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

**THE CARCINOGENICITY OF PERFLUOROOCCTANOIC ACID (PFOA) –
MODE OF ACTION FOR EFFECTS IN RAT LIVER**

Background

1. The COT is considering the toxicology of perfluorooctanoic acid (PFOA) and requested advice from COM and COC regarding the mutagenicity and carcinogenicity of PFOA. The COC discussed the carcinogenicity of PFOA (CC/05/16) at the July 2005 meeting.
2. In a two-year dietary study in Sprague Dawley rats PFOA induced dose-related non-neoplastic liver effects including megalocytosis, cystoid degeneration and portal mononuclear infiltration (Sibinski 1987). PFOA also induced an apparent dose-related increase in Leydig cell adenomas, which was not significant compared to historical control incidence. The pancreas showed the occurrence of proliferative lesions of the pancreatic acini. A second study investigated a single high dietary dose of PFOA for 24 months and reported increased incidences of hepatocellular adenomas, Leydig cell adenomas and pancreatic acinar cell adenomas (Biegel *et al.* 2001).
3. COC discussed the hypothesis put forward which proposes that PFOA induces liver, Leydig cell and pancreatic acinar cell tumours via PPAR-alpha activation (Klaunig *et al.* 2003). Members were informed of a single study in PPAR-alpha null mice (the minutes of the July meeting are incorrect in stating that this study was in rats) that demonstrated increased liver weight following treatment with PFOA, but not with Wyeth-14,643 (Yang *et al.* 2002). Members were not provided with this paper to consider at the July meeting (now provided as Annex 1). On the basis of this information, the COC considered that it was not possible to propose modes of action for the liver tumours reported by Biegel *et al.* (2001).
4. The conclusions of the discussion were included in the 'First draft working paper on the tolerable daily intake for perfluorooctanoic acid' considered by COT at their October meeting.
5. Comments have been received from a COT member on the draft working paper noting the points above. The COT member questions whether the single experiment in mice provides sufficient reason to discount significant evidence in rats supporting a mode of action, and to conclude that it was not possible to propose MOAs for the liver tumours.

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Advice from COC

6. The COC is asked to consider the publication of Yang *et al.* (2002 – Annex 1) and to advise on whether it is satisfied to conclude that it is not possible to support the MOA.

Questions on which the views of the Committee are sought

7. The COC is invited to consider the following questions:
- I. Is the weight of evidence sufficient to support the mode of action for liver tumours proposed by Klaunig *et al.* (2003)?
 - II. Do the data on PFOA-induced liver effects in PPAR-alpha null mice give members reason to question this mode of action, or do they provide evidence of an additional mechanism of liver growth in mice?
 - III. Taking into account kinetic and dynamic factors, is the animal mode of action for liver tumours relevant to humans?

References

- Biegel, L. B., Hurtt, M. E., Frame, S. R., O'Connor, J. C., and Cook, J. C. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicological Sciences* 60[1], 44-55. 2001.
- Klaunig, J. E., Babich, M. A., Baetcke, K. P., Cook, J. C., Corton, J. C., David, R. M., DeLuca, J. G., Lai, D. Y., McKee, R. H., Peters, J. M., Roberts, R. A., and Fenner-Crisp, P. A. PPARalpha agonist-induced rodent tumors: modes of action and human relevance. *Crit Rev.Toxicol* 33[6], 655-780. 2003.
- Sibinski, L. J. Final report of a two-year oral (diet) toxicity and carcinogenicity study of fluorochemical FC-143 (perfluorooctanane ammonium carboxylate) in rats. 1987. 3M Company.
- Yang, Q., Xie, Y., Alexson, S. E., Nelson, B. D., and DePierre, J. W. Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. *Biochem.Pharmacol.* 63[10], 1893-1900. 2002.

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ANNEX 1

The annex contains the following paper:

Yang, Q., Xie, Y., Alexson, S. E., Nelson, B. D., and DePierre, J. W. (2002) Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. *Biochem. Pharmacol.* 63(10), 1893-1900.

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