3 Toxicological considerations

General toxicological principles

3.1 For many chemical contaminants it is possible to set intake levels at which no harmful effects are expected to arise. At intakes below a certain point (the threshold) the contaminant either has no effect or its effects are reversed by the body's defence mechanisms. This is often referred to as the threshold approach to risk assessment. When this approach is valid it is possible to estimate the amount of a substance that can be ingested daily over a lifetime without appreciable health risk. There are several terms to describe this intake, those most commonly used for chemical contaminants are the Tolerable Daily Intake (TDI) in the UK/EU and the Reference Dose (RfD) in the USA. Although there are minor differences in the precise definitions of these terms, they are safety guidelines based on similar principles. Whilst absolute safety cannot be guaranteed, these safety guidelines represent an intake where there is essentially no risk, as far as can be judged from the available scientific evidence. They are expressed in relation to the bodyweight (bw) in order to allow for different body size, such as for children of different ages. Some advisory committees use terms with longer referencing periods, such as Provisional Tolerable Weekly Intake (PTWI), for chemical contaminants that accumulate in the body.

3.2 The usual practice is to base the safety guideline on the most sensitive and relevant study. Adequate human data would be the preferred basis, but are rarely available and it is often necessary to rely on data from animal studies. A safety guideline is normally set by identifying an exposure that has shown no harmful effect in the most relevant study, and dividing it by uncertainty factors to allow for possible differences between the experimental animals and humans, and between the average and most sensitive humans. These are sometimes referred to as safety factors, but uncertainty is a more appropriate term, because we generally do not know the extent of variability between species or between different people. The uncertainty factors relate to the fate of the substance within the body, and to sensitivity to the toxic effects of the substance. Additional uncertainty factors may be used to allow for gaps in the scientific evidence. Smaller factors may be used if specific human data are available.

3.3 A safety guideline, such as the TDI, represents an intake that is without appreciable risk, but gives no indication of the possible risk at intakes above the guideline. Exceeding the safety guideline does not necessarily result in harmful effects, even in the most sensitive people. Assessing risk associated with exceeding the safety guideline requires consideration of information relating to the toxicity of the substance, the way in which the safety guideline was derived and the length of time and amount by which it has been exceeded.

Organic contaminants

Dioxins and dioxin-like PCBs

3.4 Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) are very persistent chemicals which are ubiquitous in the environment and are generally present in low concentrations in foods, especially fat-containing foods including milk, meat and fish. PCDDs and PCDFs are commonly referred to as dioxins and the co-planar PCBs, which exhibit a similar mechanism of toxicity, are referred to as the dioxin-like PCBs. There has been a significant reduction in emissions of dioxins into the environment during the past decade and dietary intake has fallen by about 85% since 1982 (MAFF 1997, FSIS 105;FSA 2000, FSIS 4/00, FSIS 38/03).

Dioxins and PCBs in fish

3.5 In August 1999 the Ministry of Agriculture, Fisheries and Food (MAFF) published a survey (MAFF 1999a, FSIS 184) for dioxins, furans and PCBs in 132 samples of cod, haddock, plaice, whiting, red fish, herring, mackerel, salmon and fish fingers. This work complemented an earlier survey for these chemicals in samples of farmed trout (MAFF 1998a, FSIS 145) and eels from commercial fisheries (MAFF 1997, FSIS 105). Concentrations of dioxins and PCBs on a fat basis were higher in herring, red fish and plaice than in the other species. Concentrations of dioxins and PCBs on a fat basis were lower in haddock and mackerel. Concentrations also showed significant seasonal variations. Table 3.1 shows concentrations of dioxins and PCBs expressed on a fresh weight basis.

Table 3.1: Concentrations of dioxins and PCBs in edible tissue samples from marine fish, collected in 1995/96 (ng WHO-TEQ/kg fresh weight)

Fish type	Concentrations (ng WHO-TEQ/kg fresh weight)					
	Dioxins		PCBs		Dioxins and PCBs	
	Mean	Range	Mean	Range	Mean	Range
UK landed:						
Cod	0.04	0.01-0.08	0.08	0.01-0.30	0.12	0.03-0.38
Haddock	0.03	0.01-0.07	0.03	0.01-0.06	0.06	0.03-0.10
Plaice	0.28	0.06-0.52	0.47	0.17-0.84	0.75	0.23-1.27
Whiting	0.04	0.01-0.08	0.11	0.01-0.33	0.14	0.02-0.38
Herring	2.44	0.34-3.76	6.15	0.46-10.38	8.59	0.8-13.85
Mackerel	0.66	0.14-1.70	2.45	0.34-6.02	3.11	0.48-7.49
Salmon	0.82	0.62-0.99	2.38	1.28-2.99	3.20	2.15-3.95
Trout	0.27	0.07-0.74	0.86	0.22-2.35	1.13	0.30-3.09
Fish fingers	0.06	0.03-0.17	0.12	0.03-0.49	0.18	0.08-0.52
Imported:						
Cod	0.03	0.01-0.09	0.05	0.01-0.16	0.09	0.03-0.25
Haddock	0.03	0.01-0.05	0.03	0.01-0.08	0.06	0.02-0.13
Plaice	0.30	0.25-0.34	0.46	0.32-0.64	0.76	0.57-0.94
Salmon	0.57	–	2.03	–	2.60	–
Red fish	0.50	0.40 - 0.59	1.51	1.42 - 1.59	2.00	1.82 - 2.18

Notes:
Results are given to 2 significant figures. Total concentrations of dioxins and PCBs may not equal the sum of individual dioxins and PCBs values due to rounding, and because the highest and lowest concentrations of dioxins and PCBs were not always found in the same samples.

3.6 In general, concentrations of chemicals such as dioxins and PCBs in fish depend on their fat content, the extent to which the fish migrate, the number of times they spawn, and their ages, size and feeding habits (Larrson *et al.,* 1996). For example, plaice are bottom-feeding fish and therefore may be more exposed to dioxins and PCBs bound to sediment. Herring has a relatively high fat content and is non-migratory, which renders it more subject to localized contamination sources (Strandberg *et al.,* 1998). The Scottish Office has found that concentrations of total PCBs in herring from the River Clyde are higher than in those from the North Sea and River Forth (Kelly *et al*., 1994). A recent study of contaminants in salmon (Hites *et al*., 2004) reported similar levels in UK farmed salmon to those found in the MAFF study (MAFF 1998a).

3.7 The concentrations found in the MAFF survey were broadly similar to those found elsewhere. However, higher concentrations have been found in fish taken from the Baltic Sea, a sea that is known to be contaminated.

Long term monitoring of PCBs in herring from the Baltic Sea since 1978 has shown that concentrations of PCBs have fallen by 6.3-13% per year (Bignert *et al.,* 1998). There is also some evidence that concentrations of dioxins and PCBs in fish from the South Atlantic are lower (Brevik, 1990).

3.8 The FSA is currently carrying out a major survey of fish, particularly oily fish and farmed and wild salmon.

Effects of dioxins and dioxin-like PCBs

3.9 Dioxins and dioxin-like PCBs exhibit similar types of biological effect, primarily mediated through interaction with the Aromatic hydrocarbon (Ah) receptor. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD or TCDD) has been studied in most detail and is one of the most potent dioxins. The potency of other dioxins is expressed as fractions of the TCDD potency, called toxic equivalents, which have been agreed internationally based on a scheme proposed by the WHO (referred to as TEQs or WHO-TEQs).

3.10 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), Carcinogenicity (COC) and Mutagenicity (COM) of Chemicals in Food, Consumer Products and the Environment. COT and COC completed the most recent review of the available data in 2001 (COC 2001, COT 2001).

3.11 Reports of effects in humans mainly relate to workers in chemical plants or exposure resulting from accidental contamination of the environment (e.g. Seveso in Italy) or edible oils (e.g. Yusho in Taiwan), with much higher levels of dioxin exposure than the general public. These studies have shown that exposure to high levels of dioxins causes the skin condition chloracne. There is still some debate with respect to cancer; in 1997 the International Agency for Research on Cancer (IARC) concluded that TCDD should be considered as a definite human carcinogen, whereas the COC reconfirmed that it should be regarded as a probable human carcinogen, at its latest evaluation in 2001. Weaker evidence suggests increased risks of cardiovascular disease and reproductive effects. A

number of other effects have been observed in people exposed to dioxins, but there is insufficient information to draw conclusions.

3.12 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 administered to pregnant rats. The most sensitive and consistent effect 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 dioxin exposure *in utero*, which is consistent with observations seen at higher doses in a multigeneration study in rats.

3.13 The COC and COT decided that, despite the evidence of carcinogenicity, there was sufficient information to assume a threshold existed for the effects of dioxins and hence a TDI could be established. This conclusion was based on the considerable evidence that dioxins do not directly damage the genetic material, and the 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.

3.14 The available human data could not be used as the basis for the TDI because:

a) the exposure data were rough estimations and did not include all the dioxins and dioxin-like substances of concern.

b) the studies did not adequately consider other possible causes of the observed effects.

c) in all except a series of Dutch developmental studies, the patterns of exposure included periods of high level exposure rather than continual low level exposure from food.

d) 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).

3.15 The COT considered several studies of developmental effects in animals. Of these, a study by Faqi *et al.* (1998) identified the lowest TCDD exposure that decreased sperm counts. This study had a number of limitations, but these were not sufficient to discount the results and so the Faqi study was considered to be the key study for deriving 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 mathematical corrections to compare to continual low level exposure from the diet, based on the distribution studies of Hurst *et al.* (2000 a and b).

3.16 The data supported the use of chemical-specific uncertainty factors based on the following elements:

a) Body burdens are used to indicate the concentration of TCDD in the fetus and it is therefore not necessary to correct for differences in toxicokinetics in different species – uncertainty factor of 1.

b) Rats are generally more sensitive to the adverse effects of dioxins than humans, but it could not be discounted that the most sensitive humans could be as responsive as rats. It was therefore not necessary to correct for differences in sensitivity either between species, or within the human population – uncertainty factor of 1.

c) There may be variability between humans in accumulation of the different dioxins and dioxin-like PCBs. This was allowed for by a factor to account for the potential increased body burden of dioxins and dioxin-like PCBs in the most susceptible individuals – uncertainty factor of 3.2.

d) The key study (Faqi *et al*., 1998) did not identify a level without effect – uncertainty factor of 3 used for extrapolation from a lowest observed adverse effect level (LOAEL) to a no observed adverse effect level (NOAEL).

3.17 The maternal body burden calculated from the Faqi study was divided by these adjustment factors to derive a tolerable human maternal body burden, which was estimated to result from a long-term daily intake of about 2 pg TCDD/kg bw per day. Because long term exposure is important, other scientific advisory committees have recommended tolerable intakes related to periods of one week or one month, but the COT considered that a tolerable daily intake could be more readily compared with intakes expressed on a daily basis.

3.18 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, the COT concluded it would also protect against the risk of other adverse effects, including carcinogenicity.

Uncertainties in the TDI

3.19 There are a number of uncertainties involved in assessing the evidence, setting a TDI and comparing this to realistic exposures:

a) The key studies were conducted on TCDD whereas exposure is to a mixture of dioxins, which is allowed for by the TEQ approach. Toxic equivalents are agreed international ratios of toxicity to the nearest half order of magnitude for different congeners based on various parameters (comparative toxicity and Ah receptor binding). They are usually rounded up, which is precautionary.

b) The maternal body burden in the Faqi study was measured, and relied on the best estimates of TCDD kinetic parameters in the rat – these could be under- or over-estimates.

c) Other studies did not find the same effects at such low exposure levels as those in the Faqi study, thus use of the Faqi study is precautionary.

d) Uncertainty whether the adjustment factors are too high or too low.

3.20 The TDI represents the best scientific judgement, but on balance the approach is precautionary because of the uncertainties involved.

Evaluations in other countries

3.21 The approach to the COT evaluation and resultant TDI is consistent with the evaluations of the EU Scientific Committee on Food (SCF) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA), although those committees used longer referencing periods (SCF: 14pg WHO TEQ/kg bw/week; JECFA: 70pg WHO TEQ /kg bw/month). In contrast the US Environmental Protection Agency (EPA) favours an extreme precautionary approach based on quantitative cancer risk assessment. The EPA began a reassessment of dioxins in 1991, and has still not completed it deliberations. However, its most recent estimate was of a cancer risk of 1 in 1000 at an intake of 1 pg/kg bw/day. The COC consider that these estimations were not appropriate.

Dietary exposure to dioxins and PCBs

3.22 Dietary exposure to chemical contaminants is estimated by determining the concentrations of chemicals in different foods, combined with information on consumption of those foods obtained from diet and nutrition surveys. The 1994-6 MAFF survey (MAFF 1999a, FSIS 184) was carried out to enable the calculation of dietary exposure to dioxins and PCBs for consumers of fish. Intake of dioxins and PCBs from the consumption of fish only using 1986 consumption data (Gregory *et al.,* 1990) was estimated to be 0.5 pg WHO-TEQ/kg bodyweight/day for an average UK adult consumer and 3.6 pg WHO-TEQ/kg bodyweight/day for a high level adult consumer (Table 3.2). The average concentrations of dioxins and dioxin-like PCBs in UK and imported samples of a given fish species were used. Intake calculations have been repeated using food consumption data from the 2000/01 adults survey (Henderson *et al.,* 2002). The slight increase in oily fish consumption is reflected in a slight increase in dietary intake of dioxins and dioxin-like PCBs. *Upper bound* intakes from fish only were estimated to be 0.6 pg WHO-TEQ/kg bodyweight/day for an average UK adult consumer and 3.9 pg WHO-TEQ/kg bodyweight/day for a high level adult consumer (Table 3.3). *Lower bound* intakes have also been estimated (Table 3.4) and after approximation do not differ from the *upper bound* intakes.*

- *Upper bound* intakes are calculated by using the limit of detection for those values below the limit of detection. *Lower bound* intakes assume a value of zero for concentrations below the limit of detection.

3.23 Estimated adult intakes of dioxins and dioxin-like PCBs from the whole diet are reported in Table 3.5. These dietary intakes were calculated using the concentrations of dioxins and dioxin-like PCBs found in the 1982, 1992, 1997 and 2001 TDS samples, including fish. These calculations refer to average and high level consumers of all food categories and not average and high level consumers of fish only as Tables 3.2, 3.3 and 3.4. For this reason the values in Tables 3.2, 3.3 and 3.4 are not directly comparable to the values in table 3.5.

3.24 In 2001, the COT referred to the intake estimates of 1.8 and 3.1 pg TEQ/kg bw/day (based on the results of the 1997 TDS) for the average and high level adult consumers, respectively and concluded:

a) There are no short-term measures that can be used to decrease the body burden of dioxins and dioxin-like PCBs in humans because of their long half-lives and widespread presence at low levels in food.

b) Similarly, because of the long half-life, short-term exceedances of the tolerable intake are not expected to result in adverse effects. Nevertheless, it is not possible to identify a duration and degree of exceedance at which adverse effects might occur.

3.25 Recalculation of the dietary exposure using the latest consumption data and the 1997 TDS results indicates a slight increase for high level consumers but not for average consumers (Table 3.5). However the intakes of dioxins and dioxin-like PCBs from the whole diet calculated using the latest TDS data (2001) (Table 3.5) have decreased considerably (approximately a half) compared to 1997.

Table 3.2: Estimated upper bound adult dietary intakes (pg WHO-TEQ/kg bodyweight/day) of dioxins and dioxin-like PCBs via individual species of fish (estimated using food consumption data from the adults survey 1986).

Fish type	Mean		High level	
	Consumption (g/day)	Estimated *upper bound* adult dietary intakes of dioxins and PCBs (pg TEQ/kg body weight/day)**	Consumption (g/day)	Estimated *upper bound* adult dietary intakes of dioxins and PCBs (pg TEQ/kg body weight/day)**
Cod	22.8	0.04	67.5	0.1
Haddock	18.1	0.02	40.4	0.04
Plaice*	22.7	0.3	46.2	0.6
Whiting*	18.4	0.04	36.3	0.09
Misc. white fish	13.7	0.09	41.8	0.3
Fish fingers/fish cakes	14.0	0.04	40.2	0.1
All white fish	26.3	0.1	72.7	0.4
Herring	23.4	3.4	46.9	6.7
Mackerel	15.1	0.8	48.2	2.5
Salmon	12.6	0.7	39.4	2.1
Trout*	22.2	0.4	35.5	0.7
Misc. oily fish	9.4	0.06	45.4	0.3
All oily fish ***	18.6	1.1	67.7	5.1
All fish ***	30.3	0.5	89.2	3.6

Notes:

Intakes were estimated from the average concentrations found in UK and imported samples of a given fish species

* Fewer than 60 recorded consumers. High level intakes to be regarded with caution.

** Estimates assume a typical adult bodyweight of 60 kg.

*** The total intakes of dioxins and PCBs by the high level consumer or by the mean average consumer for all fish types combined are not equal to the sum of the intakes from the individual fish species. They refer to the dietary intakes by a consumer of one or any combination of the fish species containing that chemical. These values are derived from a distribution of the consumers' consumption patterns with regard to the individual fish species.

There were no recorded consumers of red fish.

Table 3.3: Estimated upper bound adult dietary intakes (pg WHO-TEQ/kg bodyweight/day) of dioxins and dioxin-like PCBs via individual species of fish (Estimated using food consumption data from the adults survey 2000/1).

Fish type	Mean		High level	
	Consumption (g/day)	Estimated *upper bound* adult dietary intakes of dioxins and PCBs (pg TEQ/kg body weight/day)**	Consumption (g/day)	Estimated *upper bound* adult dietary intakes of dioxins and PCBs (pg TEQ/kg body weight/day)**
Cod	22.1	0.04	57.6	0.1
Haddock	19.8	0.02	42.6	0.04
Plaice*	22.4	0.3	58.3	0.7
Whiting**	29.9	0.07	35.1	0.08
Misc. white fish	17.3	0.1	59.3	0.4
Fish fingers/ fish cakes	10.9	0.03	36.9	0.1
All white fish	25.4	0.1	77.0	0.4
Herring	20.6	3.0	45.4	6.5
Mackerel	22.9	1.2	79.5	4.1
Salmon	19.1	1.0	60.8	3.2
Trout*	22.3	0.4	45.5	0.9
Misc. oily fish	13.4	0.09	27.4	0.2
All oily fish ****	24.4	1.3	81.7	4.6
All fish ****	31.8	0.6	90.1	3.9

Notes:

Intakes were estimated from the average concentrations found in UK and imported samples of a given fish species

* Fewer than 60 recorded consumers. High level intakes to be regarded with caution.

** Only two recorded consumers. High level intakes to be regarded with extreme caution.

*** Estimates assume a typical adult bodyweight of 60 kg. The estimates do not take account of recipes new since the young persons survey of 1998.

**** The total intakes of dioxins and PCBs by the high level consumer or by the mean average consumer for all fish types combined are not equal to the sum of the intakes from the individual fish species. They refer to the dietary intakes by a consumer of one or any combination of the fish species containing that chemical. These values are derived from a distribution of the consumers' consumption patterns with regard to the individual fish species. The same applies to the 97.5th percentile and mean consumption of fish.

There were no recorded consumers of red fish.

Table 3.4: Estimated lower bound adult dietary intakes (pg WHO-TEQ/kg bodyweight/day) of dioxins and dioxin-like PCBs via individual species of fish (Estimated using food consumption data from the adults survey 2000/1.)

Fish type	Mean		High level	
	Consumption (g/day)	Estimated *lower bound* adult dietary intakes of dioxins and PCBs (pg TEQ/kg body weight/day)**	Consumption (g/day)	Estimated *lower bound* adult dietary intakes of dioxins and PCBs (pg TEQ/kg body weight/day)**
Cod	22.1	0.03	57.6	0.09
Haddock	19.8	0.02	42.6	0.04
Plaice*	22.4	0.3	58.3	0.7
Whiting**	29.9	0.07	35.1	0.08
Misc. white fish	17.3	0.1	59.3	0.4
Fish fingers/fish cakes	10.9	0.02	36.9	0.08
All white fish	25.4	0.1	77.0	0.4
Herring	20.6	3.0	45.4	6.5
Mackerel	22.9	1.2	79.5	4.1
Salmon	19.1	1.0	60.8	3.2
Trout*	22.3	0.4	45.5	0.8
Misc. oily fish	13.4	0.1	27.4	0.2
All oily fish ****	24.4	1.3	81.7	4.6
All fish ****	31.8	0.6	90.1	3.9

Notes:

Intakes were estimated from the average concentrations found in UK and imported samples of a given fish species

* Fewer than 60 recorded consumers. High level intakes to be regarded with caution.

** Only two recorded consumers. High level intakes to be regarded with extreme caution.

*** Estimates assume a typical adult bodyweight of 60 kg. The estimates do not take account of recipes new since the young persons survey of 1998.

**** The total intakes of dioxins and PCBs by the high level consumer or by the mean average consumer for all fish types combined are not equal to the sum of the intakes from the individual fish species. They refer to the dietary intakes by a consumer of one or any combination of the fish species containing that chemical. These values are derived from a distribution of the consumers' consumption patterns with regard to the individual fish species. The same applies to the 97.5th percentile and mean consumption of fish.

There were no recorded consumers of red fish.

Table 3.5: Estimated adult intakes (pg WHO-TEQ/kg bodyweight/day) of dioxins and dioxin-like PCBs from the whole diet in 1982, 1992, 1997 and 2001

	Adults 1986*				Adults 2000/1**			
	1982	1992	1997		1997		2001	
			Lower	Upper	Lower	Upper	Lower	Upper
Average	7.2	2.5	1.5	1.8***	1.5	1.8	0.7	0.9
High level	13	4.3	2.7	3.1***	3.0	3.3	1.5	1.7

Note:
* Food consumption data from the adults survey 1986 (Gregory t al, 1990)
** Food consumption data from the adults survey 2000/1 (Henderson et al., 2002)
*** Intake estimates on which COT based its conclusion in 2001
These dietary intakes were estimated using the concentrations of dioxins and dioxin-like PCBs found in the 1982, 1992, 1997 and 2001 TDS samples. These values are not directly comparable to the values in tables 3.2, 3.3 and 3.4.

Fish oil supplements

3.26 In June 2002 the FSA published a survey for dioxins and dioxin-like PCBs in fish oil supplements (FSA 2002a, FSIS 26/02). The estimated upper bound intakes of adults of dioxins and dioxin-like PCBs were in the range <0.1 to 7.1 pg WHO-TEQ/kg bw/day. These estimated intakes did not take account of intakes from the whole diet. COT members agreed it is appropriate to consider the survey results in the light of the TDI of 2 pg TEQ/kg bw/day, in the context of intake of dioxins and dioxin-like PCBs from the UK diet. Some fish oil samples, if taken at the recommended dosage, would lead to a higher intake of dioxins than from dietary sources. The problem was particularly evident with two samples which would exceed twice the TDI (i.e. exceed 4.0 pg TEQ/kg bw/day) from intake of the oil alone in virtually all age groups (FSA, 2002b).

3.27 In the light of COT's advice the Agency asked manufacturers to withdraw the batches of products for which intakes from the oils alone would exceed twice the TDI.

Implications of exceeding the TDI

3.28 The TDI is set to protect the most sensitive individuals, and because it is based on effects on the fetus, it is assumed that pregnant women are the population at greatest risk. Dioxins accumulate gradually in the body over a period of about 30 – 40 years, after which the level of intake will be about

the same as the level of elimination from the body (steady state). Therefore the exposure to females up to the time of pregnancy is of greatest concern.

3.29 At steady state, the total body burden will be about 2000 times higher than the average daily intake. Thus, 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 harmful effect. Occasionally consuming more than the TDI would not significantly increase the body burden and would not be expected to result in harmful effects, providing that the average intake over a prolonged period is within the TDI. Similarly, modification of the diet during pregnancy is unlikely to be sufficient to alter the body burden. Because of the way in which the TDI was derived, and the uncertainties in the risk assessment, it is not possible to identify a duration and extent of intake above the TDI at which effects on the developing fetus might occur.

3.30 The TDI is set to protect against the most sensitive effect of dioxins, which is considered to be impaired development of the fetal male reproductive system, caused by fetal exposure in utero and correlated with the maternal body burden. Other developmental effects have also been reported at higher doses in animal studies. Taking also into account that dioxins accumulate in the body over many years, the most susceptible subgroup is considered to be females up to the time of final pregnancy, by virtue of exposure of fetuses that they might bear. Other populations, particularly women past child-bearing age and men, are not at risk of the developmental effects and are likely to be less susceptible to dioxin toxicity; therefore an alternative safety guideline could be proposed for these groups.

3.31 The most sensitive and relevant non-developmental effect of dioxins that can be used for risk assessment is increased cancer risk. As described at paragraph 3.14 above, the COT has concluded that the human data were not adequate to identify safety guidelines. The COC noted that the excess cancer mortality reported in the heavily exposed industrial cohorts was small and any increased risk of cancer at background levels of exposure is likely to be extremely small and not measurable by current epidemiological methods. The data from experimental animals have

therefore been used to recommend a Guideline Level of daily intake over a lifetime that would not be associated with an appreciable risk of cancer. Prior to the recent evaluation, the COT derived the dioxin TDI from the rat carcinogenicity study of Kociba et al. (1978). From this lifetime feeding study, COT identified no effect levels for TCDD of 10 ng/kg bw/day for tumours, and 1 ng/kg bw/day for hepatocellular nodules. Since TCDD is considered to have a non-genotoxic mechanism of carcinogenicity, it is appropriate to base a safety assessment on the lesion seen at the lowest dose in the target tissue for tumourigenicity, i.e. the hepatocellular nodules. The interval between dose-levels was larger than is now considered appropriate for carcinogenicity studies, and therefore derivation of the Guideline Level from the LOAEL of 10 ng/kg bw/day is justifiable.

3.32 Assuming a bioavailability of 0.5 and a half-life of 21 days in rats the steady-state body burden at an intake of 10 ng/kg/day would be 152 ng/kg. In deriving the TDI, the COT applied an adjustment factor (3.2) for variability in accumulation of different dioxin-like compounds and a factor of 3 for the use of the LOAEL. Applying this combined adjustment factor of 9.6 (3 x 3.2) to the body burden of 152 ng/kg bodyweight results in a guideline body burden of 16 ng/kg bodyweight.

3.33 This guideline body burden can be converted into a Guideline Level for long term average intake of 8 pg TEQ/kg bodyweight per day, using the equation

$$\text{daily intake (pg/kg/day)} = \frac{\text{body burden (pg/kg bw)} \times \ln 2}{\text{bioavailability} \times \text{half-life in days}}$$

assuming a bioavailability of 0.5 and TCDD half-life of 2740 days (7.5 years) in humans

3.34 Table 3.6 shows estimates of intakes of dioxins and dioxin-like PCBs by UK consumers of oily fish based on the results of analyses made in a survey of dioxins and PCBs in marine fish, 1994-1995. The estimates include the contaminant intakes from one portion of cod per week and from the rest of the diet, and assume a portion size of 140g (70g for eels) and bodyweight of 60kg.

3.35 The estimated intakes have been compared with the Tolerable Daily Intake (TDI) of 2 pg WHO-TEQ/kg bw/day. Consumption of one 140g portion per week of herring, kipper or eels, by a 60kg adult, would result in a 44-78% exceedance of the TDI. Consumption of 2 portions of salmon would lead to a 40% exceedance of the TDI, whereas 3 portions of trout could be consumed per week before the TDI would be exceeded. Exceedances would be smaller if a larger average bodyweight was assumed for adults.

3.36 The Guideline Level of 8 pg WHO-TEQ/kg bw/day is used to indicate a long term average intake that would not be expected to be associated with an appreciable increase in cancer risk (analogous to the TDI definition). Table 3.6 indicates that 2 portions per week of herring or kipper, or 3 or more portions of mackerel, salmon or trout could be consumed without exceeding the guidance level.

3.37 The above calculations are based on long term intakes. However, some women may wish to modify their oily fish consumption during pregnancy, either because of the nutritional benefits or because of concern about risks associated with contaminants. The COT has previously noted (COT, 2001):

- *there are no short-term measures that can be used to decrease the body burden of dioxins and dioxin-like PCBs in humans because of their long half-lives and widespread presence at low levels in food.*

- *Similarly, short term exceedances of the TDI are not expected to result in adverse effects. Nevertheless, it is not possible to identify a duration and degree of exceedance at which adverse effects might occur.*

3.38 COT paper TOX/2004/10 (Toxicological opinion on the results of the SUREmilk project) cites a physiologically-based pharmacokinetic (PBPK) model of the effects of lactation on a woman's body burden of dioxins. This model indicates that breast-feeding a first baby would lower the mother's body burden, which suggests that the risk of exceeding a harmful body burden would be lower if oily fish consumption was increased in a subsequent pregnancy. Furthermore, a short time (e.g. 6-12 months) of

modifying the diet may not have a significant impact on the total body burden (see Figures 1-2, AR Renwick, unpublished).

Figure 3.1: Influence of 12 months of high intake on body burden of dioxin (Renwick, unpublished)

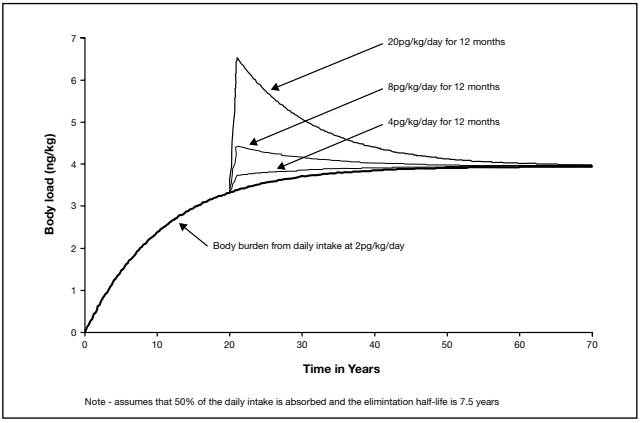

Figure 3.2: Influence of 6 months of high intake on body burden of dioxin (Renwick, unpublished)

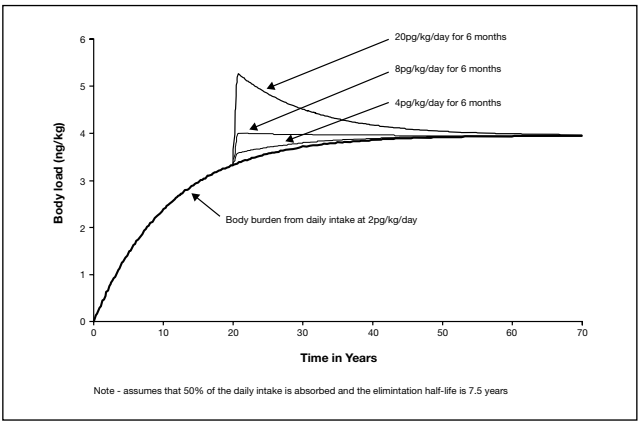

Table 3.6: Estimated dietary intake of dioxins and dioxin-like PCBs from oily fish and the rest of the diet for an adult of 60 kg bodyweight

	Herring	Kipper	Mackerel	Salmon	Trout	Eel
Mean concentration (& range)[a] (pg WHO-TEQ/g wet weight)	8.59 (0.8-13.85)	8.59[b] (0.8-13.85)	3.11 (0.48-7.49)	3.15 (2.15-3.95)	1.13 (0.30-3.09)	10.23
Intake from one portion fish per week [c] (pg WHO-TEQ/kg bw/day)	2.9	2.9	1.0	1.1	0.4	1.7
Intake from rest of the diet [d] (pg WHO-TEQ/kg bw/day)	0.7	0.7	0.7	0.7	0.7	0.7

	% TDI or guidance level											
Portions per	Herring		Kipper		Mackerel		Salmon		Trout		Eel	
week	%TDI [e]	%GL [f]	%TDI	%GL	%TDI	%GL	%TDI	%GL	%TDI	%GL	%TDI	%GL
1	178	45	178	45	87	22	88	22	54	13	120	30
2	321	80	321	80	139	35	140	35	73	18	205	51
3	465	116	465	116	191	48	193	48	92	23	290	73
4	608	152	608	152	242	61	245	61	110	28	376	94

a Average concentrations in UK and imported fish species taken from MAFF (1999), FSIS 184, MAFF (1998A), FSIS 145 and .MAFF (1997), FSIS 105.
b No concentration data were available for kipper, so it has been assumed that the concentration is the same as for herring.
c Assumes 140g portion size for all fish except eels (70g).
d Averaged daily intake of dioxins and dioxin-like PCBs from the non-fish part of the diet (0.7 pg WHO-TEQ/kg bw/day) and from one portion of cod per week (0.04 pg WHO-TEQ/kg bw/day).
e TDI = 2 pg WHO-TEQ/kg bw/day
f Guideline level for less susceptible subgroups = 8 pg WHO-TEQ/kg bw/day

Brominated Flame Retardants

3.39 Brominated flame retardants (BFRs) are widely used to reduce the risk of fire in plastics, electronic equipment and textiles. As a consequence, they have become widespread in the environment where they are bioaccumulative and are probably persistent.

Recent and current studies

3.40 The Centre for Environment, Fisheries and Aquaculture Science (CEFAS) has investigated polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDs) in fish and sediment from UK rivers and the North Sea. This work was carried out to assess the effects of BFRs on the fish (Allchin *et al.,* 1999 and 2001).

3.41 In addition to the work carried out by CEFAS, other researchers have found elevated concentrations of the chemicals in marine fish from the North Sea (Boon *et al.,* 2002). A market basket study was carried out in Sweden in which PBDE intake was investigated in samples of fish, meat, milk products, eggs, fats and oils and pastry food groups (i.e. the product groups assumed to contribute most to total intake) (Darnerud *et al*., 2000). Almost half the total intake originated from fish products whilst approximately 15 per cent was accounted for by meat, milk products and fats and oils.

3.42 Following the report by CEFAS, the Agency analysed PBDEs and HBCDs in samples of trout and eels caught at various locations in the Skerne-Tees River system and in 2001 TDS samples (FSA 2004). The COT concluded:

- We *conclude* that the uncertainties and deficiencies in the toxicological databases for PBDEs and HBCD prevent establishment of tolerable daily intakes. A Margin of Exposure (MoE) approach has therefore been used in this risk assessment.

- We *consider* that the most sensitive endpoint for the PBDEs appears to be neurodevelopmental effects resulting from a single oral administration to neonatal mice at a developmental stage comparable to infants up to one month of age, and limited data indicate that HBCD

could also have this effect. It is reassuring that infants of this age do not eat fish and therefore are not directly exposed to PBDEs from this source.

- We *note* the uncertainty in the relevance of the neurodevelopmental effects for exposure to the fetus or breast-fed infant following maternal consumption of fish containing high levels of PBDEs or HBCD. This results from the lack of neurodevelopmental studies with exposure during pregnancy and the lack of information on concentrations in breast milk that could result from consumption of fish by the mother.

- We *note* that consumption of fish from the Skerne Tees is unlikely to be widespread since there are no commercial fisheries in the area. However given the variability in BFR levels observed in this limited survey, it is not possible to exclude higher intakes in a small number of anglers or others eating their fish.

- We *consider* that comparison of the worst case estimated intakes from consumption of a single portion of eels or trout per week from the Skerne Tees with the available toxicological data indicates that these intakes are unlikely to represent a risk to health. However, in view of the uncertainties surrounding the toxicological database and exposure assessments, this conclusion should be considered tentative.

- PentaBDE and octaBDE are being phased out in 2004, which offers some reassurance that exposure to these compounds is unlikely to increase significantly. Concentrations of deca-BDE and HBCD should continue to be monitored, particularly in fatty foods.

3.43 The FSA is currently conducting a survey of PBDEs, HBCD and the other major BFRs tetrabromobisphenol A (TBBPA) and the polybrominated biphenyls in fish. The COT will be invited to advise on the toxicological implications of the data when available.

Additives

3.44 Concerns have been expressed in the media about the use of additives in farmed fish. Use of these is controlled by regulatory measures that are set to ensure that safety guidelines are not exceeded.

Inorganic contaminants

Which inorganic contaminants are present and why

3.45 Metals and other elements are present in water both from natural sources, such as the rocks of the sea bed, and as a result of human activities, such as emissions from industrial processes. These elements are taken up by marine organisms and many tend to accumulate in organisms such as predatory fish which are higher up the food chain. As a result, the concentrations in fish of many elements, including mercury, arsenic, lead, and cadmium whose potential toxicity is of concern, can be relatively high compared with levels in other foods. For instance, in the most recently published survey of metals and other elements in the TDS (MAFF, 1999b), which is representative of the average UK diet, the composite fish group contributed 94% and 33% to the total population dietary exposure for arsenic and mercury respectively. Fish can therefore make a significant contribution to the dietary intakes of these elements.

Mercury

3.46 Mercury occurs naturally as a mineral and is widely distributed throughout the environment as a result of natural and human activities (Environment Agency, 2002a). The major natural sources are volatilization from marine and aquatic environments, volcanic emissions and degassing from geological materials. The major anthropogenic sources of mercury include combustion of fossil fuels (particularly in Asian countries including China, India, South and North Korea), and emissions and discharges from industrial processes such as cement production, production of non-ferrous metals and iron and steel, and disposal of waste containing mercury.

3.47 Mercury cycles between atmosphere, water and terrestrial compartments, undergoing a series of complex and physical transformations, not all of which are fully understood. Wet deposition is the main way in which

mercury is transported from the atmosphere to surface waters (US EPA, 1997). Mercury deposited on land can also be washed into water and it is also present naturally from mercury containing rocks of the sea bed. Thus the flux of mercury between atmosphere to land or water at any one location is comprised of contributions from the natural global mercury cycle, regional and local sources which also include direct discharges to water in addition to air emissions.

3.48 Mercury typically enters bodies of water as elemental mercury, or inorganic mercury salts. It may be adsorbed onto organic sediment particles and is likely to remain bound unless consumed by aquatic organisms. Ingestion of elemental or inorganic mercury by biological organisms, mainly sulphur-reducing forms of anaerobic bacteria and other organisms of the first trophic level, results in the biotransformation of mercury into methylmercury (Friberg *et al.,* 1986). Methylmercury is a fat soluble molecule that passes easily through cell membranes, and is readily taken up by aquatic organisms. It progressively accumulates in the tissues of fish and other aquatic /marine animals and is magnified up successive levels of the food chain. Thus longer lived, larger fish that feed on smaller fish accumulate the highest levels of methylmercury.

3.49 Methylmercury is the predominant form of mercury in fish. Studies have reported methylmercury percentages with respect to total mercury of 75 –100% in tuna (with an average of 91% -Storelli *et al*., 2002), greater than 85% in muscle of sardines (Joiris *et al.*, 1999), between 67% and 100% in swordfish muscle and canned tuna (Kamps and Miller, 1972) and 81 – 100% in shark (Storelli *et al.,* 2001).

Are some types of fish/geographical locations better/worse?

3.50 There are a number of variables that can influence mercury fish tissue concentrations, including the species of fish, the size/length/age of the fish and the proximity of the fish during its lifetime to sources of mercury. FSA surveys to date have measured mercury in a variety of different fish species that are consumed in the UK, but considerations of size/length or geographical location were not factored into these surveys. A brief review of some of the available scientific literature gives an indication (as

described below) as to the importance of these factors, but it should be borne in mind that this review was not extensive.

Species

3.51 As discussed above, predatory fish can contain relatively high levels of mercury because they are high up the food chain. Unlike dioxins and PCBs, mercury is not specifically associated with oily fish. This was apparent in the results of a recent FSA survey of mercury in imported fish and shellfish, UK farmed fish and their products (Table 3.6) (FSA 2002c), in which shark, swordfish and marlin were found to contain higher levels of mercury than other marine fish. Other fish, such as fresh tuna and orange roughy were in the middle of the range of concentrations found, containing on average 2 – 4 times less mercury than those fish containing the highest levels of mercury. Canned tuna was found on average to contain half the amount of mercury as fresh tuna. This is because different species and smaller more immature fish are used for canning. Levels of mercury in other fish were relatively low and similar to those found in a previous multi-element survey of the most commonly consumed marine fish. It must be stressed however that only a limited number of some species were sampled.

3.52 That some fish species accumulate higher levels of mercury is also reflected in EU legislation. EC Regulation 466/2001, as amended by EC regulation 221/2002 (Commission Regulation EC No 221/2002), sets a limit for total mercury of 0.5mg/kg in all fish, except for some species at a higher trophic level (such as shark, swordfish, marlin, pike and tuna) for which a higher maximum limit of 1 mg/kg applies. The vast majority of fish comply with these limits although occasionally samples of more exotic fish species such as shark and swordfish can contain higher levels. Increasing amounts of these fish can be found in shops, although the total amount of shark and swordfish (including marlin) imported and landed in the UK in 2001 is still minimal (around 1,500 tonnes), when compared with over 170, 000 tonnes of cod and haddock.

Table 3.7: Results of the 2002 survey of mercury in imported fish and shellfish, UK farmed fish and their products.

Fish	Samples	No of Levels of Hg (mg/kg) (adjusted for recovery) Minimum	Maximum	Median	Mean
Fresh/Frozen Fish					
Halibut	8	0.04	0.62	0.29	0.29
Hoki	2	0.08	0.31	0.19	0.19
Monkfish	2	0.1	0.30	0.20	0.20
Orange Roughy	6	0.53	0.65	0.60	0.60
Other*	13	0.006	0.661	0.04	0.11
Pollack	4	0.007	0.02	0.01	0.01
Salmon	14	0.03	0.08	0.05	0.05
Sea Bass	4	0.03	0.09	0.07	0.07
Sea Bream	4	0.05	0.06	0.05	0.05
Shark	5	1.00	2.2	1.4	1.5
Swordfish	13	0.15	2.7	1.4	1.4
Marlin	7	0.41	2.2	0.88	1.1
Trout	14	0.01	0.1	0.05	0.06
Tuna	20	0.1	1.5	0.31	0.40
Processed Smoked					
Other **	9	0.01	0.93	0.23	0.31
Salmon	9	0.04	0.08	0.05	0.06
Trout	9	0.05	0.09	0.07	0.07
Processed Canned					
Anchovy	9	0.03	0.06	0.05	0.05
Other ***	9	0.003	0.08	0.01	0.02
Pilchard	9	0.005	0.05	0.01	0.02
Salmon (Pink)	19	0.008	0.04	0.03	0.03
Salmon (Red)	13	0.01	0.07	0.03	0.04
Sardine	9	0.01	0.10	0.03	0.04
Tuna	54	0.03	0.71	0.15	0.19

Notes:

1 Atlantic icefish

* Fresh/frozen fish - 'Other' included samples of: hake, red tilapia, plaice, sardines, St Peter's fish, snapper, Mekong catfish, Antarctic ice fish, haddock and anchovies.

** Processed, smoked 'Other' included samples of: haddock, halibut, eel, swordfish, tuna, marlin, mussels and oysters.

*** Processed canned 'Other' included samples of: lumpfish caviar, vongole, crab, clams, oysters, cockles, cod roe, shrimps and herring.

3.53 The last two FSA/MAFF surveys of fish have covered those fish which are most widely or frequently consumed in the UK. However, there is likely to be a number of species consumed in the UK that have the potential to accumulate relatively high levels of mercury and on which we have no data. These could include predatory species such as pike and bass. We also

have limited data on variation in fish families – for instance shark and tuna. In the FSA survey, fish labelled as shark were analysed, but other members of the shark family such as huss and dogfish – popular in fish and chip shops – were not sampled.

Size

3.54 A large number of studies in the scientific literature have reported a positive correlation between the size of fish and mercury levels reflecting an accumulation with age (Holsbeek *et al*., 1997; Polak-Juszczak and Sobolewska, 1999; Burger *et al*., 2001). This is not surprising as those fish species which live longer and grow to greater sizes have longer for methylmercury to build up in their bodies. It has previously been proposed that this correlation may be strong enough to be used as an approach to regulating mercury in fish, that is to establish fish size limits with safe heavy metal concentrations (Storelli *et al*., 2002).

Geographical location

3.55 Studies of fish from areas of known mercury pollution have found higher levels of mercury than in fish from less contaminated areas (Diaz *et al.,* 1994; Abreu *et al.*, 2000; Gerstenberger and Dellinger, 2002) and location is considered to be an important factor in predicting mercury fish tissue concentration (Qian *et al.,* 2001). This may reflect that the uptake of mercury can be faster by fish in contaminated areas and hence they can achieve a higher tissue mercury content in a shorter period of time (Castilhos *et al*., 2001).

3.56 However, it is often difficult to compare the results of different studies investigating the relationship between geographical location and mercury content because of the inconsistency in information provided in terms of sample size and fish length and weight, which are significant variables in themselves (Storelli *et al*., 2002). A number of studies have not demonstrated a significant difference in mercury fish muscle levels from different locations (Burger *et al*., 2001), which may reflect the movements or migration patterns of the fish (Polak-Juszczak, 1996).

Origin labelling

3.57 The Fish Labelling (England) Regulations came into force on 28th March 2003. The new Regulations require that certain fish products* must be labelled with:

a) A commercial designation (i.e., an agreed name for that species)

b) The production method (i.e., whether it is farmed, or caught in the wild)

c) The catch area (i.e., an area of the ocean in the case of sea caught fish; the member state or country of origin in the case of farmed fish or fish caught in inland waters.).

Effects of mercury

3.58 Humans may be exposed to three forms of mercury: elemental, inorganic and organic. There is a common mechanism of mercury toxicity, binding of mercuric ions to thiol groups in proteins leading to alterations in cell function and cell death. However, the organs affected vary as a result of differences in the physicochemical properties between the three forms. The mercury present in fish is methylmercury (organic form), whereas inorganic mercury is more likely to be present in other foods. Organic mercury is considered to be more toxic than other forms of mercury following ingestion. The threshold approach is considered to be appropriate.

3.59 Acute toxicity of methylmercury affects the kidneys and the central nervous system. The developing central nervous system of the fetus is particularly at risk. High exposure *in utero* has resulted in cerebral palsy or severe mental retardation in the neonate. Based on a number of poisoning incidents (Minamata, Niigata, Iraq), JECFA concluded that a minimum level of toxicity would be associated with exposures resulting in 200 μg/L

* The fish products covered are those included in Chapter 3 of the customs tarrif codes. Broadly speaking, this is fish and shellfish that has not been cooked / processed, and that does not contain any additional ingredients, e.g. fresh, frozen and chilled fish, smoked fish, boiled crustaceans and molluscs, shelled/peeled crustaceans and molluscs. Value added products such as fish fingers and ready meals are not covered.

mercury in blood or 50 μg/g mercury in hair. This association was used to derive a PTWI for methylmercury of 3.3 μg/kg bw/week (corresponding to a blood mercury level of 33 μg/L or hair mercury level of 8.25 μg/g in a 70kg adult). JECFA noted that pregnant women and nursing mothers may be at greater risk than the general population (WHO, 2000).

3.60 Exposure in pregnant women, at levels without effect in other adults, has been reported to cause subtle neurological defects such as delays in reaching milestones (walking, talking) and reduced learning capacity. A number of epidemiological studies have been conducted in an attempt to establish a threshold for the effects on the neurodevelopment of children, the major ones based in the Faroe Islands and Seychelles Islands (Grandjean *et al.*, 1997; Davidson *et al.,* 1998). These studies have investigate whether effects are occurring in populations with exposures associated with maternal hair mercury concentrations in the region of 10 μg/g, correlating with a dietary intake of about 0.7 μg/kg bw/day. However the epidemiological evidence is inconsistent, the Faroe Islands study has demonstrated detrimental effects, whereas that in the Seychelles has not. In contrast, higher scores (enhanced performance) in some measures were associated with higher mercury exposure in the Seychelles study, which the researchers considered to be possibly due to the assumed beneficial effects of fish consumption. Based on the data from the Faroe Islands, and earlier incidents in Iraq, the US Environmental Protection Agency (EPA) concluded that effects would be expected in 5% of the population with 12 μg mercury/g of maternal hair. This was used in setting a reference dose (RfD) for methylmercury of 0.1 μg/kg bw/day (NRC, 2000).

3.61 In June 2003, JECFA revised its PTWI to 1.6 μg/kg bw/week, in order to be protective of the developing fetus. This evaluation took into account new data from the Seychelles Child Development Study, re-analyses of the Faroes study, and additional epidemiological data, including inconclusive evidence of an association with cardiovascular disease.

Uncertainty in the TDI & RfD

3.62 There are a number of uncertainties involved in assessing the evidence, setting the safety guideline and comparing this to realistic exposures:

a) Inconsistencies in the epidemiological evidence lead to uncertainty over which data should be used in establishing a safety guideline

b) The EPA took a more precautionary approach than JECFA, basing its RfD on a minimal human effect level for the high risk groups, using an uncertainty factor of 10 for human variability. An uncertainty factor of 10 is normally used to extrapolate from the average to the most sensitive individuals and may be unnecessarily high to allow for variability within the high risk group.

c) There are differences between the affected populations and the UK population

Dietary exposures to mercury

3.63 The estimated dietary exposure to total mercury from the UK diet is 3.1 µg/day for an average adult consumer (equivalent to 0.044 µg/kg bw/day for a 70.1 kg adult) and 6.4 µg/day for a high-level consumer (equivalent to 0.09 µg/kg bw/day for a 70.1 kg adult). These results come from a survey of metals in the 1997 UK TDS (MAFF, 1999b) and are similar to estimates for other countries.

3.64 Dietary exposure of UK consumers of fish were estimated from the results of a survey of mercury and other metals in various commonly-consumed fish and shellfish and reported in May 1998 (MAFF, 1998b). In this survey, a high-level adult consumer of fish or shellfish had an estimated exposure to mercury of 11 µg/day (equivalent to 0.16 µg/kg bw /day assuming average bodyweight of 70.1 kg).

3.65 An FSA survey of mercury in exotic fish species including shark, swordfish and marlin, as well as other imported fish products like fresh and canned tuna, and UK farmed salmon and trout was recently carried out. The aim was to provide data on fish and shellfish on which we previously had limited or no information, and to keep our exposure estimates up-to-date. The following tables are the exposure estimates for fish where consumption data were available (Table 3.8), or for fish for which there is no consumption data in the NDNS, the averaged intakes arising from one

weekly portion of fish (canned tuna is included for comparative purposes) (Table 3.9).

Table 3.8: Estimated mean and high level dietary intakes of mercury from salmon, prawns, canned tuna and the whole diet.

Consumer group	Mercury Intake - µg/kg bw/day 1							
	Salmon [2]		Prawns [2]		Canned Tuna [2]		Whole Diet [3, 4]	
	Mean	97.5%	Mean	97.5%	Mean	97.5%	Mean	97.5%
Infants	0.0014	0.0014	0.00	0.00	0.0057	0.019	0.0086	0.02
Toddlers	0.026	0.076	0.019	0.064	0.12	0.35	0.12	0.29
Young People aged 4–6	0.026	0.056	0.013	0.049	0.076	0.23	0.11	0.26
Young People aged 7–10	0.016	0.051	0.0086	0.021	0.056	0.18	0.089	0.20
Young People aged 11–14	0.013	0.033	0.0057	0.019	0.046	0.14	0.061	0.17
Young People aged 15–18	0.011	0.021	0.0057	0.016	0.039	0.097	0.051	0.12
Adults	0.0086	0.034	0.0057	0.02	0.036	0.089	0.05	0.12
Adults Women only	0.0086	0.026	0.0057	0.017	0.039	0.089	0.049	0.11

Notes:

1 Consumption data for salmon, prawns and tuna are taken from the following sources:
- Dietary and Nutritional Surveys of British Adults (Gregory et al., 1990).
- Food and Nutrient Intakes of British Infants Aged 6-12 Months (Mills and Tyler, 1992).
- National Diet and Nutrition Surveys Children Aged 1.5 – 4.5 years (Gregory et al., 1995).
- National Diet and Nutrition Survey: young people aged 4-18 years. Volume 1 report of the diet and nutrition survey (Gregory et al., 2000)

2 Mercury intake from eating the named fish only, for the mean and 97.5th percentile consumers.

3 Mercury intake from consumption of fresh salmon, prawns, canned tuna and the rest of the normal UK diet (based on the 1997 TDS) for consumers of fish 27. The total mercury intakes do not equal the sum of the mercury intakes from the named fish because the populations of consumers differ (for example not all fish consumers eat prawns).

4 The measurement of mercury does not distinguish between inorganic and organic mercury. Therefore although methylmercury is the major contributor to mercury intake from fish, the estimate of intake from the whole diet also includes inorganic mercury.

Table 3.9: Mercury intake from one portion of shark, swordfish, marlin, fresh tuna or canned tuna.

Age group (years)	Body Weight (kg)	Average Portion Size (g)	Weekly methylmercury intake assuming one portion of fish per week (µg/kg bw/day)				
			Shark	Swordfish	Marlin	Fresh Tuna	Canned Tuna
1.5 – 4.5	14.5	50	0.75	0.66	0.54	0.20	0.094
4 – 6	20.5	60	0.63	0.56	0.46	0.17	0.080
7 –10	30.9	85	0.60	0.53	0.43	0.16	0.074
11 – 14	48.0	140	0.63	0.56	0.46	0.17	0.079
15 – 18	63.8	105	0.36	0.32	0.26	0.094	0.044
Adults	70.1	140	0.43	0.38	0.31	0.11	0.054

Notes:

1 The average portion size that each age group of the population would consume at a single meal event for fish consumption, as recorded in the following National Diet and Nutrition Surveys (NDNS):
•1995 National Diet and Nutrition Survey: Children aged one-and-a-half to four-and-a-half years (Gregory et al., 1995).
•2000 National Diet and Nutrition Survey: young people aged 4 to 18 years (Gregory et al., 2000).
•1990 The Dietary and Nutritional Survey of British Adults (Gregory et al., 1990).

2 This intake estimate does not include the intake from the rest of the diet, which is estimated to be 0.052 µg/kg bw/day for a 60kg average consumer (0.36 µg/kg bw/week). However not all of this will be methylmercury.

COT assessment

3.66 The COT considered methylmercury toxicity in 2002 following the survey of mercury levels in imported and UK farmed fish (COT, 2002). COT concluded that because of the risk to the developing brain and nervous system of the fetus or neonate, pregnant women, women who may become pregnant within the next year and breast feeding mothers should be considered as high risk groups when considering methylmercury toxicity. Whilst the JECFA PTWI was sufficiently protective for the general population, the EPA reference dose would be more applicable for the high-risk groups since it is based on the effects on the developing fetus.

3.67 The COT concluded:

a) Average and high-level dietary exposure to mercury is within the JECFA PTWI for methylmercury for all age groups.

b) Adult women who are high level consumers of fish may marginally exceed the EPA reference dose for methylmercury but this would be unlikely to result in adverse effects to the developing fetus.

c) Consumption by adults of one weekly portion of shark, swordfish or marlin would result in a dietary exposure close to or exceeding the JECFA PTWI. This consumption was not expected to result in adverse effects in the general population, but could be harmful to the fetus or breast-fed infant. For children less than 14 years of age, the occasional consumption of these fish would not be expected to result in adverse effects.

d) Consumption of one portion (140g) of fresh tuna or two medium-size cans of tuna a week (with a drained weight of about 140g per can) by pregnant women, women who may become pregnant within the next year and breast feeding mothers would not be expected to result in adverse effects on the developing fetus or neonate.

3.68 Following the revision of the JECFA PTWI in June 2003, the COT reviewed its opinion and issued an updated statement (COT, 2003). The updated COT conclusions were:

- We *note* that there has been no new information published to indicate that the 2000 PTWI of 3.3 µg/kg bw/week is not sufficiently protective of the general population. We therefore *consider* that a methylmercury intake of 3.3 µg/kg bw/week may be used as a guideline to protect against non-developmental adverse effects.

- We *conclude* that the 2003 JECFA PTWI of 1.6 µg/kg bw/week is sufficient to protect against neurodevelopmental effects in the fetus. This PTWI should be used in assessing the dietary exposure to methylmercury of women who are pregnant, and who may become pregnant within the following year.

- We *consider* that a guideline of 3.3 µg/kg bw/week is appropriate in considering intakes by breastfeeding mothers as the intake of the

breast-fed infant would be within the new PTWI of 1.6 µg/kg bw/week.

- We *consider* the NDNS blood level data are reassuring with respect to average and high level consumption of fish. The adults surveyed had blood mercury levels indicating that 97.5% of the population had dietary intakes below 1.6 µg/kg bw/week.

- We *conclude* that average and high-level dietary exposure to methylmercury, resulting from the wide range of fish for which consumption data are available, is not likely to be associated with adverse effects in the developing fetus or at other life stages.

- We *note* that consuming one weekly 140 g portion of either shark, swordfish or marlin would result in a dietary methylmercury exposure close to or above 3.3 µg/kg bw/week in all age groups. We *consider* that this consumption could be harmful to the fetus of women who are pregnant or become pregnant within a year, but would not be expected to result in adverse effects in other adults.

- We *note* that the mercury content of tuna is lower than that of shark, swordfish or marlin, but higher than that of other commonly consumed fish. We *consider* that consumption of two 140g portions of fresh tuna, or four 140g portions of canned tuna, per week, before or during pregnancy would not be expected to result in adverse effects on the developing fetus.

- We *recommend* that further research should include development of analytical methodology to allow direct measurement of methylmercury, mechanistic studies to help elucidate population groups more at risk and research integrating the risks with nutritional benefits of fish consumption.

3.69 The Inter-Committee Subgroup has further reviewed estimated intakes of mercury from 1 to 3 portions of oily fish per week (Table 3.10). These values are compared with the PTWI and Guideline Level for methylmercury. Non-fish sources of mercury are not included in this

comparison, since they are likely to be inorganic forms, which are less well-absorbed and therefore less toxic via the oral route. Furthermore, not all mercury in fish is expected to be methylmercury, and therefore this comparison is precautionary.

3.70 These data demonstrate that commonly consumed oily fish, other than swordfish and fresh tuna, are unlikely to result in exceedance of the PTWI.

Mercury in fish oils

3.71 The levels of mercury measured in fish oil supplements were analysed in a survey of dietary supplements reported in 1998 (MAFF, 1998c) and were found to be lower than those found in fish. The COT considered these results and concluded that estimated dietary intakes of metals from the supplements analysed in addition to the rest of the diet were not a cause for concern.

Mercury in infant foods

3.72 The FSA has recently carried out a multi-element survey of a wide range of manufactured infant foods (FSA 2004). 189 samples of commercial baby foods (infant formulae, manufactured ready-to-eat and dried baby foods, desserts, rusks and infant drinks) were analysed for mercury and 11 other metals and elements. Infants consume a diet that is different in many ways from that of adults and of children old enough to eat conventional adult foods. Infants' diets are made up of a more restricted range of foods, particularly before and in the early stages of weaning when the diet is made up entirely or largely of breast milk and/or commercial infant formulae. On weaning, solids may be given, a large proportion of which may be commercially available baby foods. The composition of commercial infant formulae and baby foods can be very different from the foods that make up the diet of the general population.

3.73 Mercury was detected at concentrations at or above the Limit of Detection (LOD) in about one quarter of the samples in this survey, most of which are dried foods. The mean mercury concentration was 0.003 mg/kg, with a range of less than 0.0005 mg/kg to 0.02 mg/kg. Both the mean and maximum mercury concentrations are twice that of the last infant food

Table 3.10: Estimated dietary intake of mercury from oily fish and the rest of the diet for an adult of 60 kg bodyweight

	Herring	Mackerel	Salmon	Trout	Fresh Tuna	Swordfish
Concentration [a] (µg /g wet weight)	0.09	0.05	0.05	0.06	0.4	1.4
Intake from one portion fish per week [b] (µg/kg bw/week)	0.21	0.12	0.12	0.14	0.93	3.27
Intake from rest of the diet [c] (µg/kg bw/week)	0.21	0.21	0.21	0.21	0.21	0.21

	% PTWI or guidance level for methylmercury											
Portions per week	Herring		Mackerel		Salmon		Trout		Fresh Tuna		Swordfish	
	%PTWI [d]	%GL [e]	%PTWI	%GL	%PTWI	%GL	%PTWI	%GL	%PTWI	%GL	%PTWI	%GL
1	13	6	7	4	7	4	9	4	58	28	204	99
2	26	13	15	7	15	7	18	8	117	57	408	198
3	39	19	22	11	22	11	26	13	175	85	613	297
4	53	25	29	14	29	14	35	17	233	113	817	396

a Concentrations in oily fish species and cod taken from surveys for mercury in marine fish 1995-97 (cod, herring and mackerel) and 2002 (salmon and trout). Predominantly but not exclusively in the form of methylmercury.

b Assumes 140g portion size for all fish

c Averaged weekly intake of mercury from the non-fish part of the diet (0.06 (mg/kg bw/week) and from one portion of cod per week (0.15 mg/kg bw/week). Provided for information, but not included in the comparison with the PTWI and guidance level

d PTWI = 1.6 mg/kg bw/week for methylmercury

e Guideline level for less susceptible subgroups = 3.3 mg/kg bw/week for methylmercury.

survey reported in 1998 (mean of 0.0014 mg/kg, range <0.0003 mg/kg to 0.01 mg/kg). However, the increase in the mean concentration of mercury is in part due to the slight decrease in sensitivity for mercury analyses in this survey. This resulted in increased LODs which will effect the upper bound mean values reported (compared to LODs in previous survey, the higher LODs have increased the mean by about one third).

3.74 In the absence of current consumption data for this age group (the most recent UK infant dietary survey is 1986), three approaches were taken to estimate infant exposure. The COT used two of these approaches (the third was not considered appropriate because of insufficient supporting data). Exposures were estimated using consumption data from the 1986 infant survey (6-12 month olds), and using manufacturers feeding recommendations (from birth to 12 months), thus providing a range of exposures that could be compared to relevant safety guidelines. The approach based on manufacturer's feeding recommendations is a worst case, as it does not take into account wastage/non-retention of food by the infant. A summary table of exposures is given below (Table 3.11).

3.75 The major contribution to dietary mercury exposure was from ready-to-feed manufactured meals. Fish containing meals (7 samples) made a significant contribution to the mean concentration of mercury in this food group, accounting for approximately half of the mercury reported (although they only accounted for a small proportion of the overall mean mercury concentration for all foods surveyed – about one thirtieth). Fish containing meals contributed about one fifth of the dietary exposure to mercury using this approach. However, since this survey was carried out, the manufacturers of the fish meals covered in this survey either no longer manufacture fish containing infant foods or have ceased to manufacture infant foods entirely.

3.76 Fish containing meals made less of an overall contribution to mercury exposures estimated using the other approach which was based on manufacturers feeding recommendations.

Table 3.11: Dietary exposures to mercury from manufactured infant foods using Approach 1 (6-12 month old UK infant survey) and Approach 2 (manufacturers feeding recommendations).

		Intake for each age range (mg/kg bw/day)			
		0-3	4-6	7-9	10-12
Approach 1	Mean			0.04	
	97.5%			0.11	
Approach 2	Normal Diet	0.07	0.18	0.18	0.19
	Soya Diet	0.07	0.19	0.19	0.20

COT Assessment

3.77 The COT considered that the increase in the concentrations of mercury in infant foods could, in part, be accounted for by the number of fish meals and the higher limit of detection for mercury in this survey compared to the previous one.

3.78 In considering the exposure estimates the COT took a precautionary approach, assuming that all of the mercury was in the more toxic organic form and that the 2003 JECFA PTWI for methylmercury of 1.6 μg/kg bw/week (0.23 μg/kg bw/day) was the most appropriate safety guideline. The COT concluded that:

a) The consumption of the infant foods sampled in the survey would not result in the intake of such quantities of any of the analysed elements such as would give concern for the health of infants.

b) The levels of mercury in the foods should continue to be monitored to ensure that they are not rising.

Other inorganic contaminants that can accumulate in fish that are of toxicological concern.

Arsenic

3.79 Arsenic can enter the environment from natural sources, such as rocks and sediments, and as a result of human activities such as coal burning, copper smelting, dye production from tanneries and processing of mineral ores (National Academy of Sciences, 1977). Arsenic has a high ability to

accumulate in bottom sediments (Svobodova *et al.,* 2002), so arsenic levels are higher in the aquatic environment than on land. Therefore, marine and mainly marine crustaceans and molluscs strongly accumulate arsenic compounds.

Toxicology

3.80 Arsenic in drinking-water (primarily inorganic, as arsenate and to a lesser extent arsenite) is classed as "carcinogenic to humans" (Group 1) on the basis of "sufficient evidence" for an increased risk for cancer of the urinary bladder, lung and skin (IARC, 2002). Chronic exposure to arsenic in drinking water has also been associated with peripheral vascular diseases, cardiovascular diseases and possibly with diabetes and reproductive effects.

3.81 Most arsenic in fish (>90%) is in the form of arsenobetaine which is also the main form found in crustaceans and bi-valve molluscs, the remainder is arsenocholine and a small amount of inorganic arsenic (usually < 1%) (Kohlmeyer *et al.*, 2002). Fish is the main source of arsenic in the diet; arsenobetaine is therefore the main form of arsenic present in food.

3.82 The fate of organic arsenic has not been clearly defined in experimental animals or in humans. In general organoarsenicals are thought to be less extensively metabolized than inorganic arsenic and more rapidly excreted. Limited data indicate that organic arsenic compounds such as arsenobetaine and arsenocholine are not converted to inorganic arsenic *in vivo.* Despite the limited database, the organic forms of arsenic are generally assumed to be less toxic than the inorganic compounds. In contrast to mercury, there are no reports of toxicity in man or animals from the consumption of organoarsenicals in seafood. Limited data indicate that arsenobetaine and arsenocholine are not genotoxic in mammalian cells *in vitro*.

3.83 The COT has concluded that there are no relevant tolerable intakes or reference doses by which to assess safety of either inorganic or organic arsenic in the diet. Inorganic arsenic is genotoxic and a known human carcinogen, and therefore exposure should be as low as reasonably practicable (ALARP) (COT 2003).

Exposure

3.84 Fish generally contains relatively high levels of arsenic compared with other foods and is the most significant source of arsenic in the UK diet. In the 1997 UK TDS (MAFF, 1999b), the fish group contained the highest average concentrations of arsenic [4.4 mg/kg in comparison with other food groups which contained average arsenic concentrations ranging between 0.0004 and 0.007 mg/kg]. Fish consumption contributed 94% of the average population dietary exposure to arsenic in comparison to the next most significant dietary contributor of 2% (jointly, bread, miscellaneous cereals and beverages which each contributed 2%).

3.85 Inorganic arsenic was measured for the first time in the 1999 UK TDS. Again in this survey, the fish group contained the highest average level of total arsenic (3.2 mg/kg, 44 times greater than the poultry food group, which contained the second highest average level, 0.073mg/kg). Inorganic arsenic was only measurable in three out of the twenty food groups that make up the TDS - fish, poultry and miscellaneous cereals. This is because all other food groups contained levels of total arsenic below the LOD for inorganic arsenic. The highest average level of inorganic arsenic was recorded for the fish group (0.0159 mg/kg).

3.86 Fish consumption again contributed the major portion (almost 90%) of the average population dietary exposure to total arsenic. Most of this exposure is to organic species of arsenic as can be seen from consumer exposure estimates. For an average adult consumer, dietary exposure to total arsenic from fish is 1.63 μg/kg bw/day, whereas exposure to inorganic arsenic is 0.008 μg/kg bw/day. For a high level consumer, dietary exposure to total arsenic from fish is 4.64 μg/kg bw/day, whereas exposure to inorganic arsenic is 0.023 μg/kg bw/day.

COT Assessment

3.87 The COT noted that fish is a major contributor to dietary exposure to arsenic with the predominant form of arsenic in fish being organic. Members also noted that the general assumption that organic arsenic is less toxic than inorganic arsenic is based on an extremely limited database. However they considered that there is no evidence that exposure to organic

arsenic through high levels of fish consumption would result in harmful effects, and therefore concluded that the dietary exposure to organic arsenic identified in the survey was unlikely to constitute a hazard to health.

3.88 The COT were also reassured that the average population dietary exposure to total arsenic was lower than that estimated for previous years, indicating that dietary exposure to total arsenic through food is not increasing

Manufactured infant foods

3.89 As described in the above section on mercury, the FSA has recently completed a multi-element survey of infant foods.

3.90 Arsenic was detected in most samples but generally at very low concentrations (mean 0.023 mg/kg, range of less than 0.0002 to 0.78 mg/kg), with the highest concentrations found in products containing fish. Higher levels were also seen in manufactured meals containing poultry and rice, although these were lower than the levels measured in fish-containing dishes. These results are consistent with results obtained for the foods making up the adult diet and with other scientific literature. The mean value for all foods is similar to the mean of 0.016 mg/kg found in a 1998 MAFF survey of infant foods. (MAFF, 1998d)

3.91 Exposures to arsenic from manufactured infant foods were estimated as described in the section on mercury and are summarized in table 3.11 below.

Table 3.12: Dietary exposures to arsenic from manufactured infant foods using Approach 1 (6-12 month old UK infant survey) and Approach 2 (manufacturers feeding recommendations).

		Intake for each age range (µg/kg bw/day)			
		0-3	4-6	7-9	10-12
Approach 1	Mean			0.25	
	97.5%			0.87	
Approach 2	Normal Diet	0.09	1.3	1.8	1.8
	Soya Diet	0.18	1.6	2.0	1.9

3.92 The COT considered that whilst the intakes of arsenic calculated using manufacturers feeding recommendations (approach 2) were high, those calculated using approach 1 are comparable to those seen in the previous survey and so it is unlikely that there has been an increase in exposure to arsenic. This was corroborated by the similar levels of arsenic found in infant foods compared to those seen in the previous survey. They concluded that:

a) The consumption of the infant foods sampled in the survey would not result in the intake of such quantities of any of the analysed elements such as would give concern for the health of infants.

b) There are no relevant tolerable intakes or reference doses by which to assess safety of either inorganic or organic arsenic in the diet. Inorganic arsenic is genotoxic and a known human carcinogen therefore exposure to inorganic arsenic should be as low as reasonably practicable (ALARP). However it was reassuring that since the previous survey arsenic intakes do not appear to have increased.

Lead and Cadmium

3.93 EC Regulation 466/2001, as amended by EC Regulation No 221/2002, sets limits for lead, cadmium, mercury and 3-monochloro propandiol (MCPD) in those foods which contribute significantly to dietary exposure. There are limits for both lead and cadmium in fish. However, in comparison to other food groups that make up the typical UK diet, fish is not one of the top 5 dietary contributors of either contaminant in the UK (MAFF, 1999b).

Cadmium

3.94 Cadmium occurs naturally in association with other metals and ores, and is widely distributed in the Earth's crust. It is also released by human activities and is a pollutant that is not degraded in the environment. Some cadmium enters the general environment from the natural weathering of minerals, from forest fires and volcanoes, but much larger amounts are released by human activities. These include production of non-ferrous metals and of iron and steel, combustion of fossil fuels, waste incineration,

and application of phosphate fertilizer and sewage sludges (Environment Agency, 2002b).

3.95 Some forms of cadmium can dissolve in water, either in rivers and ponds or in soil water. Cadmium is not very soluble and is found mainly in sediments and suspended particles. In general, cadmium enters the marine environment from atmospheric deposition and from effluent discharges. Aquatic animals, notably fish and invertebrates, absorb cadmium directly from the water, as well as from food. Cadmium is taken up directly from seawater by absorption through the cell membrane. Cadmium is reported in the literature at higher levels in fish detoxifying organs and in some species which can naturally accumulate higher levels of cadmium (Mason *et al.,* 2000). This is reflected in the EC Regulation that set a higher maximum limit for certain fish species, and only applies to muscle meat. Levels of cadmium reported in a multi-element survey of the most commonly consumed marine fish in the UK (MAFF, 1998b) were all below EC limits.

Exposure

3.96 Food and tobacco smoke constitute the most important routes for human exposure to cadmium (Friberg *et al.,* 1986). Cadmium is present at low concentrations in most foods, with those that are consumed in larger quantities making the greatest contribution to population dietary exposure. For example, from the 1997 TDS (MAFF, 1999b), cadmium concentrations in food were highest in the offal (0.077 mg/kg) and nuts (0.059 mg/kg) food groups, whereas the bread and potatoes food groups contributed the most to dietary exposure of the general population (i.e. each contributed 25% of the dietary exposure). The fish group contributed 2% of total dietary exposure to cadmium.

Lead

3.97 Lead occurs naturally in the silicate lattice of rocks and is released into the environment by a number of processes such as weathering of rocks, volcanic activity and its uptake, and subsequent release by plants. Forest fires, sea spray, plant uptake and release and windblown dusts redistribute lead in the environment (Environment Agency, 2002c).

3.98 Anthropogenic sources such as the effects of lead mining, smelting and processing, the burning of fossil fuels over many thousands of years and its long residence time in the environment have resulted in lead becoming an ubiquitous environmental pollutant. Currently, lead is used in paints, plastics, batteries, roofing materials, etc.

3.99 Like cadmium and some other inorganic chemical contaminants, lead associates with sediment. It is also labile and may be highly available for up-take by organisms. Some species of fish naturally accumulate higher levels of lead, and this is reflected by a higher limit for those species (EC Regulation 466/2001).

Exposure

3.100 Food is one of the major sources of lead exposure in the UK, the others being air and water. Dietary exposures of the general UK population have declined from 0.12mg/day estimated from the 1980 TDS to 0.026 mg/day from 1997 TDS (MAFF, 1999b). Although exposure has decreased over this period, the extent of the decrease is in part an artefact of the reduction in the limit of detection for lead over this period. The cause of this decrease is partly because of a lowering of the LOD for lead, but an actual decrease in exposure is also evident. This decrease in dietary exposure reflects the success of the measures taken by the UK and the EC to reduce lead exposure and contamination of food. Mean concentrations of lead in the 20 food groups analysed were all below 0.1 mg/kg, with the highest mean concentration of lead seen in the offals group (0.09 mg/kg). Beverages made the greatest contribution to the population dietary exposure (54%), because of the high levels of consumption of this food group. The fish group was reported with a mean concentration of 0.02 mg/kg, and fish consumption accounted for less than 1% of the overall population dietary exposure to lead.

3.101 A survey reported in 1998 (MAFF, 1998b) on the concentration of metals and other elements in commonly eaten marine fish, reported levels close or below the limit of detection for all samples, which were within the EC limit for lead of 0.2 mg/kg.

Other organic environmental contaminants

3.102 A large number of other contaminants may accumulate in fish, and there are varying amounts of information on the toxicity of these. Fish containing high levels of dioxins and PCBs are also likely to contain high levels of non-dioxin like PCBs. There is currently no agreed method of risk assessment for these compounds, although this is the subject of combined discussions of the European Food Safety Authority, US EPA and World Health Organization, scheduled for completion in December 2004.

Other inorganic environmental contaminants

3.103 In addition it should not be assumed that substances generally viewed as nutrients are necessarily safe when ingested in large amounts. For example, daily use of selenium supplements together with high level dietary exposure results in a selenium intake that is at the Safe Upper Level (SUL) recently proposed by the Expert Group on Vitamins and Minerals. High fish consumption could potentially result in the SUL being exceeded for an individual who is also taking supplements. The implications of this may depend on the simultaneous presence of methylmercury in fish as there is evidence that selenium counteracts the harmful effects of methylmercury.

Mixtures of chemicals

3.104 The evaluation of dioxins and dioxin-like PCBs allows for the combined additive effects of these substances, because they are considered to act by a common mechanism. The COT recently completed a comprehensive evaluation of the risk assessment of mixtures of pesticides and similar substances, the conclusions of which are also relevant to mixtures of other classes of chemicals. The COT concluded that when exposure levels of chemicals within a mixture are within the no-effect levels, and the components have different modes of toxic action, no additivity or potentiating interactions are found.

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