

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

SECOND DRAFT WORKING PAPER ON THE TOLERABLE DAILY INTAKE FOR PERFLUOROCTANE SULFONATE

Background

1. The COT discussed the paper TOX/2005/07 in April, May and July 2005. This paper reviewed the toxicology of the perfluoroalkyl acid perfluorooctane sulfonate (PFOS). The COM discussed the mutagenicity of PFOS (paper MUT/05/14) in May 2005, and the COC discussed the carcinogenicity and epidemiology of PFOS (paper CC/05/16) in July 2005.
2. In the July 2005 discussions the COT recommended a teratologist be consulted for advice on the reported developmental effects in rodents. In October 2005 COT discussed the draft working paper (TOX/2005/25) which summarised the data from TOX/2005/07 and the conclusions of the COM and COC, and included the evaluation and conclusions of the COT, based on the discussions in April, May and July.
3. In light of comments received from Members following the COT meeting in October 2005, a number of changes have been made. In particular, the draft working paper (attached in Annex A) specifically addresses the uncertainties in the data in order to clarify the decision-making process of the Committee in reaching the current recommendation.
4. The FSA has received results from the survey for fluorinated compounds in the 2004 total diet study samples. The draft Food Survey Information Sheet (FSIS) is provided in Annex B.

Question asked of the Committee:

5. Members are asked to consider the second draft working paper in Annex A and the draft FSIS in Annex B.

COT Secretariat

May 2006

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SECOND DRAFT WORKING PAPER ON THE TOLERABLE DAILY INTAKE FOR PERFLUOROOCTANE SULFONATE

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Introduction

1. Perfluorooctane sulfonate (PFOS) has the potential to enter the food chain and could have a negative health impact on humans. The Food Standards Agency has commissioned analysis of the 2004 Total Diet Samples for PFOS and the Committee was invited to consider the toxicology of PFOS in advance of receiving the results of the analysis.

Background

2. Perfluorooctane sulfonate is part of the large chemical class of fluorochemicals referred to as perfluorinated alkyl compounds. All perfluorinated substances are of anthropogenic origin. These fluorochemicals have excellent surfactant properties and are widely used in the manufacture of plastics, electronics, textile, and consumer material in the apparel, leather, and upholstery industries ¹. The term PFOS covers its anionic, acid and salt forms, and the PFOS-moiety (the C₈F₁₇SO₂ group) is incorporated into a variety of compounds (referred to as PFOS-related substances) that have the potential to degrade subsequently to PFOS either metabolically or through environmental processes. PFOS is widely distributed on a global scale and has been identified in various food chains ².

3. The major US manufacturer 3M announced in 2000 the voluntary cessation of production of PFOS and related chemistries due to reports of persistence and widespread exposure to wildlife and humans. Subsequent limited availability of PFOS-related substances and action within relevant industry sectors to decrease dependence on these substances has led to a significant reduction in the use of PFOS across the EU since 2002.

4. A hazard assessment for PFOS has been produced under the Existing Chemicals Programme of the Organisation for Economic Co-operation and Development (OECD) ³. Given the widespread occurrence of PFOS the OECD evaluation recommended that national or regional exposure information gathering and risk assessment may need to be considered. The Environment Agency for England and Wales consequently reviewed the environmental risks of PFOS use and concluded that PFOS meets the criteria for classification as a Persistent,

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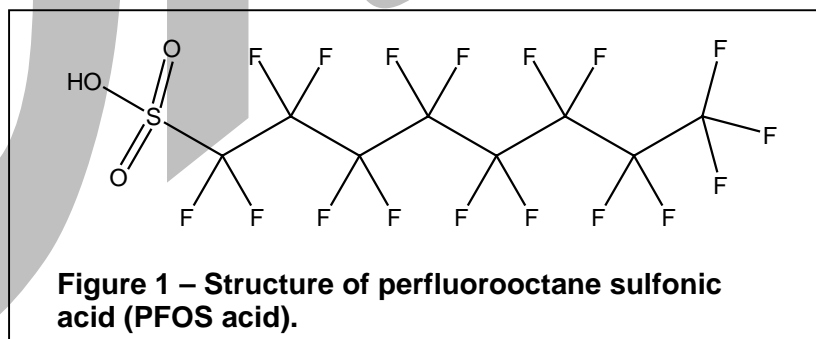
Bioaccumulative and Toxic (PBT) substance ⁴. In June 2005 the Swedish Environment Ministry announced that it will propose a ban for PFOS to the United Nations under the Stockholm Convention. Sweden also filed a national ban on PFOS to the European Commission.

Evidence considered in this evaluation

5. The COT has not previously evaluated PFOS. From an initial assessment of the relevant information it was considered essential to have advice from the Committees on Mutagenicity (COM) and Carcinogenicity (COC) regarding the genotoxicity of PFOS and whether it was appropriate to assume the existence of a threshold for carcinogenicity. The recommendations provided by the COM and COC are summarised in this statement.
6. The evaluation considered published literature and unpublished final reports of toxicology studies largely conducted by, or on behalf of, 3M.
7. Specialist teratology advice was sought from Professor Aldert Piersma (National Institute for Public Health and the Environment, The Netherlands) and his recommendations regarding the reported teratology findings are gratefully acknowledged.

Chemical information

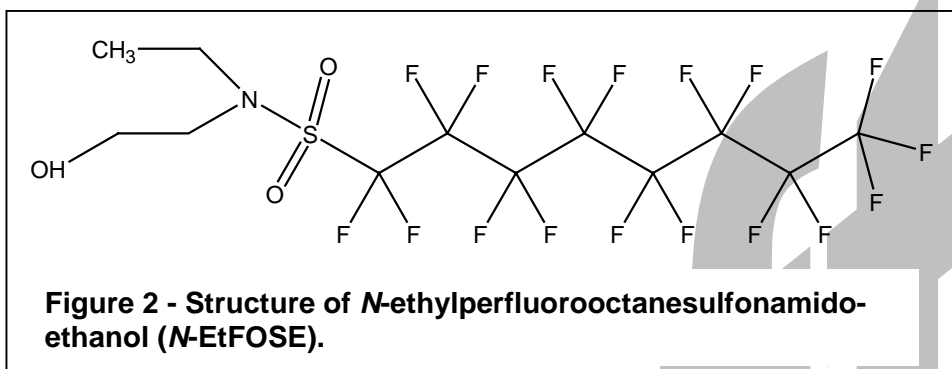
8. The high ionization potential and low polarizability of fluorine lead to weak inter- and intra-molecular interactions that are reflected by the extremely low surface tension of the perfluoroalkyl acids. Their partitioning behaviour is also unique; when they are mixed with water and hydrocarbons, three immiscible phases are formed, indicating the hydrophobic and oleophobic nature of these chemicals. Consequently, these compounds are ideal surfactants. Due to the strength of the carbon-fluorine bonds, these compounds are highly stable leading to their persistence and bioaccumulative properties ².



9. The perfluorooctane sulfonate anion (PFOS), does not have a CAS number, but that of the perfluorooctane sulfonic acid (Figure 1, C₈F₁₇SO₃H, molecular weight: 500) is 1763-23-1.

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10. The Environment Agency has published a draft list of 96 PFOS-related substances which have the potential to degrade to PFOS⁴. Current information strongly supports a conclusion that PFOS or its salts cannot be broken down further chemically³. However, only limited data are available on the toxicology of the PFOS-related substances, such as 2-(*N*-ethylperfluorooctanesulfonamido)ethyl alcohol (*N*-EtFOSE, Figure 2).



11. PFOS and PFOS-related substances are manufactured by a process known as Simons Electro-Chemical Fluorination (ECF). 3M reports a final product from ECF of approximately 70% linear PFOS and 30% branched impurities, including odd and even chain lengths. The same proportion is assumed to apply to PFOS-related substances manufactured by ECF.

12. Two determinations of the water solubility of PFOS have been reported. The average results were 519 mg/L at 20±0.5°C, and 680 mg/L at 24-25°C. The surface active properties of the substance make a direct determination of the octanol-water partition coefficient impossible. In a preliminary study reported by 3M an inseparable emulsion was formed. 3M determined the solubility of PFOS in octanol as 56 mg/L.

Toxicological profile

13. The majority of the toxicology studies of PFOS have been conducted with the potassium salt of PFOS (approximately 70% linear PFOS and 30% branched impurities), a white crystalline powder at normal temperature and pressure. No data are available on the relative toxicity of the non-linear contaminants of the test chemical.

Toxicokinetics – rat

14. Toxicokinetic data for potassium perfluorooctane sulfonate are available from five studies for the rat but no data are available for other experimental animals. Studies show that rather than bioconcentrating in the lipid fraction, PFOS tends to bind to plasma proteins.

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15. Over 95% of an oral dose of ^{14}C -PFOS was absorbed within 24 hours by male rats (8 weeks old) ⁵. The half-life of elimination from plasma was 179 hours (7.5 days).

16. In two repeat dose studies to investigate the toxicokinetics of PFOS over the course of gestation, non-radiolabelled PFOS was administered by oral gavage to F₀ female rats. In the first study, PFOS was administered daily for 42 days prior to mating and continued through gestation day (GD) 20 at dose levels of 0, 0.1, 0.4, 1.6, and 3.2 mg/kg bw/day ⁶. In GD 21 fetuses, serum PFOS levels were comparable to dams, but the fetal liver PFOS levels were considerably lower than in dams. In the second study female rats were dosed daily for 43 days prior to mating and through until confirmation of mating at three dose-levels, 0, 0.1, and 1.6 mg/kg bw/day PFOS ⁷. As with the earlier study there was a dose-related increase in the levels of PFOS in the liver and serum, with much higher levels present in the liver than in the serum of both dams and pups.

17. Tissue distribution and extent and route of excretion of ^{14}C -PFOS was investigated in 8 week old male rats treated with a single dose of 4.2 mg/kg bw (i.v. tail vein) ⁸. By post-dosing day 89 mean urinary excretion was 30% of administered ^{14}C , compared with 13% of administered ^{14}C excreted via faeces. Only liver and plasma contained a substantial percentage of dose at 89 days post dose, 25% and 2.8%, respectively. Elimination of only 42.8% of the dose through urine and faeces after 89 days indicated that the **terminal** half-life of elimination from the body was probably >89 days in the male rat.

18. PFOS undergoes considerable enterohepatic recirculation in the rat ⁹. A 9.5-fold higher elimination of PFOS via faeces was observed in rats with disrupted enterohepatic circulation (induced by cholestyramine treatment) than for animals with normal enterohepatic circulation.

Toxicokinetics – non-human primates

19. The pharmacokinetics and urinary excretion of PFOS, following a single i.v. bolus dose of 2 mg/kg bw, has been reported for male and female cynomolgus monkeys ¹⁰. The serum terminal half-life of PFOS ranged from 122 to 146 days in male monkeys and from 88 to 138 days in female monkeys. The results provided no clear indication that the pharmacokinetics of PFOS were different in male and female monkeys.

20. In a six month study of PFOS toxicity in cynomolgus monkeys (6/sex/group) by intragastric intubation of a capsule dose for at least 26 weeks ^{11,12}, two monkeys/sex/group in the control, 0.15 and 0.75 mg/kg bw/day dose groups were monitored for one year following the end of treatment. The serum PFOS elimination curves, during the recovery phase, were multiphasic in the high dose group and linear in the low dose group. Elimination half-lives were estimated at the end of the one-year recovery period to be approximately 200 days for animals dosed at 0.75 and 0.15 mg/kg bw/day. This study did not show differences in pharmacokinetics between male and female monkeys.

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Toxicokinetics – human

21. In 1976, Taves *et al.*,¹³ reported that human serum samples contained non-ionic (organic) fluorine, from perfluorocarbons. Preliminary evidence in 1979 from a 3M fluoropolymer production facility, showed that total serum organic fluorine levels for five employees were 4.1-11.8 parts per million (ppm), and that 55-80% of that was PFOS¹⁴. More recently PFOS was detected in 50% of non-occupationally exposed human blood donor samples in India and 100% of human blood samples in Poland, Italy, Belgium, USA and Japan¹⁵.

22. There is some inconsistency with regard to the half-life of PFOS in humans. One study following 3 retired 3M workers for five and a half years suggested a mean elimination half-life of 1 428 days (approximately 4 years)¹⁶.

23. The first report from an ongoing study following 27 retirees from a 3M production plant derived an elimination half-life of 139-640 days¹⁷. A mean serum half-life for PFOS of 8.7 years (S.D. = 6.1; range 2.3 – 21.3) was reported more recently¹⁸. The investigators have listed a number of limitations, and a number of attempts have been made to minimise the experimental error using selected subjects. No effort was made to determine, or control for, retiree re-exposure or endogenous metabolism of other perfluorinated chemicals to PFOS, both potentially leading to artificially long half-life estimations.

24. An analysis of PFOS concentrations in Kyoto City residents identified a sex-related pharmacokinetic difference¹⁹. Pre-menopausal females had higher serum PFOS concentrations than post-menopausal females and males. At an approximate age of 60 years, serum concentrations in post-menopausal females decreased to the level in males. Elimination in urine was approximately one-fifth of total PFOS elimination, assuming a one-compartment model.

25. PFOS can cross the human placenta²⁰. PFOS concentrations in Japanese maternal blood samples were 4.9-18 ng/mL, whereas those in fetal samples were 1.6-5.3 ng/mL. The mean ratio of cord to maternal blood PFOS concentrations was 0.32 (range 0.23-0.41), indicating that PFOS does may not pass into the fetal circulation completely.

26. A number of studies have assessed the levels of PFOS in blood of non-occupationally exposed humans, however, there have been no reports of PFOS levels in UK subjects. The largest PFOS biomonitoring study of adults in the United States²¹ (598 Red Cross blood donors aged 20 – 69), reported a geometric mean serum concentration of 35 ng/mL (ppb, ~~95% CI 33-37 ng/mL~~). The upper bound of the 95th percentile estimate, below which the true mean serum concentration of the samples falls with 95% confidence, -was 100 ng/mL.

27. A comparison of PFOS levels in 59 paired samples collected in 1974 (serum) and 1989 (plasma) from volunteer participants of a large community health study indicated serum concentrations of PFOS were significantly higher in 1989 than 1974 (median concentrations of 34.7 ng/mL and 29.5 ng/mL, respectively²². However, the

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levels of PFOS in 1989 were comparable with the levels in the Red Cross blood donor study²¹.

28. In blood samples collected from the United States, Colombia, Brazil, Belgium, Italy, Poland, India, Malaysia and Korea PFOS was the predominant perfluorochemical detected¹⁵. The highest concentrations were in samples from the U.S. and Poland (> 30 ng/mL). Levels were lowest in India (<3 ng/mL) and the others were in the range of 3 – 29 ng/mL. No age- or sex-related differences were found.

29. The primary binding proteins in human plasma have been identified by incubating PFOS with isolated human plasma protein fractions²³. The percentage of PFOS found bound to human plasma proteins was 99.8% for albumin, 95.6% for beta-lipoprotein, 59.4% for alpha-globulin, 24.1% for gamma globulin, and <0.1% for each of fibrinogen, alpha-2-macroglobulin, and transferrin.

Acute and sub-acute toxicity

30. The oral LD₅₀ in rat is 230 and 270 mg/kg bw (160-340 and 200-370 mg/kg bw, 95% confidence limits) for males and females, respectively²⁴.

31. Five sub-acute studies of PFOS have been conducted: two dietary studies in rats (a 90-day study²⁵ and a combined 4- and 14-week study²⁶), two 90-day gavage studies in rhesus monkeys^{27,28} and a 26 week study in cynomolgus monkeys^{11,12}.

Rat

32. In the 90-day study²⁵, Sprague-Dawley rats (5/sex/group) were administered potassium PFOS in the diet (mean achieved doses; 0, 2, 6, 18, 60, and 200 mg/kg bw/day). All the animals in the 18, 60, and 200 mg/kg bw/day dose groups died. Increased relative and absolute liver weights were reported at 2 and 6 mg/kg bw/day.

33. The second study²⁶, describes data from interim sacrifices at 4 and 14 weeks of a 2-year cancer bioassay. PFOS (potassium salt) was administered in the diet (mean achieved doses; 0, 0.05, 0.20, 0.42, and 1.6 mg/kg bw/day at 4 weeks, and 0, 0.04, 0.14, 0.37, and 1.40 mg/kg bw/day at 14 weeks) to Sprague-Dawley rats (5/sex/group) for 4 or 14 weeks.

34. Statistically significant effects were reported for the 1.6 mg/kg bw/day dose group at 4 weeks and the 1.4 mg/kg bw/day dose group at 14 weeks. At 4 weeks relative liver weights were significantly increased but absolute liver weights were unchanged. Male rats had lower serum glucose levels and females had elevated aspartate aminotransferase (AST) levels. Palmitoyl CoA oxidase activity was 2-fold higher than in controls.

35. At 14 weeks in the 1.4 mg/kg bw/day dose group, absolute and relative liver weights were significantly higher in males and relative liver weight was significantly higher in females. Concentrations of PFOS in the livers were comparable between

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the sexes, but PFOS levels in serum were 31-42% higher in females than males. Compared with controls, males showed moderately lower serum cholesterol concentrations, mildly raised alanine aminotransferase (ALT) values and both sexes had mildly raised urea nitrogen values. Palmitoyl CoA oxidase activity was not significantly different from controls. Centrilobular hepatocytic hypertrophy and midzonal to centrilobular vacuolisation was seen in males of the 0.37 mg/kg bw/day and 1.4 mg/kg bw/day dose groups and females of the 1.4 mg/kg bw/day group.

36. Serum and liver PFOS concentrations were used to provide a measure of estimating internal doses that can be associated with effects and NOAELs. The lowest average serum PFOS concentration associated with the NOAEL (0.37 mg/kg bw/day, on the basis of liver weight changes at 14 weeks) was 44 µg/mL in males and 67 µg/mL in females. These doses corresponded to PFOS levels in the liver of 360 µg/g and 670 µg/g in males and females, respectively. A re-analysis of the data derived the lower 95% confidence interval of the benchmark dose at the 10% response level (BMDL₁₀) for relative liver weights, the most sensitive endpoint in this study, of ~~0.12 and 0.20~~ mg/kg bw/day for males and females, ~~respectively~~²⁹.

Non-human primate

37. The two 90-day subchronic studies in rhesus monkeys provide few reliable quantitative data. In the first study²⁷, animals (2/sex/group) were treated by gavage with PFOS at 0, 10, 30, 100, and 300 mg/kg bw/day. All treated animals died by day 20. Similar signs of toxicity were shown by all dose groups including decreased activity, emesis with some diarrhoea, general body trembling, twitching and convulsions. Necropsy showed yellowish-brown discoloration of the liver (no microscopic lesions on histological examination) in the 100 and 300 mg/kg bw/day groups. Congestion, haemorrhage and lipid depletion of the adrenal cortex was noted in all treatment groups.

38. Goldenthal *et al.*,²⁸ reported on a 90-day subchronic rhesus monkey study of 2 animals/sex/group dosed at 0, 0.5, 1.5, and 4.5 mg/kg bw/day via gavage.

39. All monkeys in the highest dose group (4.5 mg/kg bw/day) died or were sacrificed *in extremis* between weeks 5 and 7 of the study, having exhibited signs of gastrointestinal tract toxicity. After 30 days of treatment, there was a significant decrease in serum cholesterol and a 50% drop in serum alkaline phosphatase activity. There were no differences in mean organ weights compared to controls. In all treated animals there was marked diffuse lipid depletion in the adrenals. Both females and one male had moderate diffuse atrophy of the pancreatic exocrine cells with reduced size and loss of zymogen granules. Both males and one female had moderate diffuse atrophy of serous alveolar cells marked by decreased cell size and loss of cytoplasmic granules.

40. The 1.5 and 0.5 mg/kg bw/day dose groups survived until the end of the study and necropsy showed no treatment related lesions. However, both groups showed signs of gastrointestinal tract toxicity (soft stools and diarrhoea).

41. In a 26-week study cynomolgus monkeys (6/sex/group) were treated with 0, 0.03 (4/sex/group), 0.15, and 0.75 mg/kg bw/day PFOS by intragastric intubation of a capsule dose for at least 26 weeks^{11,12}. Two monkeys/sex/group in the control,

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0.15 and 0.75 mg/kg bw/day dose groups were monitored for one year following the end of treatment.

42. Two male animals in the high dose group died or were killed *in extremis* before the end of the dosing period, with indications of pulmonary necrosis or hyperkalemia.

43. Females in the high dose group had significantly increased absolute liver weights and males and females in this group had increased relative liver weights. Serum PFOS concentrations showed a linear increase with time in the low- and mid-dose groups but the serum PFOS concentration in the high-dose group was non-linear over time and appeared to plateau. Average liver to serum PFOS concentration ratios were not dose-related and ranged from 0.9:1 to 2.7:1.

44. High-dose group males had lower haemoglobin levels that was considered to be a treatment-related effect. Serum total cholesterol values were significantly reduced in both sexes of the low- and high-dose groups. HDL cholesterol values were significantly lower for males in the low-dose group, females in the mid-dose group and for both sexes in the high-dose group. Due to the apparent lack of a dose response, the observed decreases in HDL cholesterol values in males given 0.03 mg/kg bw/day was considered, by the authors, unlikely to be an adverse reaction. The significance of the decrease in HDL cholesterol values in 0.15 mg/kg bw/day dosed females was considered difficult to interpret, given the small number of study animals, lack of pre-study and interim HDL values and lack of proportionate changes in total cholesterol. In 0.15 and 0.75 mg/kg bw/day dosed males at 26 weeks, thyroid stimulating hormone (TSH) values were increased and total triiodothyronine (T3) values were decreased. In the unpublished study report ¹¹ the study authors concluded that the NOAEL was, therefore, 0.03 mg/kg bw/day. Thyroid hormone values were repeated and reported by Seacat et al., ¹² the reductions in T3 and increases in TSH values in the 0.15 mg/kg bw/day dose group were not statistically significant in the second set of analyses. There was a statistically significant increase (50%) in palmitoyl CoA oxidase activity in the female 0.75 mg/kg bw/day dose group. In the 0.75 mg/kg bw/day dose group some animals presented with centrilobular vacuolisation, hypertrophy and mild biliary stasis. Taking account of the re-analysis of male thyroid hormone values and acknowledging the uncertainty concerning the significance of lowered HDL observed in females given 0.15 mg/kg bw/day, the authors considered the study NOAEL was 0.15 mg/kg bw/day.

45. ~~The serum PFOS elimination curves, during the recovery phase, were multiphasic in the high-dose group and linear in the low-dose group. At the end of the recovery the slopes of the serum PFOS elimination curves were similar in both dose groups and suggested that the elimination half-lives were approximately 200 days.~~ All toxicological effects appeared completely reversible on withdrawal of treatment.

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Mutagenicity and carcinogenicity

46. The COM considered the mutagenicity of PFOS in May 2005. PFOS has no apparent structural alerts for mutagenicity and the evidence from animal studies is that absorbed material is not metabolised.

47. Members concluded that the *in vitro* plate incorporation test using five strains of *Salmonella typhimurium* and the D4 strain of *Saccharomyces cerevisiae* gave negative results³⁰. The reverse mutation assay using *Escherichia coli* gave negative results³¹. For the *in vitro* chromosomal aberration assay in human lymphocytes³², the Committee noted the difficulty in formulating adequate suspensions of PFOS but agreed that this study had yielded negative results. The *in vitro* UDS assay in rat liver primary hepatocytes also gave negative results³³.

48. PFOS has also been tested in the mouse bone-marrow micronucleus test³⁴. Members noted that only 1000 micronuclei had been evaluated at each dose level and that there was difficulty in adequately formulating PFOS for oral dosing. However, overall the study was considered to be acceptable and provided negative results.

49. The COM agreed that the studies undertaken with PFOS were acceptable and that PFOS should be regarded as not mutagenic.

50. The carcinogenicity and epidemiology studies relating to PFOS³⁵ (and a carcinogenicity study of the PFOS-related substance *N*-EtFOSE³⁶) were considered by the COC in July 2005.

51. One dietary carcinogenicity study in Sprague-Dawley rats was available in which PFOS was administered in the diet for 104 weeks³⁵. Interim sacrifices were made at 4, 14 (reported in²⁶) and 52 weeks. Survival was considered to be adequate in this study. Non-neoplastic effects reported in the liver included increased absolute and relative liver weight, hepatocellular cystic degeneration and hepatocellular hypertrophy (often associated with vacuolation). No signs of hepatotoxicity were evident 52 weeks after cessation of a 52 week high-dose treatment. The NOAEL for non-neoplastic liver pathology was 2 ppm, i.e. a mean achieved dose of 0.16 and 0.14 mg/kg bw/day for males and females, respectively. [This was based on a consideration of the low incidence of liver hypertrophy, the borderline statistical significance and the lack of effect on liver weight at 2 ppm not representing an adverse effect.](#)

52. The incidence of hepatocellular adenomas was significantly increased at 20 ppm (mean achieved dose of 1.43 and 1.50 mg/kg bw/day for males and females, respectively). There was a single hepatocellular carcinoma in the female high dose (20 ppm) group. The incidence of thyroid follicular cell adenoma was significantly increased in the male high-dose recovery group, but not in the male and female high dose groups fed PFOS for 104 weeks.

53. A dietary carcinogenicity study in Sprague Dawley rats was also available in which *N*-ethylperfluorooctanesulfonamido ethanol (*N*-EtFOSE) was administered in the diet for 104 weeks³⁶. No significant treatment-related effects were observed on

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2-year survival rates, although survival in all groups including the controls was relatively poor. There was evidence of hepatocellular hypertrophy in high dose animals (mean achieved dose of 5.9 and 4.2 mg/kg bw/day for males and females, respectively). The incidence of hepatocellular adenomas was slightly higher in high dose male and female groups than in controls. This difference was statistically significant in the high-dose males. A single hepatocellular carcinoma was observed in a high dose female.

54. Two limited human epidemiological studies (a retrospective mortality study and an 'episodes of care' analysis) have been conducted in occupationally exposed populations. Cohorts were relatively small and also relatively young. In the retrospective cohort mortality study, when restricted to workers with at least one year of employment and high exposure to PFOS, standardised mortality ratios (SMR) were below one for all causes of death and all malignant neoplasms. There were three deaths from malignant neoplasms of the bladder (0.63 expected) in males with over 5 years in high-exposure jobs. This excess was statistically significant (SMR 16.12; 95% CI 3.32-47.14). Members questioned the adequacy of exposure assessment by using job categories. It was noted that there had been potential exposure of the workers to benzidine, a known bladder carcinogen. Members advised that, overall, it was not possible to draw definite conclusions from this study. Further evaluation across all PFOS manufacturing sites would have provided more appropriate information. Members considered that the 'episode of care' analysis was unusual in design and uninformative.

55. In conclusion, the COC agreed that there was equivocal evidence for carcinogenicity limited to hepatocellular adenoma in the animal studies. The NOAEL for tumourigenicity was 0.15-0.57 and 0.19-0.56 mg/kg bw/day in males and females, respectively. COC were not convinced that adequate evidence had been provided for a mode of action incorporating peroxisome proliferation. Considering both the COM conclusions and the carcinogenicity data Members agreed that a threshold approach could be used for risk assessment.

Reproductive toxicity

56. Teratological studies have been conducted in rat, mouse, and rabbit with agreement of observation across the species examined. Observed developmental effects include reduction of fetal weight, cleft palate, anasarca, delayed ossification of bones (sternebrae and phalanges), and cardiac abnormalities (ventricular septal defects and enlargement of the right atrium). The majority of these findings were seen in the highest dose groups where significant reductions of weight gain and food consumption were also observed in the pregnant dams.

Rat

57. Time-mated female Sprague-Dawley rats were administered 0, 1, 5, and 10 mg/kg bw/day potassium PFOS by gavage from gestation day (GD) 6 to GD 15³⁷. Animals were sacrificed on GD 20. A NOAEL of 5 mg/kg bw/day and a LOAEL of 10 mg/kg bw/day for maternal toxicity was indicated based on significant reductions in mean body weights during GD 12-20. No other signs of maternal toxicity were reported. A LOAEL of 1 mg/kg bw/day for developmental toxicity was indicated on

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the basis of reductions in fetal weights. Developmental toxicity evident at doses of 10 mg/kg bw/day consisted of reductions in the mean number of implantation sites, corpora lutea, resorption sites and in the mean number of viable male, female and total fetuses, and fetal weights.

58. A repeat study in pregnant Sprague-Dawley rats ³⁸, with the same dosing regime, reported NOAELs for maternal toxicity and developmental toxicity of 1 mg/kg bw/day. The LOAEL for maternal toxicity was 5 mg/kg bw/day, based on clinical signs of toxicity, decreases in body weight and food consumption, decreases in uterine weights, and an increased incidence in gastrointestinal lesions. The LOAEL for developmental toxicity was 5 mg/kg bw/day, based on decreased fetal body weight and increases in external and visceral anomalies and variations. Signs of developmental toxicity included a dose-related trend toward an increased incidence of late resorptions, total resorptions, number of dead fetuses, and fetal loss, although these findings were not statistically significant. Significant decreases in mean fetal weights for both males and females were observed in the 5 and 10 mg/kg bw/day dose groups. Statistically significant increases in incomplete closure of the skull were observed in the low- and high-dose groups. Also observed in the high-dose group were delayed ossification and skeletal variations.

59. Thibodeaux *et al.*, ³⁹ and Lau *et al.*, ⁴⁰ reported maternal and developmental toxicity studies in rats. Pregnant Sprague-Dawley rats were given 1, 2, 3, 5 or 10 mg/kg bw/day by gavage from GD 2 to GD 21. Maternal weight gains were suppressed by PFOS in a dose-dependent manner, attributed to reduced food and water intake. Serum PFOS levels increased with dosage and liver levels were approximately four-fold higher than serum levels. Serum thyroxine (T₄) and triiodothyronine (T₃) in the PFOS-treated dams were significantly reduced (1 week into treatment schedule). However, no feedback response of thyroid-stimulating hormone (TSH) was seen. Serum triglycerides (though not cholesterol) were significantly reduced, particularly in the high-dose group.

60. Fetuses had detectable levels of PFOS in liver tissue, at almost 50% that in the maternal livers, regardless of dose level. PFOS did not alter the numbers of implantations or live fetuses at term. Birth defects noted included, cleft palate, anasarca, ventricular septal defect and enlargement of the right atrium, primarily in the 10 mg/kg bw/day dose group. Maternal doses estimated to correspond to the BMDL₅s for sternal defects and cleft palate were 0.12 and 3.3 mg/kg bw/day, respectively.

61. In the highest dose group (10 mg/kg bw/day) neonates became pale, inactive and moribund within 1 hour of birth, with death following quickly. Neonates in the 5 mg/kg bw/day dose group survived for between 8 and 12 hours and approximately 50% of offspring died at 3 mg/kg bw/day. Cross-fostering the 5 mg/kg bw/day dose group neonates to control nursing dams failed to improve survival. The maternal dose corresponding to the BMDL₅ for survival of rat pups at postnatal day 8 was estimated at 0.58 mg/kg bw/day.

62. Small but significant and persistent growth lags were detected in surviving pups, and slight delays in eye opening were noted. Serum levels of PFOS in neonates were comparable to those of the dam at term, suggesting that PFOS

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equilibrated across the placenta. Unlike the situation in the adult there did not appear to be preferential accumulation of PFOS in the ~~neonate~~-neonatal liver.

63. Grasty *et al.*⁴¹ investigated critical windows of PFOS toxicity during gestation. Exposure of pregnant rats to 25 mg/kg bw/day PFOS for a 4 day period during pregnancy demonstrated an increased incidence of neonatal death administration was later in gestation, reaching 100% mortality in the group treated on GD 17–20.

Mouse

64. Thibodeaux *et al.*³⁹ and Lau *et al.*⁴⁰ also reported maternal and developmental toxicity studies in mice. Pregnant CD-1 mice were treated with 1, 5, 10, 15, and 20 mg/kg bw/day from GD 1 to GD 17. Maternal weight gains were suppressed by PFOS in a dose-dependent manner, attributed to reduced food and water intake. Serum PFOS levels increased with dosage, and liver levels were approximately four-fold higher than serum levels. Serum T₄ levels were significantly reduced after 1 week of treatment. Serum triglycerides (though not cholesterol) were significantly reduced, particularly in the high-dose groups. Mouse dams in 10 mg/kg bw/day and higher dose groups had markedly enlarged livers.

65. PFOS did not alter the numbers of implantations or live fetuses at term. Birth defects noted were similar to those seen in the rat, namely cleft palate, anasarca, ventricular septal defect and enlargement of the right atrium, primarily in the 20 mg/kg bw/day dose group. Estimated maternal doses corresponding to BMDL₅s for sternal and cleft palate defects in fetuses were 0.016 and 3.5 mg/kg bw/day, respectively.

66. All animals were born alive and initially appeared to be active. In the highest dose group (20 mg/kg bw/day) neonates became pale, inactive and moribund within 1 hour with death following quickly. Neonate mice in the 15 mg/kg bw/day dose group also became moribund but survived for between 8 and 12 hours. Approximately 50% of offspring died at 10 mg/kg bw/day. The maternal dose corresponding to the BMDL₅ for survival of pups at postnatal day 6 was estimated at 3.9 mg/kg bw/day, approximately six times higher than that of the rat.

67. Serum levels of PFOS in neonates were comparable to those of the dam at term, suggesting that PFOS equilibrated across the placenta. There was no evidence of preferential accumulation of PFOS in the liver of the neonates.

Rabbit

68. Case *et al.*,⁴² carried out oral developmental toxicology studies on mated female New Zealand white rabbits at dose levels of 0, 0.1, 1.0, 2.5, 5.0, 10, and 20 mg/kg bw/day by gavage. Treatment was from GD 6 to GD 20 and rabbits were sacrificed on GD 29. PFOS was not a selective fetal toxicant and did not cause fetal malformations in the rabbit.

69. A NOAEL and LOAEL of 0.1 and 1.0 mg/kg bw/day, respectively, were indicated for maternal toxicity, based on abortions, incidences of scant faeces, and decreases in body weight gains and food consumption. The NOAEL and LOAEL indicated for developmental toxicity were 1.0 and 2.5 mg/kg bw/day, respectively,

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based on reductions in mean fetal body weight and increased incidences of fetal alterations such as delayed ossification. Abortions occurred in one 2.5 mg/kg bw/day dose group doe (GD 25) and ten of the 3.75 mg/kg bw/day dose group animals (between GD 22 and GD 28).

Two-generation reproductive study

70. A two-generation reproductive toxicity study was conducted in Sprague-Dawley rats⁶. Five groups of 35 rats/sex/dose were administered PFOS by oral gavage at 0, 0.1, 0.4, 1.6, and 3.2 mg/kg bw/day for six weeks prior to and during mating. Treatment in males continued for approximately 22 days, and female rats were treated throughout gestation, parturition and lactation. F₁ generation rats were administered PFOS beginning on lactation day (LD) 22 and continuing through until one day prior to sacrifice.

71. No mortality occurred in the F₀ generation females, and there did not appear to be any effects on oestrous cycling, mating and fertility parameters. There were no treatment-related signs of toxicity, effects on mating or on any of the fertility parameters evaluated in the F₀ generation male rats. The 1.6 and 3.2 mg/kg bw/day dose groups did exhibit reductions in body weight gains during the pre-mating period and terminal body weights were also significantly reduced. Absolute weights of seminal vesicles and the prostate in the 3.2 mg/kg bw/day dose group were significantly lower than controls.

72. The most significant finding in the F₁ generation offspring was reduced pup viability at the two highest dose levels. No pups survived beyond LD 1 in the 3.2 mg/kg bw/day dose group and over 26% of pups in the 1.6 mg/kg bw/day dose group died between LD 2 and 4. Clinical observations in the 0.1 and 0.4 mg/kg bw/day dose groups F₁ generation male and female rats were unremarkable.

73. Evidence of treatment-related effects in the F₂ generation pups consisted of reductions in mean pup body weights (on a per litter basis) observed at 0.1 and 0.4 mg/kg bw/day on LD 7. Body weights were comparable to control levels by LD 14 (0.1 mg/kg bw/day group) and by LD 21 (0.4 mg/kg bw/day group).

74. Based on reductions in body weight gain and food consumption, the NOAEL was 0.1 mg/kg bw/day for the F₀ generation and female F₁ generation. A NOAEL for the F₁ generation parental males was not established, but was greater than 0.4 mg/kg bw/day. The NOAEL for the F₁ generation offspring was 0.14 mg/kg bw/day, based on statistically significant reductions in mean pup weight gain, the number of implantation sites, litter size, pup viability, pup body weight and survival. For the F₂ generation offspring the NOAEL was 0.1 mg/kg bw/day, based on statistically significant reductions in mean pup body weight, litter size, pup viability and survival.

75. A cross-fostering study was conducted with female Sprague-Dawley rats administered 0 and 1.6 mg/kg bw/day PFOS beginning 42 days prior to mating with untreated males, and continued throughout gestation and into LD 21⁷. Litters were placed with either a control or PFOS-treated dam for rearing, producing four groups of litters: *in utero* exposure only; un-exposed (controls); *in utero* and post-natal exposure; and post-natal exposure only.

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76. Pups with post-natal exposure only had a similar mortality rate (1.1%) as pups in the control group (1.6%). Pups exposed to PFOS only *in utero* and those exposed both *in utero* and postnatally had mortality rates of 9.6% and 19.2%, respectively, indicating that *in utero* exposure is the main contributor to reduced pup survival.

Mechanistic studies

77. A small number of recently published studies have investigated more specific effects of PFOS.

78. An acute study demonstrated that PFOS, but not *N*-EtFOSE, administered via a single intraperitoneal injection at 100 mg/kg bw to male Sprague-Dawley rats, induced markers of peroxisome proliferation (induction of lauroyl CoA oxidation and lowering of serum cholesterol) in the absence of hepatomegaly⁴³. PFOS did not cause a significant change in liver weight but there was a significant increase in liver-to-body weight ratio (a 12% increase) due to body weight loss.

79. With its highly hydrophobic and rigid perfluorinated carbon tail and strongly polar sulfonyl head group PFOS somewhat resembles a fatty acid. Luebker *et al.*,⁴⁴ demonstrated that PFOS and *N*-EtFOSE can interfere with the binding affinity and capacity of liver-fatty acid binding protein for fatty acids.

80. Gene expression studies in rats treated with PFOS (5 mg/kg bw/day for 3 days or 3 weeks) identified twenty three genes induced significantly and nineteen genes suppressed significantly⁴⁵. Induced genes were primarily genes for fatty acid metabolising enzymes, cytochrome P450s, or genes involved in hormone regulation. One cytosolic enzyme, long-chain acyl-CoA hydrolase, showed a 90-fold induction on treatment. This enzyme cleaves acyl-CoA to free fatty acid and CoA, and leads to increased cytosolic free fatty acid concentrations. PPAR- α mRNA expression levels were unchanged on treatment, however, a number of genes that are indicative of peroxisome proliferation were affected. The activities of the phenobarbital inducible genes carboxyesterases and CYP2B1 were also increased by PFOS treatment, but no evidence for PFOS acting directly on the arylhydrocarbon receptor has been found.

81. A study in mice suggested that PFOS was almost as potent as perfluorooctanoic acid in causing increases in peroxisomal fatty acid beta-oxidation, peroxisomal catalase activity, omega-hydroxylation of lauric acid, cytosolic epoxide hydrolase activity and cytosolic DT-diaphorase activity⁴⁶. The authors proposed that the study results challenge the hypothesis that the first step in peroxisome proliferation is formation of a thioester between the carboxylic group of a proliferator and coenzyme A.

COT evaluation

82. In accordance with the advice of COM and COC, we considered it appropriate to take a threshold approach to establishing a tolerable intake for PFOS. This is based upon the negative genotoxicity in standard assays and the equivocal

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evidence for carcinogenicity. We, therefore, reviewed the toxicology data in order to identify the most sensitive end-points.

83. The toxic effects occurring at the lowest dose levels are in the teratology studies, in particular Thibodeaux *et al.*,^{40,39} and Lau *et al.*⁴⁰ Conclusions on the teratology data were:

- The finding of delayed ossification (manifested as bipartite and bilobed sternbrae) would be more appropriately considered a “variation” rather than a “defect” as it regularly occurred in control animals;
- delayed ossification is often a sign of general developmental delay but this is not entirely clear in this study where fetal weight effects only occur in the highest dose group. There is a dose-response in both species (rats and mice) in terms of the number of sternbrae per fetus with the variation. However, in the absence of details about the extent of the effects it is not possible to draw firm conclusions about their significance;
- the authors description of “notable skeletal defects” is not explicitly explained but probably relates to the sternal and phalangeal findings in the rat and to the sternal findings in the mouse. In the mouse, roughly half of the litters show these “notable skeletal defects” in the control and in both highest doses, indicating that this is not a generalized phenomenon throughout all litters, and moreover, a dose-response is not apparent;
- taken together, the sternal findings should not be interpreted as malformations but as indications of delayed development. In view of the above and given the additional fetal observations in this study the sternal findings do not determine the developmental NOAEL in this study.

84. The BMDL₅ indicated for sternal defects in the mouse fetus was approximately two orders of magnitude below the lowest dose of PFOS tested^{40,39}. Insufficient information was provided on the modelling procedures to verify the validity of this value, which indicated considerable variability. In view of the uncertainties in the BMD modelling, it was considered more practical to define an overall developmental NOAEL, which was 2 mg/kg bw/day in the rat on the basis of anasarca³⁹, and 5 mg/kg bw/day in the mouse on the basis of heart defects³⁹.

85. Overall, the data from the mechanistic studies^{43,44,45,46}, the rat carcinogenicity study^{26,35} and the 26-week capsule study in cynomolgus monkeys¹² provide little evidence to indicate **that PFOS is a potent inducer of** peroxisome proliferation. Electron microscopy of livers of PFOS-exposed rats did not reveal peroxisome proliferation. The 50-95% increases in liver palmitoyl CoA oxidase levels, although statistically significant, were not considered to be biologically significant. There was evidence for some liver growth inducing agents also increasing the incidence of thyroid tumours, however, with respect to PFOS more information is required.

86. ~~The BMDL₁₀ and NOAEL indicated in the 14-week dietary study in rats and~~ Re-analysis by COT of the data reported in 14-week rodent study²⁶ derived a BMDL₁₀ for relative liver weights, the most sensitive endpoint in this study, as 0.20 mg/kg bw/day for males and females. In the 26-week cynomolgus monkey study^{11,12} the NOAEL indicated was 0.15 mg/kg bw/day on the basis of reduced high-

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density lipoprotein in males. Non-neoplastic effects in the two-year rat carcinogenicity study³⁵ indicated NOAELs of 0.16 and 0.14 mg/kg bw/day for males and females, respectively, and the two-generation reproductive toxicity study in rats⁶ indicated NOAELs of 0.1 mg/kg bw/day for F₀, F₁ and F₂ generations. On the basis of these studies a dose level of 0.1 mg/kg bw/day was selected as a suitable point of departure for deriving a tolerable daily intake (TDI) for PFOS.

87. Given the bioaccumulative properties of PFOS and the relatively long half-life of elimination from serum estimated for the male rat it may be more appropriate to relate the toxic effects to a body burden rather than to a daily dose. However, there is incomplete understanding of the pharmacokinetics of PFOS in rodents and humans, and the Committee considered that equilibrium between plasma and target organ concentration is unlikely to have been reached in the sub-acute studies in animals. The use of a body burden approach would therefore involve excessive uncertainty on the basis of the currently available data.

88. ~~To allow for inter- and intra-species variation a~~ An uncertainty factor of 100 was applied to the ~~NOAEL-dose of 0.1 mg/kg bw/day. indicated as having no effect in a range of studies, including a 104-week dietary study in rats of 0.1 mg/kg bw/day, to allow for inter- and intra-species variation.~~ Therefore, the TDI indicated for PFOS is 1 µg/kg bw/day.

Exposure assessment

89. The Food Standards Agency has completed an analysis of composite food groups samples from the 2004 Total Diet Study (TDS) for a range of fluorinated chemicals, including PFOS and PFOA. The TDS models the typical UK diet and is fully described in Food Survey Information Sheet 38/03⁴⁷.

90. PFOS was detected at concentrations above the limit of detection in the potatoes, canned vegetables, eggs and sugars and preserves food groups. PFOA was detected in the potatoes food group. Five of the other perfluorinated chemicals were not detected in any food groups and the others detected only occasionally. Ten different fluorinated chemicals were found in the potatoes food group.

91. The estimated average adult intake of PFOS from the whole diet in 2004 was 0.1 µg/kg bw/day (upper bound figure). The corresponding high level adult dietary intake was 0.2 µg/kg bw/day. ~~Since this value is based on limits of detection for most food groups, intakes could be very much lower than this estimate.~~ These estimated intakes of PFOS from the diet are significantly below the TDI recommended by the COT. However, as PFOS can be formed by degradation from a large group of related perfluorinated substances, the significance of detecting a number of other fluorinated chemicals in food groups is currently uncertain.

Conclusions

92. We conclude that PFOS has the potential to cause adverse health effects. Given the bioaccumulative properties of PFOS a body burden approach may be

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most appropriate, but the current knowledge of the pharmacokinetics of PFOS does not permit this to be performed.

93. We recommend a tolerable daily intake (TDI) of 1 µg/kg bw/day be established for PFOS. We consider that the TDI is adequate to protect against other possible effects, such as cancer and effects *in utero*.

94. We note the results of the Food Standards Agency analysis of composite food group samples from the 2004 Total Diet Study (TDS) that estimated high level adult dietary intakes of PFOS are at least five times lower than the recommended TDI. The results are, therefore, not of concern regarding human health. However, we consider the impact of other perfluorinated chemicals in the diet on total PFOS exposure an area that is not currently well understood.

~~88. We note that a survey of the 2004 Total Diet Samples for PFOS is underway and will discuss the implications of the estimated dietary exposure when the results are reported in early 2006.~~

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ANNEX B to TOX/2006/17

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

**DRAFT FOOD SURVEY INFORMATION SHEET – FLUORINATED CHEMICALS:
UK DIETARY INTAKES**

[This is a draft for Committee information and will be published after finalisation.]