COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

LAY SUMMARY OF THE COT STATEMENT ON THE TOLERABLE DAILY INTAKE FOR DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

Dioxins and dioxin-like PCBs – How the tolerable daily intake (TDI) was set.

What are dioxins and PCBs?

Dioxins are members of a large group of substances with similar chemical structures. They are not deliberately produced, but are formed during fires and most forms of combustion (e.g. in fires, bonfires, incinerators, automobile engines), and as trace contaminants in the synthesis of some chemicals and some industrial processes. Some members of another group of substances, the dioxin-like polychlorinated biphenyls (PCBs) are also included in the assessment because they have similar biological activities. There are many other PCBs which do not have dioxin-like properties.

Dioxins remain in the environment for a long time and accumulate in all living things. Dioxins are known to cause a wide range of toxic effects in animals, some of which have been seen at very low doses. These effects may have significant consequences for human health.

All the dioxins exhibit similar types of biological effect. One compound (2,3,7,8-tetrachlorodibenzo-p-dioxin, which is referred to as 2,3,7,8-TCDD or TCDD) has been studied in most detail. TCDD is usually considered the most potent dioxin. The potency of other dioxins is expressed as fractions of the TCDD potency, called toxic equivalents (TEQs). These toxic equivalents have been agreed internationally, based on a scheme proposed by the World Health Organisation (WHO).

Some people have been exposed to dioxins at work in chemical factories, but the general population is exposed to dioxins mainly from food. It is now possible to detect extremely low levels of dioxins and PCBs, and they can be detected in almost all types of food. Highest concentrations are found in meat, fish, eggs and dairy products. However, major components of the diet with lower concentrations, such as cereals, fats and oils, contribute significant proportions of the total dioxin and PCB intake. The amount of dioxins and dioxin-like PCBs in the UK diet has declined substantially over the past 20 years. In 1997, the average person consumed only one quarter of the amount that an average person consumed in 1982. This decrease has largely

occurred due to controls on emissions to the environment and the discontinuation of the production and use of PCBs. It is expected that environmental controls will continue to reduce levels of dioxins in food.

What were the UK regulations for dioxin intake?

The risks associated with dioxins have been assessed several times in the last 20 years by the UK independent expert advisory committees, the Committee on Toxicity (COT), the Committee on Carcinogenicity (COC) and the Committee on Mutagenicity (COM). The COT set a UK Tolerable Daily Intake (TDI) of 10 pg/kg bw/day for dioxins in 1991 and this was revised to include the dioxin-like PCBs in 1997.

A **Tolerable Daily Intake** (TDI) is the amount of a substance that can be ingested daily over a lifetime without appreciable health risk. It is expressed in relation to the bodyweight (bw) in order to allow for different body size, such as for children of different ages. A daily intake of 10 pg/kg bw/day is 600 pg for an average 60 kg person. [There are 1,000,000,000,000 pg (picogram) in one gram.]

The Food Standards Agency was aware of the increasing amount of scientific information available on dioxins. It was also aware of recent and current reviews of dioxins being conducted by the WHO, the European Union Scientific Committee on Food (SCF), the Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) and the US Environmental Protection Agency. The Agency therefore asked the COT to consider whether the existing UK TDI was sufficiently protective of consumer health.

How did COT decide its approach to setting a TDI?

COT considered the recent and on-going international assessments. From the available information the COT could not determine which, if any, of these was the most scientifically justified. The COT therefore concluded that it should conduct its own review of the available data and the approaches taken by the other expert committees, in order to decide on a TDI for dioxins and dioxin-like PCBs in the UK.

The COT asked the COC to evaluate the evidence concerning human cancer risks for dioxins. The COC's evaluation (statement and minutes of meetings) is available from its Website at http://www.doh.gov.uk/coc.htm. This was a crucial step in deciding the approach to risk assessment.

What approach did they choose?

The COC and COT decided there was sufficient information to assume a threshold existed for the effects of dioxins and hence a TDI could be established.

The **threshold approach** is used when it is possible to set intake levels where no effect is expected. At intakes below a certain point (the threshold) the chemical either has no effect or its effects are reversed by the body's defence mechanisms.

For a small number of substances (e.g. those which damage the genetic material) effects could occur from damage to a single cell. For these, a precautionary approach assumes there is no threshold and therefore no safe intake.

Why did they choose to use a threshold approach?

There were two critical components to this decision.

- There is considerable evidence that dioxins do not directly damage the genetic material.
- There is considerable understanding of the biological reactions by which dioxins cause harmful effects, and evidence that these reactions will not occur at sufficiently low levels of exposure.

Because the COT decided to use a threshold approach, it needed to review the evidence for all possible effects of dioxins, not just cancer. A TDI should be set to protect the most vulnerable population against the harmful effect that could occur at the lowest level of exposure.

What is the evidence for effects in people?

The human studies are mainly on workers in chemical plants or following accidental contamination of the environment (e.g. Seveso in Italy) or edible oils (e.g. Yusho in Taiwan). These people had much higher levels of dioxin exposure than the general public. These studies provided evidence that dioxins are associated with increased risk of cancer. Weaker evidence suggests increased risks of cardiovascular disease. A number of other effects have been observed in people exposed to dioxins, but there is insufficient information to draw conclusions.

Two Dutch studies looked at the effects of dioxins and dioxin-like PCBs on the development of children. These studies compared children from rural and urban backgrounds. Their mothers would have been exposed to different background levels of dioxins and dioxin-like PCBs from their environments and the children were exposed through the mother whilst in the womb and during breast-feeding. The COT concluded that it was not possible to determine whether any reported differences were real effects on development, and if they were real, whether they were due to dioxins or some other cause.

The COT calculated the total amounts of dioxins that could have been present in the bodies of the people in these studies, referred to as their body burden. The COT tried to identify a body burden at which there was no increased risk of harmful effects, which could then have been used to set a TDI.

What are the effects in animals?

A wide range of toxic effects has been observed in animal studies, including cancer and effects on the immune and reproductive systems. The effects

occurring at the lowest dose levels were observed when dioxins were given to pregnant animals. The most sensitive and consistent effect seen was on the developing reproductive system of the male offspring, particularly changes in sperm production and quality. These changes indicate decreased fertility of the male, resulting from exposure to high levels of dioxins in the womb.

Which studies were used to set the TDI?

The human data were not used as the basis for the TDI because:

- the exposure data were rough estimations and did not include all the dioxins and dioxin-like substances of concern
- the studies did not adequately consider other possible causes of the observed effects
- in all apart from the Dutch developmental studies, the patterns of exposure included periods of high level exposure rather than continual low level exposure from food
- in the occupational studies, exposed workers were mostly male and therefore the wrong population for the critical effect seen in animal studies (effects on the fetus)

The Committee's usual practice is to base the TDI on the most sensitive and relevant study. The COT considered several studies of developmental effects in animals. Of these, a study by Faqi and colleagues identified the lowest TCDD exposure that decreased sperm counts. The strengths and weaknesses of this study were considered carefully by the Committee. None of the weaknesses were sufficient to ignore the results and so the Faqi study was considered to be the key study for establishing the TDI. The COT considered that, because of the long-term accumulation of dioxins in the body, the effects were related to the total body burden rather than to a daily dose. The dose used in the Faqi study was converted into a maternal body burden, making appropriate mathematical corrections to compare to continual low level exposure from the diet.

How was the key study used to set the TDI?

A TDI is normally set by dividing a level that is without effect in animal studies (the No Observed Adverse Effect Level, NOAEL) by uncertainty factors to allow for possible differences between the experimental animal and humans, and between people. Each of these differences may relate to the fate of the substance within the body, or to the sensitivity to the toxic effects of the substance, giving a total of 4 different factors to be considered. Usually, a total uncertainty factor of 100 is considered appropriate, but this may be broken down into individual components where relevant data are available. An additional factor is needed if the key study did not identify a NOAEL.

The uncertainty factor should not be viewed as a safety margin. It allows for the uncertainties in predicting the possible effects in the most sensitive individuals in order to identify an intake that is considered to be without appreciable health risk.

In the evaluation of dioxins, the COT decided that the data allowed the use of chemical-specific adjustment factors based on knowledge of the fate and toxicity of dioxins, rather than the usual uncertainty factor of 100. A total adjustment factor of 9.6 was used. This was based on the following elements:

- Body burdens are used to indicate the concentration of TCDD in the fetus and it is therefore not necessary to correct for differences in fate in different species; therefore a factor of 1 is used to extrapolate from animals to humans.
- Rats are generally more sensitive to the adverse effects of dioxins than humans, but the most sensitive humans could be as responsive as rats to the effects of dioxins. It was therefore not necessary to correct for differences in sensitivity either between species, or within the human population, and a combined factor of 1 was used for these two components.
- There may be variability between humans in accumulation of the different dioxins and dioxin-like PCBs. This was allowed for by a factor of 3.2, which was considered appropriate to account for the potential increased body burden of dioxins and dioxin-like PCBs in the most susceptible individuals.
- The key study (Faqi) did not identify a level without effect (NOAEL). Therefore a factor of 3 was used to extrapolate from the lowest adverse effect level (LOAEL) to a level that would be expected to be without effect.

What is the TDI?

The maternal body burden calculated from the Faqi study was divided by the adjustment factor of 9.6 in order to estimate a tolerable human maternal body burden. This body burden is estimated to result from a lifelong daily intake of about 2 pg TCDD/kg bw per day. Some other scientific advisory committees have recently recommended tolerable intakes related to periods of one week or one month. The COT considered that because intakes are usually expressed on a daily basis, a tolerable daily intake was more appropriate and transparent, but that it is long term exposure that is important.

Taking into account the possible effects of other dioxins and dioxin-like substances, the COT recommended a TDI of 2 pg TEQ/kg bw per day. As this TDI is based on the most sensitive end-point, it will also protect against the risk of other adverse effects, including carcinogenicity.

What if the TDI is exceeded?

Dioxins accumulate gradually in the body over a period of about 30 years, after which the level of intake will be about the same as the level of elimination from the body. The total body burden will then be about 2000 times higher than the average daily intake. For example, an intake of 10 times the TDI on a single day would result in a 0.5% increase in the body burden, which would not be sufficient to have any effect. Occasionally consuming more than the TDI would not be expected to result in harmful effects, providing that the average intake over a prolonged period is within the TDI.

Comparison of the UK TDI with other recent evaluations

Several other international assessments have been completed or are on-going, as listed below. Some other committees concluded that the tolerable intake should be expressed over a longer period over time. However, because intakes are estimated on a daily basis, the COT considered that it was more appropriate to set a TDI than a Tolerable Weekly Intake or Tolerable Monthly Intake.

Organisation	**Key end-point**	**Value**
WHO	Developmental effects	1-4 pg TEQ /kg bw per **day**
SCF	Developmental effects	14 pg TEQ/kg bw per **week**
JECFA	Developmental effects	70 pg TEQ/kg bw per **month**
COT	Developmental effects	2 pg TEQ/kg bw per **day**
US-EPA	Cancer	Reference dose not yet finalised