TOX/2017/05

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

FSA Funded Study on Chlorinated and Brominated Dioxins, Furans, Biphenyls and Diphenylethers in Adipose Tissue, Liver Tissue, and Blood in Obese and Control Groups in the United Kingdom

Background

1. The term “dioxins” is commonly used to refer to a group of 75 polychlorinated dibenzo-p-dioxin (PCDD) and 135 polychlorinated dibenzofuran (PCDF) congeners, of which fewer than 20 are considered to be biologically active. Dioxins are produced in a number of thermal reactions, including incineration of municipal waste, domestic fires and bonfires, forest fires and in internal combustion automobile engines. They are also generated as trace contaminants during the synthesis of many organochlorine compounds and during some industrial processes

2. PCBs are environmentally stable, lipophilic chemicals that were widely manufactured for a range of industrial applications between the 1930s and 1970s. Use of PCBs for industrial purposes has been discontinued but these substances may still be released to the environment during disposal of materials and obsolete equipment. There are 209 theoretically possible PCB congeners, of which 12 non-ortho or mono-ortho compounds exhibit similar biological activity to PCDDs and PCDFs, and are therefore referred to as “dioxin-like PCBs”.

3. These compounds are persistent in the environment and tend to accumulate in biological systems, particularly in fatty tissues. One of the most potent and extensively studied PCDD congeners, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), exhibits a broad range of toxic effects in laboratory animals, some at very low doses. Since the toxicity of the various dioxins and dioxin-like congeners is generally accepted to be mediated by the aryl hydrocarbon receptor (AhR), and experiments using mixtures of congeners are consistent with an additive model; a system of toxic equivalency factors (TEFs) has been devised by the World Health Organisation (WHO) to enable total TCDD toxic equivalents (TEQ) to be calculated. This was initially developed in the 1980s and has subsequently been subjected to periodic review, to ensure the system incorporates newly acquired data and knowledge. Estimates of dietary

exposure are expressed in terms of WHO TEQ. The TEQ is defined as the sum of the products of the concentration of each congener, multiplied by the TEF.

2001 COT Evaluation

4. In 2001, the COT undertook an extensive review of dioxins and dioxin-like PCBs. The Committee on Carcinogenicity (COC) advised that TCDD should be regarded as probably carcinogenic to humans, based on the available data and, although there were uncertainties regarding the mechanism of action, it was likely that a threshold approach to risk assessment was appropriate.

5. The COT concluded that the available human data did not provide a sufficiently rigorous basis for establishment of a tolerable intake because:
    - the epidemiological studies did not reflect the most sensitive population identified by animal studies;
    - there were considerable uncertainties in the exposure assessments and inadequate allowance for confounding factors; and
    - the patterns of exposure did not reflect the main route of exposure experienced in the general UK population, which is mainly from diet.
    - It was, therefore, considered necessary to base the evaluation on the data from studies conducted in experimental animals.

6. The Committee concluded that the most sensitive indicators of TCDD toxicity were the effects on the developing reproductive system of male rat fetuses exposed *in utero*. These endpoints had also been used to derive tolerable intakes by Joint Food and Agriculture Organisation (FAO) / WHO Expert Committee on Food Additives (JECFA), 70 pg WHO TEQ/kg bw per month; and EU Scientific Committee on Food (SCF), 14 pg WHO TEQ/kg bw per week.

7. The key studies used different strains of rats and tended to give contradictory findings. A change in anogenital distance (AGD) was found after single oral doses given on day 15 of gestation (GD15) of 50 ng/kg bw, 200 ng/kg bw and 1000 ng/kg bw. However, the Committee considered that the data on AGD were not robust because of lack of correction for body weight or other means of normalisation, and should be regarded as an intermediate marker with no functional significance in itself. Decreases in sperm numbers, production, reserve or morphology were found shortly after puberty (postnatal day (PND) 49-70) and in adulthood (PND120 onwards), after single oral doses of 50 ng/kg bw and above on GD15 and following weekly subcutaneous dosing to give a body burden of 25 ng/kg bw; although these changes were not seen in one acute oral study, dosing 800 ng/kg bw on GD15. Changes in the weight of the urogenital complex, including the ventral prostate were reported after an oral dose of 200ng/kg bw on GD15 but not at 300ng/kg bw subcutaneously.

8. Despite these inconsistencies, the Committee considered that the effects on sperm production and morphology represented the most sensitive effects. These were indicative of the functional adverse reproductive effects in the rat that were produced by long-term administration in a multigeneration study, at doses resulting in a 10-fold higher body burden than those in the studies of sperm production. The Committee also noted that the sperm reserve in the human male is much less than that in the rat, and therefore these changes were considered relevant. The study of Faqi provided the lowest LOAEL, but no NOAEL. Limitations in this study were noted but it was considered that the results could not be discounted; therefore, this was used as the basis for deriving the tolerable intake. The Committee considered that a tolerable intake based on these effects would also protect against any risk of carcinogenicity from dioxins and dioxin-like PCBs since a significant increase in incidence of tumours was only found at doses that were higher than the LOAEL in the Faqi study.

9. Several studies reported adverse effects in male rat offspring following a single oral dose of TCDD given on GD15, and one following repeated weekly subcutaneous injections. In all cases the effects were observed postnatally , although the pattern of both *in utero* and postnatal exposure would be different between single and repeat dose studies. The JECFA and SCF evaluations used the data from toxicokinetic studies to model the fetal body burdens on GD16, on the assumption that the postnatal effects were the result of exposure of fetal tissue at GD16.

10. The COT used a similar approach, albeit with simpler toxicokinetic modelling Derivation of a tolerable intake for humans involved: calculation of the fetal body burden of rats under the experimental conditions; correction of the corresponding maternal body burden in rats to represent chronic daily intake via the diet; the use of uncertainty factors to give an equivalent tolerable human maternal body burden; and finally, derivation of a daily intake by humans that would result in the tolerable human maternal body burden.

The 2006 WHO TEFs

11. The WHO has, on a number of occasions, convened Expert Panels to discuss toxic equivalency factor (TEF) values. This is because the Expert Panel has stated that the TEF concept should be thought of as an interim methodology, which should be subject to periodic review as new scientific information becomes available. The Expert Panel initially set TEF values at a meeting in 1993 and re-evaluated them at a subsequent meeting in 1997. These re-evaluated TEFs were published in 1998 and endorsed by the COT in the same year[2]. In 2001, the COT undertook an extensive review of dioxins and dioxin-like chemicals, which resulted in the adoption of a Tolerable Daily Intake (TDI) of 2 pg WHO-TEQ/kg bw/day.

12. In 2004 the European Food Safety Authority (EFSA) organised a scientific colloquium to discuss the risk assessment of dioxins and dioxin like chemicals. This colloquium highlighted some differences in approaches to the risk

assessment of these compounds and concluded that it was timely to review the TEF scheme. The WHO-IPCS Expert Panel was reconvened in June 2005 to perform the next periodic re-evaluation of the TEF values and to discuss and develop the TEF concept

13. The 2005 WHO-IPCS re-evaluation was based on a recently published relative effect potency (REP) database, which was constructed using refined inclusion/exclusion criteria. 47% of the REP values from the previous database, used in the 1997 TEF reassessment, met the more stringent criteria. These 381 REP values were combined with 253 REP values from new studies, forming the 2005 REP database. A combination of these unweighted REP values, expert judgement and point estimates were used to re-evaluate TEF values, considering additional data where necessary.

14. This re-evaluation used half order of magnitude increments on a logarithmic scale (0.03, 0.1, 0.3 etc). TEF values represent 'order of magnitude estimates', therefore, a degree of uncertainty is implicit. The Panel considered that these increments would be useful in the future so that the uncertainty of TEF values can be described using statistical methods. Previous evaluations used increments of 0.01, 0.05, 0.1 etc.

15. The COT agreed with the scientific rationale for the re-evaluated TEF values, although concurring with the opinion of the WHO Expert Panel, that this should be thought of as an 'interim' methodology, until a more suitable method of estimating exposure to dioxins and dioxin-like chemicals can be found.

16. The COT concluded that the revision of the TEFs did not raise additional concerns regarding exposure to dioxins and dioxin-like compounds, and that the new TEFs should be used in future UK assessments of dietary exposure to dioxins and dioxin-like compounds.

The FSA funded Dioxins Risk Assessment project (T01034)

17. In evaluating the available toxicity data to set the 2001 TDI, the Committee identified gaps related to the risk assessment of dioxins during pregnancy. In light of this, the FSA commissioned a developmental toxicity study, conducted in accordance with Good Laboratory Practice (GLP), using Computer Assisted Sperm Analysis (CASA) for robust collection of seminology data, and using large group sizes to increase the statistical power and reliability of the analyses. This project aimed to relate dose of TCDD to maternal burden, fetal burden and biological endpoints, within the same study. In view of the complexity of TCDD toxicokinetics, it was considered essential to have both an acute dose study, so as to be directly comparable with previous studies which dosed on GD15; and a sub-chronic repeat dose dietary study where TCDD administration was more representative of human exposure.

18. Previously, a LOAEL maternal body-burden of 33 ng/kg bw had been calculated for the Faqi study using toxicokinetics data from Hurst *et al.*. Uncertainty factors accounting for human variation in toxicokinetics (3.2) and the use of a LOAEL

(3) were applied to yield a human maternal body burden. This was converted to a human maternal dietary intake using a bioavailability of 50% and a half-life of 7.5 years for TCDD. This resulted in a dietary intake of 1.7 pg/kg bw/day, which was rounded to a TDI of 2 pg/kg bw/day due to the various uncertainties in the risk assessment.

19. In the FSA funded sub-chronic study, delay to BPS was observed in the lowest dose group, hence this study also provided a LOAEL. The maternal steady-state body burden for this dose group was determined analytically to be very similar to that calculated for the Faqi study, which was used in the 2001 risk assessment. Thus, the LOAEL body burden from the FSA funded study provided additional evidence that the current TDI of 2 pg/kg bw/day was protective for the developing male fetus.

20. Data considered during the 2001 risk assessment, indicated that GD16-21 represents a critical window of exposure in the rat. However, whilst delay in BPS was seen following acute dosing on GD15 in the FSA funded study; sub-chronic administration, at doses which gave rise to similar maternal and fetal body burdens, resulted in a greater delay in BPS. The difference in magnitude of the effect highlights uncertainty regarding the critical window of exposure in the rat.

21. The more pronounced delay in BPS in the sub-chronic study may be due to fetal exposure to the maternal body burden *in utero* prior to GD15, possible increased postnatal exposure prior to puberty, or a combination of the two. The 2001 risk assessment assumed that the effects on the reproductive system of the male offspring resulted from *in utero* exposure to the maternal TCDD body burden. However, if the critical window of exposure is post natal, the differences in toxicokinetics and relative onset of puberty between rats and humans are likely to affect the relative susceptibility of the two species. In the absence of robust data relating to the critical window of exposure, it was appropriate to assume that the effects occurred *in utero*, since basic modelling of rat and human TCDD toxicokinetics indicated that this would result in a more conservative risk assessment.

22. Having reviewed the FSA funded study, COT were content with the study design and satisfied that the statistical power of the study, seminology and analytical data were robust.

23. COT considered that the new study provided additional evidence that the current TDI of 2 pg/kg bw/day was protective for effects on the developing male fetus. Therefore, COT concluded a review of the TDI was not a priority on the basis of this study.

COT symposium 2015.

24. Two Food Standards Agency-funded research projects (Toxicodynamics of dioxins in an obese population; and BFR: Brominated compounds:

Determination of levels of brominated chemicals in a human population) were set up to measure dioxins and brominated compounds of morbidly obese and comparative control individuals, and investigate the toxicodynamics of these compounds and their distribution in adipose tissue. The projects aimed to characterise the burden of dioxins and brominated compounds in liver and adipose tissue, and the relationship with blood levels of dioxins, in a UK population.

25. The 2015 COT symposium brought together experts from the field to discuss possible approaches for maximising value from the data from the two FSA-funded research projects. There were a series of presentations and discussions around the impact of obesity on toxicokinetic parameters and the current risk assessment paradigm and whether this is protective for obese individuals. Paper TOX/2015/20 contained information on the symposium programme and summaries of the discussions

26. Members noted that the issue of mobilisation of POPs during lactation and the potential impact of obesity on the amounts of these chemicals in breastmilk had not specifically been discussed

27. COT concluded that there were not currently sufficient data for a statement but the outcomes of the discussion groups provided a sufficient summary:

- *"The aim of the first discussion was to consider the tissue distribution data of persistent organic pollutants (POPs) measured in obese and non-obese patients in a FSA research project. The FSA was seeking discussion on available options and determine the optimum modelling solution for analysis of this data set. Some of the key points from these discussions were:*

- *Different modelling options, such as PBPK [physiologically based pharmacokinetics] or simpler models, available for data analyses. Discussion was also had around the modelling that may be used for the analysis of the different subsets of data in this study.*

- *There are currently follow-up data from five individuals which have shown substantial heterogeneity in the results and there was discussion around how representative these results would be. Samples from four additional individuals were awaiting analysis.*

- *The need to consider other POPs/chemicals because dioxins are a historical problem whereas levels of other POPs, for example, BFRs [brominated flame retardants] have increased in recent years.*

- *Added value of comparing data in this study to other data concerning POPs, obese individuals and POP levels in tissues. There are also reviews on the influence of bariatric surgery on certain pharmaceuticals which may provide useful information for POPs.*

- *Discussion around whether anything could have been done differently and whether further studies should be considered.*

- *Current models do not predict the initial results. Possible factors that could explain this were discussed including CYP1A2 binding. There are a number of physiologic changes that take place subsequent to bariatric surgery and/or weight loss which could impact the kinetics of dioxins/POPs. Certain medications (lipid lowering drugs and statins) could play a role in disturbing the kinetics of these chemicals. It was highlighted that the data was likely to be congener specific."*

The Hull Studies.

28. The combined report of the two projects is at Annex 1.

29. Patients undergoing Roux-en-Y gastric bypass surgery for weight loss and control patients who were undergoing abdominal surgery for non-bariatric reasons were recruited. Recruitment occurred from April 2010 until March 2015. All the participants who underwent bariatric surgery were given repeat appointments at 6 months and 1 year. Those who did not attend the follow-up visits were sent a reminder through the post to contact the research unit to make an appointment. Those participants who didn't respond to the reminders were followed up by phone calls from the research personnel inviting them for the follow-up appointment. Anthropometric parameters including height and weight were measured on the day of surgery. During surgery, samples were taken including fasted blood plasma (100 ml), liver (500 mg) and adipose tissue (visceral and subcutaneous: 40 g each). For those who consented, subcutaneous fat biopsies were taken at follow-up.

30. Dioxin TEQ concentrations in tissue samples were calculated for chlorinated dioxins, furans, and polychlorinated biphenyls using the World Health Organization 2005 Toxicity Equivalency Factors (WHO TEFs) and for brominated congeners using the WHO interim TEFs (van den Berg et al. 2013). Summary statistics for frequently detected compounds were calculated for obese and control groups. Relationships between concentrations in the different tissue depots (liver, visceral fat, and subcutaneous fat) were assessed and multivariable regressions were conducted to examine the influence of age, gender and BMI on measured concentrations of selected frequently detected congeners. All statistical analyses reported were based on lipid-adjusted concentrations

31. 106 participants were recruited for the study, 62 who underwent bariatric surgery and 44 who underwent other abdominal surgery. Participant demographics are presented in Table 1. The proportion of male participants was similar in the two groups (37% vs. 36% in bariatric and controls, respectively). Participants undergoing bariatric surgery were significantly younger than controls, with mean age (standard error) of 48.0 (1.6) years in bariatric participants vs. 69.2 (2.1) years in controls. Bariatric participants had

significantly higher BMI: mean (standard error) of 46.9 (1.4) in bariatric patients compared to 25.2 (0.7) in control participants. However, the ranges of BMIs in the two groups overlapped.

Table 1: Participant demographics

	Bariatric	Control	p value
n	62	44	
% Male	37%	36%	NS
Age, y, Mean (SE)	48.0 (1.6)	69.2 (2.1)	<0.0001
[Range]	[26-83]	[40-92]	
BMI, kg/m^2, Mean (SE)	46.9 (1.4)	25.2 (0.7)	<0.0001
[Range]	[31.5-97.5]	[15.9-34.0]	

32. The study protocol specified collection of four sample types from each participant: serum, subcutaneous fat, visceral fat, and liver. It was not possible to analyse all targeted samples for reasons varying from lack of consent or attendance to inadequate sample size for analysis of all of the target chemical groups. Thus the number of analysed samples varied by matrix and chemical compound group. Where analytical results were flagged as "indicative" and were inconsistent with other data collected for the same compounds, it was decided to exclude those analytical results from the statistical analyses. There was variability in final numbers of samples of each chemical and tissue included in the statistical analyses.

33. Detection frequencies varied by matrix and specific analyte. Limits of detection (LODs) were variable by sample due to varying lipid content and sample volumes. Means were compared between bariatric and control groups with a two-sided t-test. Statistically significant differences between participant groups were observed for a number of chlorinated and brominated compounds, with mean concentrations generally lower in bariatric participants compared to controls. However, due to the differences in age distributions in the two groups and known variability with age in levels of these compounds in the general population (Patterson et al. 2009), these differences may not be related directly to BMI

34. A more detailed examination of the relationship between BMI and analyte concentrations was conducted using multivariable regressions for a subset of analytes frequently detected in subcutaneous fat. Age, gender, and BMI were considered as independent variables in the regression. Gender was not a significant predictor for any of the analytes evaluated. Several analytes were significantly positively associated with age: BB 153 and 126; ortho-chlorinated biphenyls 153, 180, and 189; the non-ortho biphenyl 126; and both 1,2,3,7,8-PeCDD and 2,3,4,7,8-PeCDF. Chlorinated PCDD/F TEQ, but not brominated PBDD/F TEQ, was also positively associated with age. Mixed results were

observed with respect to trends with BMI for different analytes, although most showed no significant association with BMI. BB 153 and PCBs 180 and 189 were negatively associated with BMI, however, summed chlorinated TEQ was positively associated with BMI

35. The ratios of lipid-adjusted concentrations in subcutaneous fat to those in visceral fat were not different for all evaluated analytes except BDE 209 and PBB 126. Subcutaneous fat concentrations of BDE 209 were significantly lower than those in visceral fat (mean ratio 0.77, 95% CI 0.67-0.88). Although concentrations of PBB 126 tended to be higher in subcutaneous fat than visceral fat, the ratio was not significantly different from 1 (mean ratio 1.25, 95% CI: 0.96-1.55). These data confirmed the expectation based on their high lipophilicity that subcutaneous and visceral fat depots in the body appear to be in equilibrium for all of the chemicals evaluated except BDE 209.

36. It was only possible to collect sufficient volumes of subcutaneous fat for analysis in follow-up biopsies from 10 bariatric surgery group participants. These biopsies were collected an average of 2.8 years following initial surgery (range 1 to 4.8 years) from participants losing an average of 35.3% of their pre-surgery bodyweight and an estimated average of 48.6% of their body fat (range 38.1 to 60.6%). Concentrations of summed indicator PCBs and chlorinated TEQ increased by 35% to 695% in follow-up samples from eight of the nine participants whose follow-up samples could be analysed for these compounds. One individual had decreased concentrations of 28% and 25% in summed PCBs and chlorinated TEQ, respectively. Estimated body burdens of the analysed chlorinated compounds were calculated and. remained relatively constant or decreased somewhat at follow-up for six of nine participants in contrast to the observed changes in concentration. Three participants had increased estimated body burdens, but the degree of increase was much smaller than the degree of increase in measured concentrations

37. These data are generally consistent with the hypothesis that compounds stored in fat are mobilized and redistributed into remaining fat tissue following weight loss. Some decreases in total body burden would be expected over a period of 2 to 5 years through on-going slow elimination of these compounds, and decreases in estimated body burden observed in most of the participants may be consistent with this process. There was no clear explanation for the observed substantial increases in estimated body burdens observed in two of the patients.

38. Mean concentrations of lipophilic POPs in subcutaneous fat samples were frequently higher in the control than bariatric groups. However, controls were significantly older than the bariatric participants, and for many if not most of these compounds, there is evidence concentrations increase with age. Thus, the pattern of higher concentrations in controls evident in Tables 5 and 6 do not necessarily indicate an association with obesity or BMI. When age was included as a covariate in a multivariable regression, the relationship between measured concentrations and BMI varied by compound. Most compounds examined showed no association with BMI. BB 153 and PCBs 180 and 189 exhibited a significant negative relationship, with higher BMI associated with

lower compound concentrations. An opposite trend was observed for summed chlorinated TEQ, which exhibited statistically significant positive relationship with BMI.

39. Overall observed results indicated that individuals with elevated BMI do not have significantly higher concentrations of lipophilic POPs than those with lower BMI after accounting for the effect of age. In the literature inconsistent results have been reported, with various studies reporting no, negative and positive associations between lipid-adjusted tissue concentrations of neutral lipophilic POPs and BMI (reviewed in Malarvannan et al. 2013). Based on the data reported here and the inconsistent results from previous studies, elevated BMI does not appear, in itself, a risk factor for strong elevations in tissue concentrations of lipophilic POPs but is a predictor for elevations in mass of stored lipophilic compounds

40. Data on the distribution of the compounds between subcutaneous and visceral fat indicated that concentrations in the two depots on a lipid-adjusted basis were essentially equivalent for every compound examined except BDE 209, which exhibited significantly lower concentrations in subcutaneous than visceral fat. BDE 209 has the highest molecular weight of any of the compounds examined and an apparent elimination half-life in humans, on the order of 15 days. It is possible that measured concentrations of BDE 209 in subcutaneous and visceral fat are not fully in equilibrium with blood and with one another, with stored compound in visceral fat released and metabolized more slowly than from subcutaneous fat. The general agreement between subcutaneous and visceral fat lipid-adjusted concentrations for the other compounds supported the concept of equilibrium across body lipid stores and the assumption that serum lipid concentrations would mirror the fat depot concentrations on a lipid-adjusted basis.

41. Comparisons between liver and visceral fat lipid-adjusted concentrations were consistent with binding to hepatic CYP1A2 proteins, with dioxin-like compounds showing notable hepatic sequestration. In particular, brominated TEQ contributors were sequestered more than the chlorinated TEQs with ratios of lipid-adjusted concentration of total brominated TEQ in liver vs. visceral fat approaching 6 for total brominated TEQ, compared to approximately 2 for chlorinated TEQ. The elevated sequestration of brominated dioxin-like compounds in liver relative to chlorinated dioxins may have implications for the potential toxicity of these compounds. If liver is the target tissue, then a greater internal dose to the liver may result for a given intake of brominated TEQ compared to chlorinated TEQ. Conversely, if the target tissue is extrahepatic, for example, the developing fetus, the elevated sequestration in the liver of the brominated compounds may reduce the proportion of compound available

42. The degree of change in observed concentrations following weight loss differed substantially between individuals, even taking into account the different degrees of weight loss and estimated losses in fat mass. However, for each individual, the degree of change in concentration was very similar across contaminants, suggesting consistent degree of release of compound and redeposition into remaining fat mass regardless of specific contaminant. Thus the differing

degrees of change in concentration may be related to interindividual differences in the accuracy of the fat mass estimation procedure used

Questions on which the views of the Committee are sought

43. Members are invited to comment on the design, conduct and results of the study also to consider the following specific questions:

i) Do Members consider that it is possible to reach any generalisable conclusions from the results of these studies
ii) Do Members consider the results provide any reasons to alter the risk assessment of these compounds or that identify additional uncertainties that should be considered in future risk assessments
iii) Do Members consider there is any need to revisit the conclusions of the 2015 symposium
iv) Members may wish to comment on the challenges and value of such clinical studies even when the results obtained are not definitive

Secretariat

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Final report

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