*Ah*) receptor, which is present in and functions the same way in humans and laboratory species)
- there were studies showing that the concentrations of TCDD in tissues from rats exposed to carcinogenic dosage regimens in bioassays are similar to those found in the tissues of heavily-exposed human populations with an apparent increased risk of cancer (IARC 1997).

A follow-up study (Steenland et al 1999) on the largest of the industrially-exposed groups confirmed that TCDD exposure results in an increased incidence of cancer when all cancers are combined. However, the increased cancer incidence did not show any marked tissue specificity, and was limited to the most highly exposed workers. These workers were likely to have been exposed to levels that were 100–1000 times higher than those experienced by the general population, and were similar to the TCDD doses used in animal studies.

Assessment by the US EPA

The principal finding of the US EPA’s most recent report (EPA 2000) was that although dioxins can initiate biochemical and biological events potentially leading to a range of cancer types and non-cancer effects in animals and humans, *‘there is currently no clear indication of increased disease in the general population attributable to dioxin-like compounds.’* However, the US EPA stated that the lack of a clear indication of disease could not be taken as evidence that dioxins were having no effect. The report suggested that current data and scientific tools may be unable to detect effects. The EPA did not recommend a

² IARC usually applies the criterion of ‘sufficient evidence of carcinogenicity’ when a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

reference dose³ (RfD) for dioxins, reasoning that any RfD estimated using its established quantitative risk assessment methodology (on the basis of a 1×10^{-6} excess risk), would probably be 100–1000 times below current human intakes and body burdens. Hence, the EPA review has not produced an exposure standard for humans that could be considered for adoption by Australia.

Assessment by the WHO-ECEH, the EC-SCF and JECFA

The WHO-ECEH has been coordinating a program on dioxins, in collaboration with the IPCS. The program is aimed at evaluating the possible health risk, and prevention and control of environmental exposure of the general population to these chemicals. WHO-ECEH and IPCS jointly organised a consultation entitled *Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI)*. The meeting was held in May 1998 in Geneva, and was attended by 40 experts from Australia⁴, Belgium, Canada, Denmark, Finland, Germany, Italy, Japan, The Netherlands, New Zealand, Spain, Sweden, the United Kingdom and the United States (WHO 1998; van Leeuwen et al 2000).

In 2001, the EC Scientific Committee on Food (EC-SCF) also assessed the risk of dioxins (EC Health and Consumer Protection Directorate-General 2001). The EC-SCF is responsible for advising the EC on scientific and technical questions concerning the safety of food, and its advice is used as a basis for EC rules on consumer health and food safety, toxicology and hygiene in the food production chain.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated dioxins at its 57th meeting in Rome, in June 2001 (FAO/WHO 2001).⁵ JECFA serves as the scientific advisory body to the Codex Alimentarius Commission (CAC) on matters relating to food additives, contaminants, and residues of veterinary drugs in food. The CAC sets international food standards aimed at protecting the health of consumers and facilitating international trade in foods.

The following information is taken mainly from the findings of the meetings of the 1998 WHO-ECEH/IPCS consultation, EC-SCF and JECFA.

Exposure

Exposure of the general public to dioxins is predominantly through the diet, with food from animal origin being the major source. Based on measured concentrations of dioxins, furans and PCBs in food, and data on national food consumption, the 2001 JECFA evaluation estimates that median long-term intakes

³ A RfD is a health risk goal below which there is likely to be no appreciable risk of noncancer effects over a lifetime of exposure. The RfD concept is ostensibly equivalent to an acceptable daily intake (ADI) or tolerable daily intake (TDI).

⁴ The Australian participant was Professor Michael Moore, NHMRC National Research Centre for Environmental Toxicology (NRCET), Brisbane.

⁵ The Australian delegate to the 57th meeting of the JECFA was Dr Peter Abbott, Australia New Zealand Food Authority, Canberra, ACT.

of PCDDs and PCDFs are 33–42 pg TEQ/kg bw/month for an adult living in the United States or Western Europe. Estimates for New Zealand and Japan derived from measured concentration and food supply data were significantly lower, at 18 and 7 pg TEQ/kg bw/month, respectively.⁶ If dioxin-like PCBs are also included, the daily total TEQ intake increases by about 25 per cent in the United States and is approximately doubled in other regions. Recent studies from countries that started to implement measures to reduce dioxin emissions in the late 1980s, such as the Netherlands, UK and Germany, clearly show that dioxin levels in food have decreased, with a consequent reduction in dietary intake of these compounds by a factor of almost 2 over the past 7 years (WHO 1998). In Canada, regulatory and guideline initiatives have markedly reduced PCDD and PCDF emissions from waste incinerators and bleached craft pulp mills, with consequent declines in the concentrations of these chemicals in fish and shellfish (Larsen et al 1998). Similar measures have been undertaken in other countries, including Australia.

The daily intake of dioxins for breastfed babies is 1–2 orders of magnitude higher than that for adults. The latest WHO field study showed that mean levels of PCDD/PCDF and PCB in human milk were higher in industrialised areas (10–35 pg I-TEQ/g milk fat) than in developing countries (<10 pg I-TEQ/g milk fat) (WHO 1996). However, there is clear evidence of a decrease in PCDD/PCDF levels in human milk between 1988 and 1993, with the highest rates of decrease in areas with the highest initial concentrations (WHO 1996).

Mechanism of toxicity

The *Ah* receptor is important in mediating the biological and toxicological effects of TCDD and dioxin-like compounds. Although the precise chain of molecular events is not fully understood, alterations in key biochemical and cellular functions are likely to be responsible for dioxin toxicity. Activation of the *Ah* receptor has two major consequences: increased transcription of various genes (eg those coding for drug-metabolising enzymes) and immediate activation of tyrosine kinases. The *Ah* receptor may also regulate expression of other networks of genes, either directly or indirectly. Activation of the *Ah* receptor can result in endocrine and paracrine disturbances, and alterations in cell functions, including growth and differentiation. Some of these effects have been observed both in humans and animals, indicating the existence of common mechanisms of action in different species. Some of the ligands that bind the *Ah* receptor may block its activation by behaving as weak agonists, or antagonists. This means that binding of the *Ah* receptor by some members of the dioxin class could conceivably block the action of other, more toxic congeners, complicating the risk assessment of dioxin mixtures.

⁶ The New Zealand and Japanese estimates may be higher than the true intake, as food *supply* exceeds food *consumption* by at least 15 per cent.

Kinetics of dioxins and the concept of body burden

The fate of dioxins in the body is unusual, primarily because most of the congeners are extremely fat soluble but are practically insoluble in water. Following ingestion and absorption from the small intestine, dioxins are readily distributed via the blood to all organs, but they are preferentially retained in adipose (fatty) tissue. The release of stored dioxins from adipose tissue into the circulation is extremely slow, limiting the rate of metabolism by the liver and subsequent excretion in the faeces via the bile. Hence, the time to excrete half of an ingested dose of dioxins (the half-life) is usually measured in years. As discussed earlier, dioxins are composed of a mixture of compounds and each has a different half-life, but the commonly quoted average in humans ranges between 7 and 10 years (based on data from Seveso).

The long half-life of dioxins means that, over decades, even a low rate of exposure leads to accumulation of dioxins in the body. Continual exposure from contaminated food might lead in the long term to an extremely high body burden (ie the total amount of dioxins in the body). Therefore, it is important to minimise the levels of dioxins in food. The capacity of humans to store dioxins in fat is so great that it would be expected to take 40–50 years to reach a balance or steady state, where the rate of intake equals the rate of excretion. Thus, a few exposures that exceeded the accepted dietary limit by ten- or even a hundred-fold would not significantly change a body burden accumulated over several decades. A single dose of dioxins of 5000 pg or a lifelong intake of around 1 pg/day would result in a similar body burden.

The biochemical and toxicological effects of dioxins, furans and PCBs relate more closely to their concentration in the target tissue than to the daily dose. Dioxins accumulate in vital organs; therefore, it is difficult to directly measure the concentration in particular tissues, except at post-mortem. However, the body burden of dioxins correlates strongly with levels in adipose tissue and serum, and can therefore be readily estimated by measuring dioxin levels in adipose tissue or serum, or estimated from the ingested dose. Also, data on body burden integrates the differential half-lives between species. Therefore, the consultations by the WHO, the EC-SCF and JECFA concluded that the body burden is the measurement of choice for comparing risks between humans and animals. JECFA concluded that the appropriate averaging period for evaluating intake of these compounds is one month or more, whereas the EC-SCF favoured an interval of one week.

Animal data

The adverse effects reported in animals following exposure to dioxins include immunotoxicity, endometriosis in Rhesus monkeys, and developmental effects in rats (including reproductive toxicity in males and urogenital malformations in females). The animals most sensitive to dioxin-induced adverse effects were the male offspring of Wistar rats (Faqi et al 1998). In this study, dams received an initial loading dose of 25, 60 or 300 ng ¹⁴C-TCDD/kg bw two weeks prior to mating, followed by weekly maintenance doses of 5, 12 or 60 ng/kg bw

throughout mating, pregnancy and lactation. These maintenance doses were intended to prevent the maternal body burdens from declining below 20, 48 and 240 ng/kg bw, respectively, assuming an elimination half-life of three weeks for TCDD in adult rats. The study failed to demonstrate a NOEL because decreased sperm production and feminised sexual behaviour were observed in male offspring of the lowest dose group at 70–170 days of age. By reference to toxicokinetic data in pregnant rats (Hurst et al 2000a, 2000b), the EC-SCF estimated a maternal steady-state TCDD body burden of 39 ng/kg bw in dams at lowest dose, which was taken as the LOEL. JECFA applied linear and nonlinear curve fitting to the same data, and arrived at maternal steady-state body burden estimates of 25 and 39 ng/kg bw, respectively.

The lowest NOEL was found in a reproduction study by Ohsako et al (2001), in which Holtzman rats received a single oral dose of 0, 12.5, 50, 200 or 800 ng TCDD/kg bw on the 15th day of pregnancy (GD 15). Male offspring displayed reduced anogenital distance and androgen receptor mRNA levels in the ventral prostate at the LOEL of 50 ng/kg bw. The NOEL was 12.5 ng/kg bw. Assuming that 60 per cent of a single gavage dose was retained in the body at GD 16, the NOEL of 12.5 ng/kg bw and the LOEL of 50 ng/kg bw would result in maternal body burdens of 7.5 and 31 ng/kg bw, respectively. By reference to toxicokinetic data in pregnant rats (Hurst et al 2000a, 2000b), JECFA estimated a maternal body burden of 13–19 ng/kg bw at the NOEL, with a corresponding estimate of 51–76 ng/kg bw at the LOEL.

TCDD is carcinogenic in several species at multiple sites. However, short-term studies have shown a lack of direct DNA-damaging effects, indicating that TCDD is not an initiator of carcinogenesis. Tumour promotion studies in various animal species indicated a nongenotoxic mechanism. Also, the ability of TCDD to enhance proliferation and inhibit apoptotic processes in focal hepatic lesions further supports an indirect mechanism of carcinogenicity. The WHO consultation noted that the NOEL of TCDD for hepatic adenomas in a 2-year study in rats was 1 ng/kg bw/day (WHO 1996), at which dose the body burden was 60 ng/kg bw.

Human data

Epidemiological evidence from the most highly TCDD-exposed cohorts studied produces the strongest evidence of an increased cancer risk from exposure to dioxins, when the data is considered for all cancers combined. There is weaker evidence of an increased cancer risk when the data for cancers at particular sites is considered. However, the general population is exposed to levels of dioxins several orders of magnitude lower than those experienced by individuals in an industrial setting, or by the general population during the accidental exposure at Seveso.

The incidence of adverse health endpoints other than cancer was also evaluated among groups exposed to dioxins, dioxin-like and nondioxin-like polychlorinated aromatic compounds in a variety of exposure scenarios. For children exposed *in utero*, postulated adverse health effects include subtle

developmental delays and thyroid hormone alterations. Of the many health effects evaluated in exposed adult populations, many were transient and not observed when exposure ceased. Epidemiological data indicate that some conditions (eg alterations in metabolic parameters and mortality from cardiovascular and nonmalignant liver disease) may be increased in the exposed populations compared to the unexposed referent groups.

4. CONCLUSIONS FROM THE WHO CONSULTATION (1998)

In assessing the risk from dioxin-like compounds, the consultation focused on the most sensitive adverse effects (hormonal, reproductive and developmental effects) that are observed at low doses in animal studies. These effects occur at body burdens in rats and monkeys in the range of 10–50 ng/kg bw.

Human daily intakes that would lead to body burdens similar to those associated with adverse effects in animals were estimated to be in the range of 10–40 pg/kg bw/day. Since body burdens were used to scale doses across species, the consultation concluded that it was not necessary to use an uncertainty factor to account for toxicokinetic differences between species. However, the estimated human intake was based on LOELs and not on NOELs. In addition, uncertainty remains regarding potential differences in susceptibilities within the human population, the comparative susceptibility of humans and animals, and the half-lives of elimination for the different components of a mixture of dioxins and PCBs vary significantly. To account for these uncertainties, the consultation recommended a composite uncertainty factor of 10.

Based on the range of estimated daily human intakes that would lead to body burdens similar to those associated with the most sensitive adverse effects in animal studies (10–40 pg/kg bw), and applying an uncertainty factor of 10, a TDI range of 1–4 pg TEQs/kg body weight was established.

The consultation recognised that subtle adverse effects might already be occurring in the general population in some countries at current background levels of exposure to dioxins and dioxin-like compounds. It therefore recommended that every effort should be made to reduce exposure to the lower end of this range.

5. CONCLUSIONS FROM THE EC-SCF MEETING (2001)

The EC-SCF based their updated risk assessment on the LOEL for reproductive toxicity in male offspring of pregnant rats from the study by Faqi et al (1998), rather than the rat and monkey studies used by the WHO.

An estimated human daily intake (EHDI) of 20 pg/kg bw/day was calculated from the estimated steady state TCDD body burden in the rat dams at the LOEL of 25 ng/kg bw. When choosing an appropriate safety factor for deriving a TDI, an uncertainty factor accounting for interspecies variation was not considered necessary because the NOEL and LOEL were expressed in terms of body burden, thereby scaling doses from animals to humans. The committee also concluded that no uncertainty factor was required to account for differences within or between species in toxicodynamics (eg *Ah* receptor binding affinity and enzyme induction). The ultimate safety factor consisted of an uncertainty factor of 3.2 to account for variation between individuals in human toxicokinetics (ie differences in absorption, accumulation, metabolism and excretion), and an additional factor of 3 because a LOEL rather than a NOEL was used. Thus, the safety factor was 9.6 (ie 3 X 3.2).

Application of this 9.6-fold safety factor to the EHDI of 20 pg/kg bw yielded a TDI of 2 pg/kg bw/day. Due to the long half-lives of TCDD and related compounds in the human body, this figure was converted to a TWI of 14 pg/kg bw. In order to extend this TWI to include all 2,3,7,8-substituted PCDDs and PCDFs and the dioxin-like PCBs, the EC-SCF established a group TWI of 14 pg WHO TEQs/kg bw for these compounds.

The EC-SCF stressed that:

given the average dietary intakes of dioxins and dioxin-like PCBs in the European countries of 1.2–3.0 pg/kg bw/d, a considerable proportion of the European population would still exceed the TWI derived by the Committee.

6. CONCLUSIONS FROM THE FAO/WHO 57TH JECFA MEETING (2001)

The JECFA meeting concluded that a tolerable intake for TCDD could be established, based on reproductive effects in the male offspring of TCDD-treated rat dams. For assessment of tolerable intake, JECFA chose the LOEL established in the study of Faqi et al (1998) and the NOEL provided by the study of Ohsako et al (2001). Two different models were used to estimate the equivalent maternal body burden with long-term dosing: a model that assumed a linear relationship between maternal and foetal body burden, and a nonlinear model (see Table 3). After compensating for the background body burden of PCDDs and PCDFs found in untreated rats, JECFA derived estimated human monthly intakes (EHMIs) of 237 and 330 pg TEF/kg bw, using the linear and nonlinear models, respectively, from the study by Ohsako et al (2001). The corresponding EHMI values derived from the study by Faqi et al (1998) were 423 and 630 pg TEF/kg bw.

The committee then derived safety factors to apply to the EHMI values. In common with the 1998 WHO consultation, JECFA considered that the use of body burdens to scale doses from animals to humans removed the need to account for interspecies differences. To account for differences between individuals in human toxicokinetics, a safety factor of 3.2 was applied to the EHMIs associated with the NOEL identified by Ohsako et al (2001). No additional safety factor was applied to account for differences in human toxicodynamics. A larger safety factor was applied to the EHMI associated with the LOEL identified by Faqi and coworkers. JECFA considered that use of a LOEL warranted an additional safety factor of 3, leading to an overall safety factor of $(3 \times 3.2) = 9.6$. The four resulting provisional tolerable monthly intake (PTMI) values ranged from 44 to 103 pg/kg bw/month.

Table 3 JECFA derivation of provisional tolerable monthly intake values from reproductive toxicity in rats

Study	Linear model		Nonlinear model	
	Ohsako et al (2001)	Faqi et al (1998)	Ohsako et al (2001)	Faqi et al
(1998)				
End point (in male offspring of treated dams)	NOEL (decreased anogenital distance at higher doses)	LOEL (decreased sperm production, sexual feminisation)	NOEL (decreased anogenital distance at higher doses)	LOEL (decreased sperm production, sexual feminisation)
Maternal TCDD body burden (ng/kg bw)	7.6	25	7.6	25
Equivalent maternal body burden with long-term dosing (ng/kg bw)	13	25	19	39
Background body burden (ng/kg bw)	3	3	3	3
Total body burden (ng/kg bw)	16	28	22	42
Equivalent EHMI (pg/kg bw/mo)	237	423	330	630
Safety factor	3.2	9.6	3.2	9.6
Derived PTMI value (pg/kg bw/mo)	74	44	103	66

Taking the mid-point of the range, JECFA have chosen a PTMI for PCDDs, PCDFs and coplanar compounds of 70 pg TEF/kg bw/month. JECFA was satisfied that establishment of a tolerable intake based on noncancer effects would also address any carcinogenic risk.

The JECFA report stated that:

the PTMI is not a limit of toxicity and does not represent a boundary between safe intake and intake associated with a significant increase in body burden or risk. Long-term intakes slightly above the PTMI would not necessarily result in adverse health effects but would erode the safety factor built into calculations of the PTMI. It is not possible given our current knowledge to define the magnitude and duration of excess intake that would be associated with adverse health effects.

The report also indicated that ‘despite the uncertainties, the results suggest that a considerable fraction of the population will have a long-term mean intake above the PTMI’.

In view of the long half-lives of PCDDs, PCDFs and PCBs, the committee concluded that it would not be appropriate to establish an acute reference dose for these compounds.

7. SUMMARY

Each of the three international evaluations considered in this paper established that hormonal, reproductive and/or developmental effects are the most sensitive indicators of dioxin-related toxicity in experimental animals. Despite some differences in the most significant studies and in the methodology used to analyse the data, the WHO, the EC-SCF and JECFA reached similar conclusions. As shown in Table 4, when expressed in terms of daily dose, the human intake standards proposed by the EC-SCF and JECFA lie close to the mid-point of the TDI range of 1–4 pg TEQs/kg bw/day proposed by the WHO consultation.

Table 4 Comparison between the standards for human intake of dioxins, furans and dioxin-like PCBs agreed by WHO (1998), EC-SCF (2001) and JECFA (2001)

Exposure standard	pg/kg bw/day	pg/kg bw/week	pg/kg bw/month
WHO consultation (1998)	1–4	7–28	30–120
EC-SCF (2001)	2	14	60
JECFA (2001)	2.3	16.3	70

Note: The recommended exposure standards are shown in bold, with conversions to a daily, weekly or monthly basis in plain type.

Based on the assessment provided by the TGA, the NHMRC can find no reason to discount any of the three exposure standards. The NHMRC is satisfied that, based on the persistence of dioxin-like compounds within tissues, it is most appropriate to set an exposure standard that extends over a monthly interval. The NHMRC therefore favours adoption of the 70 pg/kg bw/month limit proposed by the JECFA.

8. RECOMMENDATIONS

1. Based on the WHO-ECEH/IPCS consultation (1998), the EC-SCF Opinion (2001) and the JECFA evaluation (2001), and considering the IARC classification of dioxins as a human carcinogen, it is recommended that the NHMRC establish a tolerable monthly intake (TMI) of 70 pg TEQ/kg bodyweight from all sources combined. This tolerable intake is equal to that set by JECFA, and includes polychlorinated dioxins, polychlorinated furans and dioxin-like PCBs, as specified under the WHO 1998 TEF scheme.
2. It is recommended that this TMI be reviewed following any further evaluation of dioxins by the US EPA, WHO, EC or JECFA.
3. Any future review of the potential adverse human impacts of exposure to dioxins should consider the relative contributions of IC3, PAHs and related compounds as both *Ah* receptor agonists and antagonists.

9. ACRONYMS AND ABBREVIATIONS

AFFA	Agriculture, Fisheries & Forestry Australia
bw	bodyweight
CAC	Codex Alimentarius Commission
EA	Environment Australia
EC	European Commission
EC-SCF	European Commission-Scientific Committee on Food
EHDI	estimated human daily intake
EHMI	estimated human monthly intake
FAO	Food and Agriculture Organization of the United Nations
IARC	International Agency for Research on Cancer
IC3	indole-3-carbinol
ILO	International Labour Organization
IPCS	International Programme on Chemical Safety
I—TEQ	international toxicity equivalence
JECFA	Joint Expert Committee on Food Additives
LOEL	lowest observable effect level
MRL	maximum residue level
mRNA	messenger ribonucleic acid
NHMRC	National Health and Medical Research Council
NOEL	no observable effect level
PAHs	polyaromatic hydrocarbons
PBDDs	polybrominated dibenzodioxins
PBDFs	polybrominated dibenzofurans
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzodioxins
PCDFs	polychlorinated dibenzofurans
ppt	parts per trillion
PTMI	provisional tolerable monthly intake
RfD	reference dose
TCDD	2,3,7,8-tetrachloro-dibenzo-p-dioxin
TDI	tolerable daily intake
TEF	toxic equivalency factors
TEQ	toxic equivalency
TGA	Therapeutic Goods Administration
TMI	tolerable monthly intake
TWI	tolerable weekly intake
UNEP	United Nations Environment Programme
US EPA	United States Environmental Protection Agency
WHO	World Health Organization
WHO-ECEH	European Centre for Environmental Health

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