STATEMENT BY THE COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT ON THE HEALTH HAZARDS OF POLYCHLORINATED BIPHENYLS

Introduction

Background

1. Polychlorinated biphenyls (PCBs) are a group of 209 chlorinated hydrocarbons which were widely manufactured from the 1930s to the 1970s for a range of industrial applications. They are environmentally stable, lipophilic chemicals which accumulate in biological systems. The recognition that PCBs have a substantial environmental impact has led to severe restrictions on their use and to international commitments to phase out the use of PCBs and of electrical equipment containing them. Nevertheless, PCBS may still be released to the environment, mainly during the disposal of transformers and capacitors, and, because of the properties of these chemicals, they are likely to persist as contaminants of the environment and of food for many years to come.

2. We last considered PCBs in 1983, when we recommended that the PCB content of the average national diet was unlikely to constitute a health hazard (1). Since then, a considerable amount of new toxicity data has become available and developments in the analysis of PCBs have produced more specific information on the levels of individual PCB congeners in food. Therefore, we have updated our review of the human health hazards of PCBs and our conclusions are given in this statement. We have also been asked to advise on the health significance of current intakes of PCBs from the diet and from fish oil dietary supplements by the UK population (2,3) and on intakes of PCBs by breast-fed babies in the UK (4). This advice is given below.

General Observations

3. There is a large scientific literature on the toxicity of PCBs which reports the results of conventional animal toxicology studies and of mechanistic studies to investigate further the action of PCBs on specific organ systems or toxicological endpoints. There are also many reports documenting effects in humans following high level exposure to PCBs, either in an occupational setting or following accidental exposures of the general population, such as in the Yusho and Yu-Cheng contaminated rice oil incidents in Japan and Taiwan, respectively (5,6). A few studies have been published on populations with background environmental or food exposure to PCBs. This information was presented to us largely in the form of detailed review papers prepared by our Secretariat, summarising the data from approximately 700 references. The quantity of information is such that it is not appropriate to make a detailed summary of it in this statement but we *encourage* the Secretariat to publish the detailed reviews prepared for our consideration in an appropriate scientific journal. In view of the large number

of references used, in this statement we have only referenced those papers which are specifically referred to or which are key to our risk assessment of PCBs[1].

4. There are 209 individual PCB congeners. The chemical structures of PCBs are given in Figure 1, together with those of the structurally similar environmental contaminants, polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). From a toxicological viewpoint, it is useful to subdivide PCBs into two categories: di-*ortho*-substituted PCBs, which are mostly non-coplanar, and non-*ortho*-substituted and other PCBs, which exist in a coplanar configuration. PCBs were sold and used commercially as mixtures of congeners which varied in their composition according to the manufacturer and the intended use. The mixtures were marketed under trade names such as Aroclor, Clophen or Kanechlor. The numbering system used to describe these commercial products usually includes a description of the percentage of chlorine present in the products eg Aroclor 1260 and Clophen A60 contain approximately 60% chlorine which is present in a range of different congeners. Until recently, most toxicological studies were carried out on these commercial mixtures. The individual congeners and the relative proportion of these congeners in the commercial mixtures are different from those found in food, because of differential uptake and metabolism of individual congeners along the food chain. Also, many of the commercial mixtures of PCBs used in these studies were contaminated with low levels of other pollutants, such as PCDFs, which may have confounded the results. A large number of studies are available investigating aspects of the toxicity of individual congeners but few of these are standard toxicology studies which can be used in risk assessment. All these factors have made the assessment of the human health hazards of PCBs a lengthy and difficult task.

Toxic Equivalency Factors

5. It is believed that PCDDs and PCDFs exert most of their toxicological effects by a common mechanism involving binding to an intracellular protein called the Ah (aryl hydrocarbon) receptor. This has enabled the development of "Toxic Equivalency Factors (TEFs)" for individual PCDD and PCDF congeners which have been developed and accepted on an international basis (7). This approach uses the available biological data and knowledge of the structural similarities among the PCDDs and PCDFs to generate a set of weighting factors for each congener, which expresses the potency of the congener as a proportion of that of the best studied PCDD congener, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Multiplication of the concentration of PCDD or PCDF congener by its TEF gives a TCDD Equivalent or Toxic Equivalent (TEQ). The toxicity of any mixture of PCDDs and PCDFs, relative to

[1] A list of all the references considered in this review is available from the Secretariat on request.

TCDD, is taken to be the sum of the individual TEQs. Where humans are exposed to that mixture, the risk to health can be assessed by reference to the Tolerable Daily Intake (TDI) of 10 pg/kg bw/day for TCDD. It should be noted that the TEQ approach is a simplistic approach, in that it assumes that there are no toxicological interactions between the individual PCDD and PCDF congeners; synergistic interactions would increase the toxicity whereas antagonistic interactions would reduce the toxicity of the mixture compared with that calculated using TEQs.

6. The toxicological data for some individual PCB congeners (notably certain non-*ortho* coplanar, mono-*ortho* coplanar and di-*ortho* coplanar congeners) indicate that the structure-activity relationships for a number of effects are consistent with an Ah-receptor mediated mechanism (ie "dioxin-like" activity). Therefore, as part of our review, we considered whether it would be appropriate to assign TEFs to these congeners and to assess the safety of a mixture of PCBs, PCDDs and PCDFs by reference to the TDI for TCDD (8).

Toxicity Assessment

Toxicokinetics

7. PCBs are well absorbed from the gastrointestinal tract. Some congeners may undergo metabolism in the liver to hydroxychlorobiphenyls and subsequent elimination via the faeces. There are wide differences in the rates and extent of metabolism and elimination among individual congeners. Thus there is a large range of elimination half-lives, for example, in rats, a range from 0.15 days for PCB 4 to 460 days for PCB 153 (2,2',4,4',5,5'-hexachlorinated biphenyl). PCB congeners which are not readily metabolised accumulate in lipid-rich tissues, predominantly adipose tissue. PCBs can cross the placenta. They can also be eliminated in milk, thus reducing the adipose tissue stores. Because PCBs are both stable and highly fat-soluble, they accumulate in the food chain.

Toxic Effects of PCBs

8. A number of toxic effects of PCB mixtures and individual PCB congeners have been documented in laboratory animals and the major effects are described briefly here.

General Toxicity

9. At high doses, PCBs cause overt, non-specific toxic effects in laboratory animals such as retardation of weight gain and poor clinical condition, with more selective effects at low doses. More specific effects include skin lesions (chloracne and/or lesions of the fingernails and gums); liver toxicity; and impairment of the function of both the humoral and cell-mediated immune systems. Effects have also been reported on the neurochemistry of the central nervous system in that treatment of animals with PCBs can cause a reduction in the concentrations of dopamine and its metabolites in a number of brain regions.

10. PCBs also have effects on the endocrine system such as reducing serum concentrations of the thyroid hormones thyroxine and triiodothyronine. The effect on thyroid hormones has been associated with induction by PCBs of the hepatic enzyme thyroxine-uridine diphosphate-glucuronyltransferase (UDPGT). We note the results of a recent human study on 105 mother-infant pairs which reports a correlation between PCDD, PCDF and PCB levels in human milk, expressed as TEQs, and lower thyroid hormone levels in maternal serum, and with higher plasma levels of thyroid stimulating hormone (TSH) in the infants (9). Although we have reservations about the methods used to estimate exposure in this study, these findings indicate a need for further work in a larger population to define better whether current human body burdens of PCDDs, PCDFs and PCBs are affecting thyroid hormone levels.

Reproductive Toxicity

11. Studies in a number of different animal species indicate that PCBs can affect reproduction and development. Among the effects seen are prolonged oestrus cycles in rats and mice and menstrual cycles in monkeys, impaired fetal or postnatal survival, and reduced birth weight in the offspring of PCB-treated animals. Some individual congeners are teratogenic in mice, producing a similar pattern of malformations to that documented in mice exposed to TCDD. Increased testis weight and daily sperm production have been reported in male rats receiving commercial PCB mixtures by injection in the early postnatal period although studies in older rats using dietary administration have not reported an effect on the testis. Effects on postnatal neurobehavioural development have been seen in rodents and in monkeys, although the interpretation of the findings in monkeys is complicated by the fact that the offspring and/or their mothers were exhibiting signs of severe PCB intoxication prior to testing for neurobehavioural performance.

12. Because of the importance of effects on reproduction in the animal toxicity profile of PCBs, we convened a sub-group with additional, co-opted expertise in epidemiology and psychology to examine the available data on PCB exposure and reproduction and postnatal effects in humans. The sub-group concluded that accidental exposure to high levels of PCBs, as occurred during the Yu-Cheng and Yusho rice oil contamination incidents, were probably associated with adverse effects on reproduction and postnatal development in humans. The available epidemiological studies of individuals exposed to high background dietary levels of PCBs have been inadequately conducted. There was no consistency in the effects on birth weight and gestational age reported in these latter studies which would suggest a link with exposure to PCBs. It is not possible to reach any conclusions regarding reported effects on reflexes and muscle tonicity in neonates as the magnitude of the reported effects was small and there are reservations about the methods used to assess these endpoints. Some of the epidemiological studies have documented effects on cognitive performance in infants and children but it is not possible, in

view of the inadequacy of the published studies, to associate any of the findings with background dietary exposure to PCBs. In summary, the sub-group's conclusion was that the available exposure and epidemiological data are not of sufficient quality to enable a quantitative estimate of risk of reproductive dysfunction following dietary exposure to be made. We *endorse* the conclusions of this subgroup. We have reviewed the report of a recent follow-up study on a group of children born to mothers with high background dietary exposures to PCBs (10), which concludes that *in utero* exposure to PCBs in concentrations slightly higher than those in the general population can have a long-term impact on intellectual function. We have concerns about the methodology used in this study and the lack of data on confounding factors and, because of these uncertainties, consider that the report is not sufficient to alter the sub-group's conclusions.

Mutagenicity and Carcinogenicity

13. We sought advice from our sister committees, the Committee on Mutagenicity (COM) and the Committee on Carcinogenicity (COC), on these aspects of the toxicity of PCBs. The COM has advised that most of the available data on the mutagenicity of PCBs relates to commercial preparations, principally Aroclor 1254, but also Aroclor 1242 and Kanechlor 500. These products consist of mixtures of a large number of compounds, and trace amounts of other chemical contaminants, such as PCDFs. Very limited data are available on specific PCBs. It concluded that commercial PCBs can be regarded as essentially 'non-genotoxic' and that any carcinogenesis in animal studies is likely to be produced by 'non-genotoxic' mechanisms. On specific PCB congeners, the COM advised that there is limited evidence that PCB 77 (3,3',4,4'-tetrachlorinated biphenyl) and mixtures of PCB 77 and PCB 52 (2,2'5,5'-tetrachlorinated biphenyl), but not the pure form of PCB 52, have clastogenic potential in an *in vitro* assay using human lymphocytes. There are, however, no adequate *in vivo* data on specific congeners and the absence of activity with the commercial PCBs in this regard would suggest that these congeners do not have significant mutagenic potential.

14. The COC noted that there was some evidence that PCBs acted as tumour promoters by a variety of mechanisms, possibly involving the Ah receptor or by stimulating cell proliferation and enzyme induction. A number of commercial PCBs have been shown to be carcinogenic in rats. Aroclors 1254 and 1260 and Clophen A60 induce hepatocellular carcinomas. Limited studies in mice indicate that Aroclor 1254 and Kanechlors 400 and 500 induce liver tumours in this species. The lowest effect level reported in these studies is 50 ppm in the diet (approximately 2.5 milligrams per kilogram bodyweight per day (mg/kg bw/day) given for up to 2 years). Although the data suggest that the less extensively chlorinated PCBs may be of lower carcinogenic potency, the COC has advised that it cannot be concluded that it is only the highly chlorinated PCBs that give rise to concern. Individual commercial PCB mixtures need to be

considered on a case by case basis when estimating carcinogenic potency.

15. The COC also advised that there are few data available on the carcinogenicity of PCBs in humans. In all the available studies the numbers involved were small and the results very difficult to interpret. Investigations on patients who consumed PCB-contaminated rice oil suggest that there was an increased incidence of liver cancer. Mortality studies in workers exposed to PCBs at capacitor manufacturing plants in the USA also suggest an increase in mortality from liver cancer. A report from a manufacturing site in Italy was uninterpretable because of the use of unrepresentative controls and lack of exposure data. The COC concluded that because of the inadequacies in these data it is not possible to reach a definite conclusion from the epidemiological data.

16. Several groups have investigated whether commercial PCBs (Aroclor 1254 and Kanechlor 500) have the potential to produce promoting effects in 2 stage *in vivo* models of chemically induced hepatocarcinogenesis in rats or mice. In all cases evidence of promoter activity was obtained.

17. Overall, the COC concluded that it would be prudent to assume that all PCB congeners are potential human carcinogens.

Discussion

18. A number of toxic effects of PCB mixtures and individual PCB congeners have been documented in laboratory animals. With the exception of effects on brain neurochemistry and certain effects on reproduction, the spectrum of toxicological effects seen with commercial PCB mixtures is similar to those previously reported for 2,3,7,8-TCDD and the structure-activity relationships for a number of effects are consistent with an Ah-receptor mediated mechanism (ie "dioxin-like" activity). There is evidence that effects on postnatal neurobehavioural development may be mediated through another, hormonal mechanism but there are insufficient data available to specify the critical hormonal pathways which are affected.

19. After reviewing the animal toxicity data on commercial PCB mixtures, we *conclude* that the most critical effects ie those seen at the lowest level of exposure, are those on the skin, the immune system, reproduction and postnatal behavioural development. It was not possible to derive No Adverse Effect Levels (NOAELs) for these effects from the available data but it is possible to derive Lowest Observed Adverse Effect Levels (LOAELs). A LOAEL of 5 micrograms (µg)/kg bw/day Aroclor 1254 has been identified for effects on the skin and on the immune system (11,12). The LOAEL for effects of commercial PCBs on reproduction is considered to lie in the range from 5 to 30 µg/kg bw/day, derived from studies in the monkey (11,13,14). There are problems in comparing the effects of PCBs on postnatal neurobehavioural development observed in different species of laboratory animals. However, the data indicate that the monkey is the most sensitive species and the LOAEL for this effect is 8

µg/kg bw/day based on a single generation study in the rhesus monkey using Aroclor 1016 (14,15). These LOAELs have been derived after consideration of all the available toxicological data on commercial PCB mixtures.

20. We have considered whether to set a Tolerable Daily Intake (TDI) for total PCBs by using the LOAELs for commercial PCB mixtures and application of appropriate safety factors. However, the pattern of PCB congeners present in foodstuffs does not accord with that present in commercial mixtures. We *conclude* that a TDI derived from studies on a commercial mixture of PCBs might be of value in evaluating the significance of occupational exposure to PCB mixtures, but not in evaluating the significance of dietary exposures to PCBs. Therefore, we have not set a TDI for total PCBs. We discuss below, in the context of advising on the health risk of current dietary exposures to PCBs, how the toxicological data on the commercial mixtures can be used to assess the significance of PCB contamination of food to human health for those congeners which are not "dioxin-like".

21. We also considered whether to adopt the TEF approach to estimate the risk of exposure to PCBs. We have reservations about this approach for a number of reasons. As stated above, not all toxicological endpoints of PCBs are mediated by an Ah-receptor mechanism. Many of the TEFs which have been derived for individual PCB congeners are based on limited data. Also, it should be borne in mind that most of the congeners found in food are not "dioxin-like". Interactions may exist between the "dioxin-like" and non-"dioxin-like" PCBs in a mixture which would affect a risk assessment based on strict additivity of TEFs. Nevertheless, the use of TEFs offers a pragmatic approach to the evaluation of "dioxin-like" PCBs and we *conclude* that they can be tentatively accepted and used in a limited manner for this purpose. The TEFs recommended by the WHO-ECEH/IPCS task force in 1994 (16) represent a consensus of current expert opinion and we *recommend* that these are used at present (see Table 1). The TDI of 10 pg TEQ/kg bw/day can therefore be used to assess the health risks of the intake of combinations of PCDDs, PCDFs and dioxin-like PCB congeners.

Health risk of current dietary exposures to PCBs

Adults

22. The recent data provided for our consideration are derived from a survey by the Ministry of Agriculture, Fisheries and Food (MAFF) of PCBs in UK Total Diet Study (TDS) samples collected in 1982 and 1992 (2). A total of 53 individual congeners were selected for analysis, after consultation with us, on the basis of their biological activity or distribution in food and other media.

23. We *welcome* the large decline in the estimated average UK

dietary intake of PCBs[2] from 1.0 µg/person/day in 1982 to 0.34 µg/person/day in 1992. We note that estimated high level (97.5 percentile) intakes have also decreased considerably, from 1.9 µg/person/day in 1982 to 0.6 µg/person/day in 1992.

24. The 1992 figures are equivalent to an average intake of PCBs of 0.006 µg/kg bw/day and a high level intake of 0.01 µg/kg bw/day for a 60 kg individual. These are approximately 900 times and 500 times, respectively, below the LOAELs for effects of commercial PCB mixtures on the skin, on the immune system and on reproduction in animal studies; and over 100,000 times lower than the lowest effect level for liver carcinogenicity in rodents. Although, as stated above, the mixtures of congeners in food and those tested in toxicity studies are not the same, these large margins are reassuring.

25. The upper bound[3] average dietary intakes of the individual congeners which contribute most to the overall intakes of PCBs in 1992 are given in Table 2. For those for which toxicity data are available, a comparison is made with the LOAEL identified from toxicity studies. For the two congeners for which data exist, the margins between intake and LOAEL are substantial.

26. Another comparison which can be made is between the lowest LOAEL identified in our review for an individual non-coplanar congener and the 1992 intake figures for PCBs. A LOAEL of 2.6 µg/kg bw/day was estimated for depletion of dopamine levels in rat brain in a 13-week study on PCB 128 (2,2',3,3',4,4'-hexachlorobiphenyl) (17). This is over 400 times and 200 times, respectively, above the average and high level intakes of total PCBs in 1992. Again, these are reassuringly high margins.

27. We have been given an estimate of the contribution of the 13 "dioxin-like" PCB congeners to the total intake of TEQs from the 1992 UK TDS samples. The WHO-ECEH/IPCS TEFs were used to calculate the PCB TEQs. Average intake was 143 picograms (pg) TEQ/person/day, of which 50 pg TEQ/person/day came from PCBs. High level intake was 252 TEQ pg/person/day, of which 90 pg TEQ/person/day came from PCBs. These are equivalent to 2.4 and 4.2 pg TEQ/kg bw/day, respectively, for a 60 kg adult. Both figures are below the TDI for PCDDs and PCDFs of 10 pg/kg bw/day, which we set in 1992 and confirmed in 1995 (8,18).

Schoolchildren (10-15 years)

28. We have also been provided by MAFF with estimates of the intakes of PCBs, and of the "dioxin-like" PCBs, PCDDs and PCDFs, expressed as TEQs, by schoolchildren. The estimates are based on the 1992 TDS data, combined with food consumption

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[2] Expressed as the sum of 53 congeners in food.

[3] This estimate is calculated using the assumption that where levels of PCBs in food are below the limit of detection (LOD), they are present at the LOD.

data from a national survey of 10-15 year olds (19). The upper bound average PCB intake[4] was estimated to be 0.007 µg/kg bw/day and the high level intake was 0.012 µg/kg bw/day (Table 3). In terms of TEQs, the average intake was estimated to be 2.8 pg TEQ/kg bw/day, of which 0.9 pg TEQ/kg bw/day came from PCBs; and the high level intake was estimated to be 4.6 pg TEQ/kg bw/day, of which 1.5 pg TEQ/kg bw/day came from PCBs (Table 4). These figures are only slightly higher than adult intakes.

Toddlers (1½-4½ years)

29. MAFF has also provided us with provisional estimates of the intakes of PCBs, and of the "dioxin-like" PCBs, PCDDs and PCDFs, expressed as TEQs, by toddlers (ie children aged between 1½ and 4½). This was derived by calculating the average PCB content of the UK diet, in terms of the sum of the 53 congeners measured, from the mean energy and PCB intakes of adult consumers (1992 TDS data). Multiplying this PCB content by the average daily energy intakes on a bodyweight basis recorded in a recent dietary and nutritional study of toddlers (20) gave the estimated PCB intakes by toddlers given in Table 3.

30. Taking the highest intakes by toddlers (ie those estimated for 1½ to 2½ year olds), the intakes on a body weight basis are approximately twice those of adults. Average intakes are approximately 360 times below the LOAELs for PCBs in animal studies and 97.5 percentile intakes are approximately 230 times below these LOAELs. Although these margins are not as high as for adults, they do not indicate any major cause for concern.

31. In terms of total TEQs, average intakes ranged from 5.9 pg TEQ/kg bw/day for 1½ to 2½ year olds to 5.0 pg TEQ/kg bw/day for 3½ to 4½ year old girls (see Table 4). 97.5th percentile intakes ranged from 9.3 pg TEQ/kg bw/day to 7.6 pg TEQ/kg bw/day. These intakes are below the TDI of 10 pg/kg bw/day.

Human Milk

32. As stated above, PCBs accumulate in lipid-rich secretions such as milk and thus human milk is a major source of exposure to these chemicals. Recent UK data (4) indicate that the mean estimated intake of PCBs[5] by breast-fed babies is 930 nanograms (ng)/kg bw/day at 2 months, falling to 460 ng/kg bw/day at 6 months. It should be noted that these are worst-case estimates for two reasons. Firstly, the milk samples analysed in this study were collected from mothers no more than two months

[4] Expressed as the sum of 53 congeners in food.

[5] Expressed as the sum of 28 congeners.

after delivery[6]. A mother's body burden of PCBs and other fat-soluble contaminants will decrease during the several months of breast-feeding and, consequently, the levels in her milk will decrease. Secondly, all samples were obtained from mothers nursing their first child. Since breast-feeding reduces the maternal body burden, levels of contaminants in milk fed to subsequent children are expected to be lower.

33. Comparison of these worst-case estimated intakes with the LOAELs for non-carcinogenic effects of commercial PCB mixtures shows that the safety margins are low - approximately 5 at 2 months and 25 at 10 months. In comparison, the margin between these intakes and the LOAEL for carcinogenic effects is 2700 at 2 months and over 10,000 at 10 months. As with other dietary exposures, the mixture of PCB congeners present in human milk is different from that found in commercial mixtures.

34. Comparison of the estimated mean intake of certain individual PCB congeners by infants aged 2 months with the relevant NOAEL or LOAEL identified from toxicity studies are given in Table 5. These margins range from 1,700 to 800,000, which is reassuring.

35. We have also been provided with mean estimated intakes by breast-fed infants of the 13 "dioxin-like" PCB congeners, expressed as TEQs (see Table 6). The TEQs were also calculated using the WHO-ECEH/IPCS TEFs. Estimated intakes range from 58 pg TEQ/kg bw/day at 2 months of age to 13 pg TEQ/kg bw/day at 10 months of age. The mean total intake of PCDDs, PCDFs and dioxin-like PCBs is estimated to be 170 pg TEQ/kg bw/day at 2 months, falling to 39 pg TEQ/kg bw/day at 10 months. These intakes exceed the TDI of 10 pg TEQ/kg bw/day.

36. It is clearly a matter of some concern that the margin of safety between the LOAELs for commercial PCB mixtures in animals and intakes of PCBs by breast-fed babies is so small; and that intakes of TEQs exceed the TDI, in some cases substantially. We have commented previously on the health significance of PCDDs and PCDFs in human milk (8,18,21,22) and have advised that, despite the presence of these chemicals in milk, breast-feeding should continue to be encouraged. In formulating this advice we took into account the fact that infants may be more susceptible to these compounds, and that a high level of exposure during a critical period of early postnatal development may have adverse effects whereas exposure to the same level in later life would not. However, we also took into account the fact that the period of breast-feeding is short compared with the time needed to accumulate these compounds in the body. We took into account the known benefits of breast-feeding: that it confers immunological protection on the infant, it is less likely to cause gastrointestinal disturbances, and that breast-feeding

[6] Details of sample collection are given in reference 21

protects against the development of allergies in families where there is a history of allergies. Studies have shown that there is a cognitive advantage for breast-fed babies over formula-fed babies[7], even after adjustment for socio-biological confounding (23). After consideration of all these factors, we *reaffirm* our previous advice that, despite the presence of PCDDs and related compounds in human milk, breast-feeding should continue to be encouraged on the basis of convincing evidence of the benefits of human milk to the overall health and development of the infant. Nevertheless, we *recommend* that the PCB, PCDD and PCDF levels in human milk are surveyed at regular intervals and, if levels do not continue to fall, that a review is instigated to investigate whether inputs of these pollutants to the environment can be reduced further, so as to reduce human exposure. It would be desirable to investigate the potential for accumulation of those PCB, PCDD and PCDF congeners which occur in breast milk, that is their disposition in and elimination from the body, especially in early life.

Survey of fish and fish liver oil dietary supplements and licensed medicines, 1994 and 1996

37. As previously discussed, PCBs, PCDDs and PCDFs accumulate in lipid-rich tissue, and this is particularly apparent in the livers of certain marine fish. Fish body and fish liver oils are popular dietary supplements and medicinal products in the form of either liquid oils or capsules which are consumed for their vitamin and long chain fatty acid content. Fish oil products are available as unlicensed dietary supplements and as licensed medicinal products on general sale. We have been provided by MAFF with data from a survey of the levels of PCBs, PCDDs and PCDFs in fish and fish liver oils purchased in 1994. These data confirmed findings that fish body and fish liver oils contain relatively high levels of PCBs, PCDDs and PCDFs. The survey was repeated in December 1996 to establish whether the levels of the contaminants had declined as a result of reported changes in the manufacturing process (3). The levels of PCBs, PCDDs and PCDFs in certain recently manufactured samples of salmon oil and halibut liver oil supplements appear to have declined, though it is difficult to draw firm conclusions due to the limited number of samples analysed. However, the levels of the contaminants present in other contemporary samples, particularly of cod liver oil, have not changed significantly since 1994. Data from the survey are summarised in Table 7.

<u>Estimated intakes of PCBs, PCDDs and PCDFs from fish oil dietary supplements and licensed medicines.</u>

38. The intake of PCBs, PCDDs and PCDFs from consumption of bottled or encapsulated fish oil dietary supplements and

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[7] There are no data on the concentrations of PCBs, PCDDs and PCDFs in UK milk formulas. A very limited German study suggests that the TEQs ingested by infants fed milk formula will be less than 5% of those ingested by breast-fed infants.

medicinal products has been estimated from the data obtained by MAFF (see Table 8) using the daily dosage recommended on the product packaging ("the recommended dose"). This ranged from 2.5 to 5 ml (2.3 to 4.6 g) for infants, 5 to 10 ml (4.6 to 9.2 g) for toddlers and one capsule (0.1 g) to 10 ml (9.2 g) for adults and schoolchildren. When calculated on a TEQ basis, the data show that:

Breast-fed infants

i) Consumption of the recommended dose of fish oil dietary supplements and medicinal products would increase the margin by which breast fed infants exceed the TDI of 10 pg/kg bw/day for PCBs, PCDDs and PCDFs. The maximum estimated intake from fish oil supplements is 11 pg TEQ/kg bw/day as compared to an intake of 39-170 pg TEQ/kg bw/day from breast milk.

Toddlers (1½ - 4½)

ii) Consumption of the recommended dose of certain bottled fish oil dietary supplements or medicinal products, either alone or in combination with the diet, could lead to the TDI of 10 pg/kg bw/day for PCBs, PCDDs and PCDFs being exceeded by toddlers. The maximum estimated intake from fish oil supplements is 12 to 16 pg TEQ/kg bw/day as compared to a dietary intake of 5.2 to 5.9 (mean consumer) or 7.6 to 9.3 (97.5 percentile consumer) pg TEQ/kg bw/day. The maximum estimated total intake of PCBs, PCDDs and PCDFs is 19.6 to 25.3 pg TEQ/kg bw/day for toddlers aged 1½ - 2½ and 3½ - 4½ respectively.

Schoolchildren

iii) Consumption of the recommended dose of certain bottled fish oil dietary supplements or medicinal products, in combination with the diet, could lead to the TDI of 10 pg TEQ/kg bw/day for PCBs, PCDDs and PCDFs being exceeded by schoolchildren. The maximum estimated intake being 9.1 pg TEQ/kg bw/day in addition to an intake of 2.8 to 4.6 pg TEQ/kg bw/day from the diet. The maximum estimated total intake of PCBs, PCDDs and PCDFs is 13.7 pg TEQ/kg bw/day.

Adults

iv) For adults, the maximum estimated intake of PCBs, PCDDs and PCDFs from fish oil dietary supplements or medicinal products is 6.6 pg TEQ/kg bw/day compared to an intake of 2.4 to 4.2 TEQ/kg bw/day from the diet. Thus, adults who were 97.5 percentile consumers would just exceed the TDI, consuming a maximum of 10.8 pg TEQ/kg bw/day.

Discussion of PCB, PCDD and PCDF intake from fish oil supplements

39. Consumption of the recommended dose of encapsulated fish oils (which are not recommended for infants or toddlers) does not lead to the TDI being exceeded by adults or schoolchildren. This is a result of the smaller quantity of oil present in the recommended dose of encapsulated oils compared to bottled oils, rather than any difference in the oils used in the two types of product.

40. The levels of PCBs, PCDDs and PCDFs present in the recommended doses of fish oil dietary supplements and medicinal products are unlikely to pose a risk to the health of breast-fed infants, toddlers, schoolchildren or adults. Consumption of the more highly contaminated oils by toddlers and schoolchildren could lead to the TDI being exceeded for a sustained period and would thus reduce the safety margin between intake and the toxicity observed in animal studies. This is undesirable but it is reassuring that the margin by which the TDI is exceeded decreases with age as the body weight increases.

Conclusions

i. PCBs produce a wide spectrum of adverse effects in experimental animals, including reproductive toxicity, immunotoxicity and carcinogenicity.

ii. We *accept* the advice of the COM that PCBs do not have significant mutagenic activity and that any carcinogenesis in animal studies is likely to be due to a "non-genotoxic" mechanism.

iii. We *accept* the advice of the COM and COC that it would be prudent to assume that all PCB congeners are potential human carcinogens.

iv. We *note* the results of preliminary work which indicates that current human body burdens of PCBs may be affecting thyroid hormone levels. We *consider* that further work in a larger population is required to investigate this further.

v. We *conclude* that the available epidemiological studies of individuals exposed to high background dietary levels of PCBs are not of sufficient quality to allow a quantitative estimate of risk to be made of reproductive dysfunction following dietary exposure.

vi. Most animal studies have been conducted using commercial mixtures of PCBs. The individual congeners and the relative proportion of these congeners in these mixtures are different from those found in food. There are only limited data on individual congeners. For these reasons, we have not been able to set a Tolerable Daily Intake for total PCBs.

vii. We are of the opinion that, despite the limitations in the derivation of the TEFs (see paragraphs 5 and 21 of the main text), the use of TEFs to assess the health risks of certain coplanar ("dioxin-like") PCB congeners offers a pragmatic approach to the evaluation of these compounds and we *recommend* that TEFs be tentatively accepted and used in a limited manner for this purpose. We *recommend* that the TEFs proposed by the 1994 WHO-ECEH/IPCS task force are used at present and that a TDI of 10 pg TEQ/kg bw/day can be employed to assess the health risks of combinations of PCDDs, PCDFs and dioxin-like PCB congeners. Considerable further work is necessary to improve the scientific basis for validating TEFs.

viii. Further work is needed to develop an approach to assessing the health risks of the non-coplanar PCB congeners.

ix. We *welcome* the new data on UK dietary intakes of both total and individual congeners of PCBs provided by MAFF. We note that the data on intakes by toddlers are provisional and *suggest* that further work is carried out to give more reliable estimates of intake by this age group. We *consider* that there is unlikely to be a health risk from current intakes of PCBs from food.

x. We *welcome* the new data on levels of PCBs in human milk. Although intakes of PCBs by breast-feeding babies are higher than is desirable, we *reaffirm* our previous advice that breast-feeding should continue to be encouraged on the basis of convincing evidence of the benefits of human milk to the overall health and development of the infant.

xi. We *note* the data on levels of PCBs, PCDDs and PCDFs in fish oil dietary supplements and medicinal products. The intake of such levels is undesirable, since it potentially leads to the TDI for PCBs, PCDDs and PCDFs being exceeded by toddlers and schoolchildren for a sustained period and thus reduces the safety margin between intake and the toxicity observed in animal studies. However, we *consider* that this intake is unlikely to pose a risk to health.

xii. We *recommend* that it would be desirable to carry out studies to improve the understanding of PCB, PCDD and PCDF accumulation and disposition in humans in the first year of life, eg by physiologically-based toxicokinetic modelling.

xiii. We consider that it would be prudent to seek action to ensure that consumer exposure to these contaminants is kept below the TDI. However, we recognise that PCBs are likely to persist as contaminants of the environment for many years to come. Therefore, we *recommend* that levels in food and in human milk should continue to be monitored at regular intervals to confirm that the downward trend continues. If it does not, we *recommend* that a further review is instigated to determine how human exposure can be reduced.

April 1997

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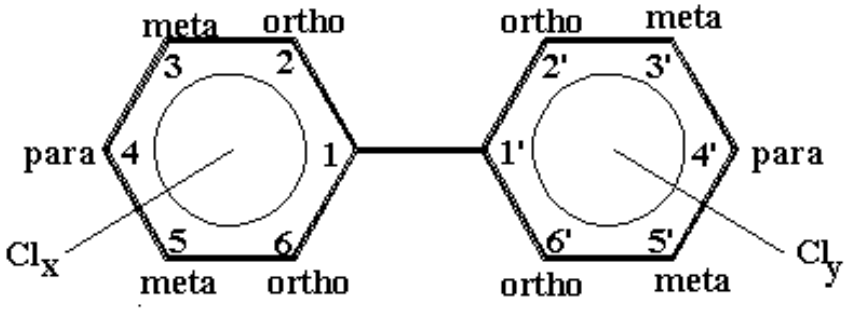
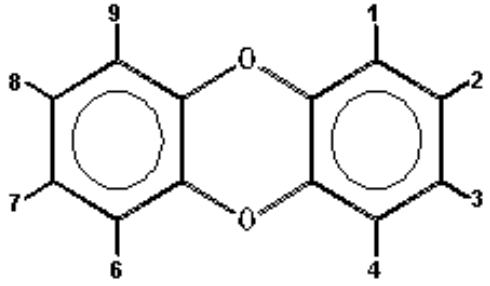
FIGURE 1

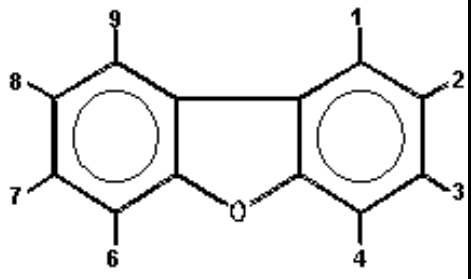
CHEMICAL STRUCTURES OF POLYCHLORINATED BIPHENYLS (PCBs), POLYCHLORINATED DIBENZO-PARA-DIOXINS (PCDDs) AND POLYCHLORINATED DIBENZOFURANS (PCDFs)



Polychlorinated biphenyl



Dibenzo-p-dioxin



Dibenzofuran

TABLE 1

TEF VALUES PROPOSED BY AHLBORG et al., 1994*

Type of Congener	PCB Congener	Congener Structure	TEF Value
Non-*ortho*	77	3,3',4,4'-tetraCB	0.0005
	126	3,3',4,4',5-pentaCB	0.1
	169	3,3',4,4',5,5'-hexaCB	0.01
Mono-*ortho*	105	2,3,3',4,4'-pentaCB	0.0001
	114	2,3,4,4',5-pentaCB	0.0005
	118	2,3',4,4',5-pentaCB	0.0001
	123	2',3,4,4',5-pentaCB	0.0001
	156	2,3,3',4,4',5-hexaCB	0.0005
	157	2,3,3',4,4',5'-hexaCB	0.0005
	167	2,3',4,4',5,5'-hexaCB	0.00001
	189	2,3,3',4,4',5,5'-heptaCB	0.0001
Di-*ortho*	170	2,2',3,3',4,4',5-heptaCB	0.0001
	180	2,2',3,4,4',5,5'-heptaCB	0.00001

*Reference 16.

TABLE 2

COMPARISON OF ESTIMATED DIETARY INTAKES OF INDIVIDUAL PCB CONGENERS BY ADULTS WITH TOXICOLOGICAL DATA

Congener	Upper bound intake (ng/kg bw/day[1])	NOAEL or LOAEL (ng/kg bw/day)	Margin between exposure and the NOAEL or LOAEL
28 (2,4,4'-triCB)	0.2	8×10^6 (LOAEL)[2]	40,000,000
41 (2,2',3,4-tetraCB)	0.2	-	-
47 (2,2',4,4'-tetraCB)	0.9	-	-
138 (2,2',3,4,4',5'-hexaCB)	0.3	-	-
153 (2,2',4,4',5,5'-hexaCB)	0.4	16×10^6 (LOAEL)[3]	40,000,000
180 (2,2',3,4,4',5,5'-heptaCB)	0.2	-	-

1. For a 60 kg individual.
2. Maternal dose on days 10-16 of pregnancy, reduced body weight in offspring (rats) (Reference 24).
3. Maternal dose on days 10-16 of pregnancy, increased liver weight in offspring (rats) (Reference 24).

TABLE 3

ESTIMATED DIETARY INTAKES OF PCBS BY SCHOOLCHILDREN AND TODDLERS IN 1992

Sub-group	Intakes of PCBs (ng/kg bw/day) Mean consumer	97.5th percentile consumer
Schoolchildren (aged 10-15)*	7	12
Toddlers aged 1½ to 2½	14	22
Toddlers aged 2½ to 3½	13	20
Toddlers aged 3½ to 4½ (boys)	13	18
Toddlers aged 3½ to 4½ (girls)	12	18

* Assuming a bodyweight of 43.6 kg for each individual.

TABLE 4

ESTIMATED DIETARY INTAKES OF PCDDS, PCDFS AND PCBS IN TERMS OF TOXIC EQUIVALENTS BY SCHOOLCHILDREN AND TODDLERS IN 1992

Sub-group	Estimated PCDD and PCDF intake (pg TEQ/kg bw/day)		Estimated PCB intake (pg TEQ/kg bw/day)		Total estimated intake (pg TEQ/kg bw/day)	
	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile
Schoolchildren (aged 10-15)	1.8	3.0	0.9	1.5	2.8	4.6
Toddlers aged 1½ to 2½	3.7	5.8	2.1	3.2	5.9	9.3
Toddlers aged 2½ to 3½	3.4	5.1	1.9	2.8	5.5	8.1
Toddlers aged 3½ to 4½ (boys)	3.4	4.7	1.9	2.6	5.4	7.6
Toddlers aged 3½ to 4½ (girls)	3.1	4.7	1.8	2.6	5.0	7.6

TABLE 5

COMPARISON OF ESTIMATED MEAN DIETARY INTAKES OF INDIVIDUAL PCB CONGENERS FROM HUMAN MILK BY BREAST-FED INFANTS WITH TOXICOLOGICAL DATA

Congener exposure	Average intakes from human milk (ng/kg bw/day)		NOAEL or LOAEL (ng/kg bw/day)	Margin between and the NOAEL/LOAEL
	Infants aged 2 mo	Infants aged 10 mo		
28	22	5.2	8,000,000(LOAEL)[1]	360,000-1,500,000
128	3.3	0.8	260,000(NOAEL)[2]	80,000-300,000
153	45	11	16,000,000(LOAEL)[3]	800,000-3,300,000
156	46	11	81,000(NOAEL)[4]	1,700-7,400

1. Maternal dose on days 10-16 of pregnancy, reduced body weight in offspring (rats); (Reference 24).
2. 13 week study, hepatic effects reported above this level (rats); (Reference 17).
3. Maternal dose on days 10-16 of pregnancy, increased liver weight in offspring (rats); (Reference 24).
4. 13 week study, several effects reported above this level including reduced body weight (rats); (Reference 25).

TABLE 6

ESTIMATED INTAKES OF PCDDS, PCDFS AND PCBS IN TERMS OF TOXIC EQUIVALENTS BY BREAST-FED BABIES

Age (months)	Mean consumption of human milk by nursing infants (g/kg bw/day)	Mean intakes via human milk (pg TEQ/kg bw/day)		
		PCDDs and PCDFs	PCBs	Total
2	160	110	58	170
3	140	100	51	150
4	124	88	45	130
5	103	73	37	110
6	79	56	29	84
7	63	44	23	67
8	42	30	15	45
10	37	26	13	39

Notes:
1. Intakes are given to two significant figures. These figures may over-estimate the actual mean exposure to PCBs, PCDDs and PCDFs via human milk, for the reasons given in paragraph 32 of the text.
2. The TDI for PCDD, PCDF and PCBs with dioxin-like activity is 10 pg TEQ/kg bw/day.

Table 7: Concentrations of dioxins, furans and PCBs (ng TEQ/kg oil) in fish oil dietary supplements and licensed medicines

Compounds	Concentration (ng TEQ/kg oil)							
	Cod liver oil 5 (bottled)			Cod liver oil 7 (capsules) *		Cod liver oil 8 (capsules)[d]*	Cod liver oil 9 (capsules)[d]*	
	1994	1996[a]		1994	1996	1996	1996	
		Mean	Range					
Dioxins and furans	11	7.1	3.6 - 10	-	6.2	1.5	9.2	
Non-*ortho*-PCBs	21	17	11 - 24	44	26	17	21	
Ortho-PCBs	1.5	7	4.4 - 9.9	-	8.1	12	8.4	
Total**	33	31	20 - 43	44[b]	41	30	38	

Compounds	Concentration (ng TEQ/kg oil)							
	Cod liver oil with fish oil 5 (bottled)[d]*	Cod liver oil with fish oil 6 (bottled)[d]*	Halibut liver oil 1 (capsules) *		Halibut liver oil 3 (capsules) *		Salmon oil (capsules)	
	1996	1996	1994	1996	1994	1996	1994	1996
Dioxins and furans	4.5	0.6	6.8	1.7	40	6.1	17	2.5
Non-*ortho*-PCBs	10	4.1	2.7	3.5	16	7.3	14	1.1
Ortho-PCBs	3.1	3.5	0.3	2.2	-	1.5	-	1.0
Total**	18	8.1	9.9	7.4	56[c]	15	31[c]	4.7

Notes: See Reference 3 for descriptions of the samples

a = Mean of 6 batches. Single sample in 1994

b = Does not include a contribution from dioxins, furans or *ortho*-PCBs

c = Does not include a contribution from *ortho*-PCBs

d = Not included in the 1994 survey

* = Samples of 2-3 batches of these products were pooled prior to analysis

** = Totals differ from sum of concentrations due to rounding errors

TABLE 8: Intakes of PCBs, PCDDs and PCDFs by infants, toddlers, school children and adults from samples of fish oil dietary supplements and licensed medicines taken in 1996 compared with intakes from other dietary sources.

Sub-group (body weight)	Intakes of PCBs, PCDDs, and PCDFs (pg TEQ/kg bw/day)			
	Fish oil dietary supplements and licensed medicines[a]		Other dietary sources[b]	
	Low	High	Mean	97.5 percentile consumer
Breast-fed infants (8.7 kg)	4.3	11	170 (at 2 months) 39 (at 10 months)	
Toddlers aged 1½ to 2½ (12.3 kg)	6.0	16	5.9	9.3
Toddlers aged 2½ to 3½ (14.6 kg)	5.1	14	5.5	8.1
Toddlers aged 3½ to 4½ (16.5 kg)	4.5	12	5.2	7.6
Schoolchildren (43.6 kg)	0.02	9.1	2.8	4.6
Adults (60 kg)	0.01	6.6	2.4	4.2

Notes

a) Intakes from fish oil products were calculated by selecting the samples containing the highest and lowest concentrations of PCBs, PCDDs and PCDFs and multiplying by the recommended dose as stated on the packaging of the product:

	Low (halibut liver oil, 7.4 ng TEQ/kg oil)	High (cod liver oil, 43 ng TEQ/kg oil)
Infants	5 ml oil (4.6 g)	2.5 ml oil (2.3 g)
Toddlers	10 ml oil (9.2 g)	5 ml oil (1 tsp, 4.6 g)
Adults and schoolchildren	1 capsule (0.1g)	10 ml oil (2 tsp, 9.2 g)

b) Estimated from concentrations of PCDDs, PCDFs and PCBs found in the UK Total Diet Study samples collected in 1992.