EXHIBIT 38

Executive Summary

EPA's Office of Pollution Prevention and Toxics (OPPT) requested that the Science Advisory Board review the "Draft Risk Assessment of the Potential Human Health Effects Associated with Exposure to Perfluorooctonoic Acid (PFOA)" (hereafter referred to as the "draft document"). A Panel of the EPA Science Advisory Board met in February 2005 for this review during which nine charge questions raised by OPPT were deliberated. These included carcinogenicity descriptors, useful models for evaluation of health effects, toxicokinetic considerations and reliance on currently available human biomonitoring exposure data.

This Executive Summary highlights the outcome of the Panel's deliberations. It includes the context for the charge questions and issues raised for consideration by OPPT, and the conclusions reached by the SAB panel. It is important to note that all of the key findings and recommendations from the Panel deliberations were based on currently available published data and the understanding that further risk assessment will proceed as more data on PFOA health effects become available.

Issue 1. Rodent PPAR-alpha Mode of Action for Hepatocarcinogenesis:

In rats, PFOA has been shown to induce liver adenomas, Leydig cell tumors (LCT) and pancreatic acinar cell tumors (PACT). The draft document concludes that liver cell tumors are due to a PPAR-alpha agonism mode of action (MOA). In this MOA, activation of PPAR-alpha leads to cell proliferation and decreased apoptosis, preneoplastic foci, clonal expansion and subsequent tumors. The draft document premises its conclusions about this MOA on studies showing that PFOA is a potent peroxisome proliferator in liver of rats and mice and, like other peroxisome proliferators, induces hepatomegaly in rats. In addition, requisite dose-response and temporal associations for some key events for this MOA have been reported.

Comment on the Weight of Evidence and Adequacy of the Data Available to Identify the Key Events for the PPAR-alpha agonist-induced Rodent Liver Toxicity and Hepatocarcinogenesis for PFOA.

The Panel's charge was to determine whether it agreed with the weight of evidence supporting a PPAR-alpha MOA. The Panel did concur that liver tumor induction could result from a PPAR-alpha MOA, based on the observations that PFOA activates the receptor, results in peroxisome proliferation, increases beta-oxidation and produces hepatomegaly, with dose and temporal responses consistent with this MOA. These events, moreover, have been shown to depend upon a functional PPAR-alpha receptor, and no other known MOA has been identified.

However, the Panel determined that at the current time, sufficient uncertainties and limitations of the data still exist with respect to concluding that PPAR-alpha is the MOA for liver tumor induction, or the only MOA for these effects. For example, one contradictory finding was that in contrast to what would be predicted, PFOA administration still increased liver weights in PPAR-alpha receptor knockout mice, i.e., in mice where PPAR-alpha activation was precluded, even while the prototype PPAR-alpha agonist WY-14,643 did not produce corresponding increases. The significance of these findings remain uncertain in the absence of a corresponding assessment of histopathology. These observations therefore raise the possibility that PFOA-induced liver tumors could occur by PPAR-alpha independent effects. Secondly, there is as yet no published evidence that the induction of PPAR-alpha results in an increase in the number of preneoplastic foci which is considered a critical step in the proposed MOA.

The Panel also concluded that additional uncertainties need to be considered in the characterization of the MOA. For example, the role of Kupffer cells, resident macrophages in the liver that do not express PPAR-alpha, but are activated by peroxisome proliferators, has not been adequately characterized in PFOA-induced liver tumors.

In addition to the uncertainties regarding the PPAR-alpha MOA for liver adenomas, it was the judgment of the Panel that the liver carcinogenic effects reported in the Sibinski et al. (1987) study were not given adequate consideration in the draft document. In that study, incidences of hepatocellular carcinoma in male rats were 6%, 2% and 10% (in response to 0, 30 or 300 ppm APFO, respectively, in a 2 year feeding study) and the incidences of hyperplastic nodules in liver were 0%, 0% and 6%. Collectively, therefore, the incidence of hepatoproliferative lesions across the three dose groups were 6%, 2% and 16%, respectively. The possibility of liver carcinogenicity in this study should be re-evaluated for the draft risk assessment and the MOAs for these effects require evaluation.

One additional issue related to a potential PPAR-alpha MOA for PFOA-induced liver tumors is its relevance to humans (see also below). While adults are considered refractory to this MOA because of fewer active PPAR-alpha receptors, it is not apparent that such insensitivity can also be extended to children and neonates, limiting any conclusions about the generality of this MOA.

Thus the Panel believed on the basis of the current evidence that it is possible that PPAR-alpha may not be the sole MOA for PFOA, that not all steps in the pathway of PPAR-alpha activation- induced liver tumors have been demonstrated, that other hepatoproliferative lesions require clarification, as does the role of Kupffer cells, and that extrapolation of this MOA across the age range in humans is not supported.

Issue 2: Descriptor for Carcinogenic Potential

The draft document reaches the conclusion of 'suggestive' evidence for potential human carcinogenicity of PFOA. This conclusion was based upon: 1) a PPAR-alpha MOA for liver tumors in rodents that was considered not relevant to humans because of their decreased sensitivity to PPAR-alpha agonism when compared to rodents, 2) the absence of hepatic cell proliferation in a 6 month study of PFOA administration in cynomologous monkeys, the species considered closest in physiology to humans; and 3) the absence of a strong association between PFOA exposure and tumors in human studies as interpreted in the draft document.

The draft document concludes that the LCT and PACT tumors produced by PFOA in rodents were probably not relevant to humans based on the lower levels of expression of the mediators leutinizing hormone (LCT) and choleocystokinin growth factor receptors (PACT) in humans, as well as differences in quantitative toxicodynamics between rats and humans. The mammary fibroadenomas reported in female rodents were considered equivocal based on their comparable rates of occurrence relative to a historical control group.

Comment on the Proposed Descriptor for the Carcinogenic Potential of PFOA

In considering the collective evidence the majority of panel members concluded that the experimental weight of evidence with respect to the carcinogenicity of PFOA was stronger than proposed in the draft document, and suggested that PFOA is a 'likely' carcinogen in humans.

According to EPA's Guidelines for Carcinogen Risk Assessment[1] (also known as EPA's Cancer Guidelines), this descriptor is typically applied to agents that have tested positive in more than one species, sex, strain, site or exposure route, with or without evidence of carcinogenicity in humans. The Panel's conclusion was based on the following:

- While human data is ambiguous, two separate feeding studies demonstrate that PFOA is a multi-site carcinogen.
- Significant uncertainties still exist as to whether PPAR-alpha agonism constitutes the sole MOA for PFOA effects on liver since PFOA, but not the prototypical PPAR-alpha agonist WY-14,643, increases liver weights in PPAR-alpha knockout mice. This finding remains of uncertain significance in the absence of liver histopathology.
- The exclusion of mammary tumors in the draft document based on comparisons to historical control levels was deemed inappropriate, since the most appropriate control group is a concurrent control group. Using that comparison, increases in both fibroadenomas (22%, 42% and 48% for rats treated with 0, 30 and 300 ppm APFO, respectively) and adenocarcinomas (5, 31% and 11%, respectively) were seen in the Sibinski et al. (1987) 2 yr PFOA feeding study.
- Insufficient data are currently available to determine the MOA for the observed Leydig cell tumors, pancreatic acinar cell tumors and mammary gland tumors. In the absence of a defined MOA for these tumor types, they must be presumed to be relevant to humans.

The Panel was not willing to state, however, an associated probability value for PFOA-induced carcinogenicity at the current time. Nevertheless, based on available evidence to date, it believed that risk assessments for each of the PFOA-induced tumors are appropriate at the current time.

Issue 3: Selection of Endpoints

The draft document proposes the use of multiple endpoints from several life stages, species and gender for risk assessment. No specific recommendations on the most appropriate parameters are stipulated at the current time.

Comment on the:

Selection of Toxicity Endpoints for the Risk Assessment

The Most Appropriate Lifestage/Gender/Species for Assessing Human Risk

The Appropriateness of the Available Animal Models

The Panel agreed with the current approach of inclusivity, particularly in light of the current uncertainties noted above with respect to carcinogenicity, as well as the paucity of information on potential PFOA effects on non-cancer endpoints. In the evaluation of carcinogenicity, the Panel supports the inclusion of multiple cancer endpoints and liver histopathology. The Panel felt that additional research including both PPAR-alpha mediated and independent effects of PFOA, as well as non-carcinogenicity endpoints clearly merit additional attention

It is not yet known whether carcinogenicity will represent the most sensitive endpoint for PFOAs. Immunotoxicity has been reported, and derivations of MOEs for such effects are encouraged. Given the prevalence of PPAR receptors, including PPAR-alpha in brain, effects on

[1] In March 2005, EPA published final Cancer Guidelines and Supplemental Guidance which can be found at the following URL: http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283

nervous system structure and function warrant attention.

Similarly, no exclusion of species should be considered at present, and differences between genders as demonstrated in rodent studies again suggest multiple MOAs for PFOAs. Moreover, no information currently exists with respect to critical periods; therefore it is important to evaluate effects across age groups. Correspondingly, the use of multiple animal models is appropriate particularly in light of the reported differences in toxicokinetics in rodents, non-human primates and humans. Resolution of most appropriate parameters must await additional research, but the process will be facilitated by the ability to measure internal dose.

The Panel also concluded that the draft document does not give adequate consideration to the data from occupational and epidemiological studies. The draft document suggests that these studies suffer from the fact that they involve multiplicity of exposures. However, the Panel felt that such studies could not be disqualified without disqualifying virtually all epidemiologic and occupational studies in the risk assessment process. Moreover, it is clear that occupationally-exposed populations have experienced the highest levels of exposure and therefore reported health effects in these studies merit consideration.

Issue 4: Risk Assessment Approach

Issue 4a: Pharmacokinetic Modeling and Use of AUC as a Measure of Internal Dose

The draft document compares internal dose metrics from animal toxicology studies and human biomonitoring studies for purposes of ultimately generating margin of exposure (MOE) information. Area under the concentration curve (AUC) was calculated from PFOA serum levels in human biomonitoring studies assuming a steady state. In some of the rat studies, serum PFOA concentrations were available, or it was considered that sufficient pharmacokinetic information was available to estimate serum levels. For this purpose, AUC was estimated from a pharmacokinetic model. Specifically, compartmental modeling of serum concentrations using single dose rat oral exposure studies were used to estimate internal dosimetry for the longer term dosing studies based upon the premise that pharmacokinetic information for rodents and humans is sufficient for this purpose and that this approach does not exceed the limits of the available data.

Comment on the Use of the One Compartment Pharmacokinetic Model

The Panel concluded that the empirical model used in the modeling in the draft document was adequate for predicting blood levels resulting from repeated dosing, but that this fitting procedure is specific to this limited data set and this particular application. Concern was expressed, therefore, that use of the descriptor "one compartment" to describe PFOA pharmacokinetics in the draft document is misleading, given the actual complexities in many of the available datasets, and the term should be stricken or replaced unless it is carefully qualified throughout the document.

Comment on the use of the AUC as a Measure of Internal Dose for Rats and Humans for Calculation of the MOE

The Panel concluded that while calculating blood AUC may be an appropriate method to estimate internal dose, it is important to note that at the current time information on PFOA health effects is limited, and as additional data becomes available, other measures may also be appropriate, such as the Cmax, the integrated dose above a minimum concentration, etc. Regardless of the choice for the measure of internal dose, a clearer rationale needs to be presented for the approach taken, and, importantly, for any choice adopted, the impact of how the internal dose measure impacts on the magnitude of the MOE should be described. The Panel also believes that caution should be exercised in assuming that the analyte is constant in serum across the period of observation, given the current information on metabolism.

Issue 4b: Cross Species Extrapolation

In extrapolating data from animal experiments to humans, a default value of 10 is typically applied, with a factor of 3 for differences in toxicodynamics and a value of 3 for toxicokinetic differences. In the PFOA draft risk assessment document, internal doses from animal toxicology studies and human biomonitoring studies were compared. Derivation of data from animal toxicology studies included both measured PFOA serum levels from non-human primates and derived values from pharmacokinetic modeling from rodent studies. The reliance on internal dose metrics was considered by OPPT to be sufficient to reduce uncertainties and therefore raised the question of the ability to either eliminate or reduce the default values for cross species extrapolation.

Comment on the Need to Use or Modify the Default Value of 10 for Cross Species Extrapolation Given the Pharmacokinetic Analysis

The use of internal dose metrics in this analysis was considered by the Panel to be a significant step toward reducing uncertainty related to cross species extrapolation. Nevertheless, it was not apparent that the extent of the uncertainty based on the current understanding of PFOA is sufficient to eliminate or even to modify the current default value. Significant uncertainties still remain, including the measured internal dose that best predicts adverse effects in human and other species, the bias inherent in measurement/modeling errors, the lack of information about non-cancer endpoints and about developmental vulnerability and the impact of gender, and the multiple PFOA environmental exposures that occur in humans vs. animals, among others. The Panel likewise stressed that bench mark dose methodologies would be preferable to the reliance in the draft document on LOAEL-driven MOE calculations.

Issue 4c: Human Biomonitoring Data

Currently available data on PFOA levels in humans includes occupational biomonitoring studies as well as three population studies within the U.S. The measurements from the population studies come from: 1) samples from 6 American Red Cross blood banks; 2) a study of Streptococcal A infection in children; and 3) elderly volunteers in a cognitive study in Seattle. The draft document utilizes only the data derived from 1 and 2 above in its calculation of the MOE. Occupational biomonitoring data were excluded in the assessment in the draft document because it was stated that sample sizes were small, data on gender were not available, and that blood monitoring data obtained from 2000 would overestimate current serum levels, since PFOA exposure of this group ceased in 2002. Measured levels from the elderly population were not utilized because values were considerably lower, for unknown reasons, than those reported in the other population studies for adults and children. From the other two population studies, geometric means and 90th percentiles were calculated across genders for calculation of MOEs.

Comment on the Adequacy of the Human Exposure Data for Use in Calculating a MOE

Several concerns were noted with regard to this approach. First are issues regarding the generality of the populations included in the MOE calculation. One relates to the potential for pregnancy to modify serum PFOA levels and the uncertainties with respect to toxicokinetics in children of 2-12 years of age (study 2). In addition, public presentations made to the Panel at the time of its meeting suggest that more highly exposed populations exist than are reflected in databases, particularly near sources of exposure. Indeed, levels in these non-occupationally exposed populations may exceed values obtained in occupational biomonitoring studies, and yet these groups are part of the "general population" for which MOEs were calculated. This raises the question of what constitutes the "general population" for which these values are intended and serves as the basis of the Panel's recommendation that occupational biomonitoring data also be included in MOE calculations.

Three different summary statistics are presented in the draft document in calculation of the MOE. Of these, the Panel deemed the use of mean values, particularly geometric means in the calculations may be inappropriate. Additionally, no rationale was provided for the choice for the 90^{th} percentile as a summary statistic, rather than the use of a higher value. Whatever the approach adopted, justification must be provided for the chosen summary measure and an explicit objective for the MOE analysis described.

INTRODUCTION

This report was prepared by the Science Advisory Board (SAB) PFOA Risk Assessment Review Panel (the "Panel") in response to a request by EPA's Office of Pollution Prevention and Toxics (OPPT) to review their *Draft Risk Assessment of the Potential Human Health Effects Associated With Exposure to Perfluorooctanoic Acid and Its Salts (PFOA)*. According to the document, OPPT has been investigating PFOA and its salts to try to understand the health and environmental issues presented by fluorochemicals, in the wake of unexpected toxicological and bioaccumulation discoveries with respect to perfluorooctane sulfonates (PFOS). PFOA and its salts are fully fluorinated organic compounds that can be produced synthetically or through the degradation or metabolism of other fluorochemical products. PFOA is primarily used as a reactive intermediate, while its salts are used as processing aids in the production of fluoropolymers and fluoroelastomers and in other surfactant uses. PFOA and its salts are persistent in the environment.

OPPT identified 4 issues where they were seeking the SAB's advice and recommendations. These included the proposed mode of action, carcinogenicity descriptors, toxicological endpoints selected and the pharmacokinetic modeling methods used in the risk assessment. OPPT's assessment focused on the potential human health effects associated with exposure to PFOA and its salts. Several toxicological endpoints and hypothesized modes of action were considered. Internal dose metrics were estimated for animal toxicology studies with pharmacokinetic modeling, and were obtained from human biomonitoring studies, assuming steady state. Margin of Exposure (MOE) values were calculated from the internal dose metrics. The SAB PFOA Review Panel was asked to comment on the scientific soundness of this risk assessment.

The Panel deliberated on the charge questions during their February 22-23, 2005 face-to-face meeting. The responses that follow represent the views of the Panel. In most cases, there was agreement by a majority of the panel members as to a particular recommendation. In some cases, there were one or more panel members that had a differing point of view; these instances have been noted throughout the report. The specific charge questions to the Panel are as follows:

Issue 1: Rodent PPAR-alpha Mode of Action for Hepatocarcinogenesis

The postulated mode of action (MOA) of PPAR• •agonist induced liver toxicity and liver tumors in rodents involves four causal key events. The first key event is activation of PPAR• •(which regulates the transcription of genes involved in peroxisome proliferation, cell cycle control, apoptosis, and lipid metabolism). Activation of PPAR• •leads to an increase in cell proliferation and a decrease in apoptosis, which in turn leads to preneoplastic cells and further clonal expansion and formation of liver tumors. Of these key events, only PPAR• •activation is highly specific for this MOA while cell proliferation/apoptosis and clonal expansion are common to other modes of action. There are also several "associative" events that are markers of PPAR• • agonism but are not directly involved in the etiology of liver tumors. These include peroxisome proliferation (a highly specific indicator that this MOA is operative) and peroxisomal gene expression.

Information that provides evidence that any specific chemical is inducing liver toxicity and tumors via a PPAR• •agonist MOA includes *in vitro* evidence of PPAR• •agonism (i.e., evidence from an in vitro receptor assay), *in vivo* evidence of an increase in number and size of peroxisomes, increases in the activity of acyl CoA oxidase, and hepatic cell proliferation. The *in vivo* evidence should demonstrate dose-response and temporal concordance between precursor events and liver tumor formation. Other information that is desirable and may strengthen the weight of evidence for demonstrating that a PPAR• •agonist MOA is operative includes data on hepatic CYP4A1 induction, palmitoyl CoA activity, hepatocyte hypertrophy, increase in liver weights, decrease in the incidence of apoptosis, increase in microsomal fatty acid oxidation, and enhanced formation of hydrogen peroxide.

OPPT has proposed that there is sufficient weight of evidence to establish that the mode of action for the liver tumors (and precursor effects) observed in rats following exposure to PFOA is PPAR• •agonism.

Question 1 - Please comment on the weight of evidence and adequacy of the data available to identify the key events for the PPAR• •agonist-induced rodent liver toxicity and hepatocarcinogenesis for PFOA. Discuss whether the uncertainties and limitations of these data have been adequately characterized.

Issue 2: Descriptor for Carcinogenic Potential-

Carcinogenicity studies in Sprague-Dawley rats show that PFOA induces a "tumor triad" similar to a number of other PPARα agonists. This "tumor triad" includes liver tumors, Leydig cell tumors (LCT), and pancreatic acinar cell tumors (PACT). OPPT has proposed that there is sufficient evidence to conclude that the liver tumors are due to PPAR• •agonist MOA, and that this MOA is unlikely to occur in humans based on quantitative differences between rodents and humans. In addition, the LCT and PACT induced in the rat by PFOA probably do not represent a significant cancer hazard for humans because of quantitative toxicodynamic differences between the rat and the human. Overall, based on no adequate human studies and uncertain human relevance of the tumor triad (liver, Leydig cell and pancreatic acinar cell tumors) from the rat studies, OPPT has proposed that the PFOA cancer data may be best described as providing "*suggestive evidence of carcinogenicty, but not sufficient to assess human carcinogenic potential*" under the interim 1999 EPA Guidelines for Carcinogen Risk Assessment, as well as the 2003 draft EPA Guidelines for Carcinogen Risk Assessment.

Question 2 - Please comment on the proposed descriptor for the carcinogenic potential of PFOA.

Issue 3: Selection of Endpoints -

OPPT has proposed the use of several endpoints from several life stages, species and gender for the risk assessment. For this draft assessment, OPPT has not made specific recommendations on the most appropriate endpoint/lifestage/species/gender. Rather, all have been presented to provide transparency.

For adults, endpoints were selected from the non-human primate and rat studies; the endpoints included liver toxicity and possibly mortality for the non-human primates and decreased body weight for rats.

For developmental endpoints, OPPT relied upon the definition of developmental toxicity outlined in the Agency's Developmental Toxicity Risk Assessment Guidelines. These guidelines state that the period of exposure for developmental toxicity is prior to conception to either parent, through prenatal development and continuing until sexual maturation. (In contrast, the period during which a developmental effect may be manifested includes the entire lifespan of the organism). Based on this definition of developmental exposure, OPPT considered developmental effects in the rat two-generation reproductive toxicity study to include reductions in F1 mean pup body weight (sexes combined) on lactation days 1, 5 and 8, an increase in mortality during the first few days after weaning (both sexes), a delay in the timing of sexual maturation (both sexes), and a reduction in mean body weight postweaning (F1 males only).

Question 3 - Please comment on the selection of these toxicity endpoints for the risk assessment.

Question 4 - Given the available data to date, please comment on the most appropriate lifestage/gender/species for assessing human risk.

Question 5 - Please comment on the appropriateness of the available animal models. Please comment on whether additional animal models should be investigated, and if so, what information would better enable us to ascertain potential human risks.

Issue 4: Risk Assessment Approach

A margin of exposure (MOE) approach can be used to describe the potential for human health effects associated with exposure to a chemical. The MOE is calculated as the ratio of the NOAEL or LOAEL for a specific endpoint to the estimated human exposure level. The MOE does not provide an estimate of population risk, but simply describes the relative "distance" between the exposure level and the NOAEL or LOAEL. In this risk assessment there is no information on the sources or pathways of human exposure. However, serum levels of PFOA, which are indicative of cumulative exposure, were available from human biomonitoring studies. In addition, serum levels of PFOA were available for many of the animal toxicology studies or there was sufficient pharmacokinetic information to estimate serum levels. Thus, in this assessment internal doses from animal and human studies were compared; this is analogous to a MOE approach which uses external exposure estimates.

Issue 4a: Pharmacokinetic Modeling and Use of AUC as a Measure of Internal Dose

As noted above, internal dose metrics from animal toxicology studies and human biomonitoring studies were compared in this draft assessment. For humans, the area under the concentration curve (AUC) was calculated from measured PFOA serum levels in human biomonitoring studies, assuming steady state. For the rat toxicology studies, the area under the concentration curve (AUC) and C_{max} were estimated from a pharmacokinetic model. The pharmacokinetic analysis could be done using a number of approaches including non-parametric analysis, physiologically based pharmacokinetic (PBPK) modeling, and classical compartmental modeling. Each has strengths and limitations given the available data. Non-parametric analyses provide a description of the data that have been collected, but have fairly limited ability to make predictions across species or to account for variations in exposures. PBPK modeling is perhaps the ideal approach for addressing PFOA for purposes of cross-species extrapolation. Extensive pharmacokinetic studies have been undertaken in rodents demonstrating complex phenomena including high tissue concentrations in liver, kidney and serum and enterohepatic recirculation of the parent compound. These could be addressed using PBPK modeling for the rodents, but the more limited information in monkeys and humans would either require substantial assumptions or preclude use of this approach. Classical compartmental modeling can be used to analyze the existing data on blood concentrations in rats, monkeys, and humans. Currently, the available pharmacokinetic information for rodents and humans is sufficient to support compartmental modeling. Comparisons of serum protein binding across species indicated a high degree of binding in all species eliminating the apparent need to address this factor in the compartmental modeling. In light of the documented differences in clearance of PFOA across sexes in rats and across species, compartmental modeling of serum concentrations provides a sound approach for estimating internal dosimetry without exceeding the limits of the available data, so this approach was selected for this risk assessment.

Question 6 - Please comment on the use of the one compartment pharmacokinetic model.

Question 7 - Please comment on the use of the AUC as a measure of internal dose for rats and humans for calculation of the MOE.

Issue 4b: Cross Species Extrapolation –

Judgments about the "adequacy" of a MOE are based on many considerations including uncertainty associated with cross species extrapolation. Typically, a value of 10 is considered which consists of a value of 3 for toxicodynamics and a value of 3 for toxicokinetics. Each of these can be decreased or increased if there are data to warrant it. In this draft assessment, internal doses from animal toxicology studies and human biomonitoring studies were compared. For humans, the internal doses were based on measured PFOA serum levels in human biomonitoring studies. For the non-human primate toxicology studies, internal doses associated with the NOAEL and/or LOAEL were based on measured PFOA serum levels. For the rat toxicology studies, pharmacokinetic modeling was used to estimate an internal dose metric associated with a NOAEL or LOAEL.

Question 8 - Please comment on the need to use or modify the default value of 10 for cross species extrapolation given the pharmacokinetic analysis.

Issue 4c: Human Biomonitoring Data –

For this draft assessment, human biomonitoring data of PFOA serum levels were available for adults and children. Similar analytical methods were used to measure the PFOA levels in both sets of blood samples. The adult data included 645 U.S. adult blood donors (332 males, 313 females) from 2000-2001, ages 20-69, obtained from six American Red Cross blood banks located in: Los Angeles, CA; Minneapolis/St. Paul, MN; Charlotte, NC; Boston, MA; Portland, OR, and Hagerstown, MD. Each blood bank provided approximately 10 samples per 10-year age interval (20-29, 30-39, etc.) for each sex.

The children's data included a sample of 598 children, ages 2-12 years old, who had participated in a study of group A streptococcal infections. The samples collected in 1994-1995 from children residing in 23 states and the District of Columbia were analyzed for PFOA in 2002.

Question 9 - Please comment on the adequacy of the human exposure data for use in calculating a MOE.

RESPONSES TO THE CHARGE QUESTIONS

Issue 1: Rodent PPAR-alpha Mode of Action for Hepatocarcinogenesis

Question 1. *Please comment on the weight of evidence and adequacy of the data available to identify the key events for the PPAR alpha agonist induced rodent liver toxicity and hepatocarcinogenesis for PFOA. Discuss whether the uncertainties and limitations of these data have been adequately characterized.*

As discussed in the EPA Draft Risk Assessment of the Potential Human Health Effects Associated with with Exposure to Perfluorooctanoic Acid and its Salts (hereafter referred to as the 'PFOA Draft Risk Assessment'), a sequence of four key events define the mode of action by which PPAR-alpha agonists induce rodent liver tumors. According to the proposed mode of action, the initial causal event is (1) activation of PPAR-alpha, which regulates the expression of genes involved in peroxisome proliferation, cell cycle control, apoptosis, and lipid metabolism. These transcriptional events lead to (2) increased cell proliferation and/or decreased cell death. The chronic increase in cell growth occurs primarily in the preneoplastic focal lesions in the liver resulting (3) in the clonal expansion of the preneoplastic lesions, which ultimately results (4) in the development of hepatocellular neoplasms. In addition, "associative" events that may or may not be causally linked to the PPAR-alpha mode of action for hepatocarcinogenesis include blockage of cell to cell communication, an increase in peroxisomes, an increase in peroxisomal enzymes, and liver and hepatocyte hypertrophy.

The weight of evidence supports the conclusion that PFOA is a PPAR-alpha agonist and can induce liver changes in adult rats that have been associated with PPAR-alpha activation. As discussed in the report, key elements to establish this mode of action have been demonstrated by appropriate experiments. In vitro studies demonstrate that PFOA is a PPAR-alpha agonist, and treatment of rats and/or mice results in peroxisome proliferation, increased beta-oxidation, and hepatomegaly with dose and temporal responses consistent with this mode of action for liver tumor induction. Studies comparing PPAR-alpha null and wild-type mice showed that PFOA-induced persoxisome proliferation, beta-oxidation, and immunotoxicity depended on the presence of a functional receptor. Not all of the causal events in the PPAR-alpha mode of action have been demonstrated for PFOA, however, including the induction of cell proliferation in the liver at early times following PFOA treatment and/or modulation of apoptosis in hepatocytes.

Besides establishing that PFOA fulfills the PPAR-alpha agonist mode of action, it is important to demonstrate that PFOA does not work through other established modes of action to induce liver cancer. The data support the conclusion that PFOA is not DNA reactive or mutagenic, and thus not involved in a genotoxic mode of action. Nor is the liver neoplastic effect due to the induction of repeated hepatocyte death and compensatory regeneration (a cytotoxic mode of action) like chloroform. No other known mode of action for the rodent liver tumor induction is currently supported by the available data.

While the PFOA Draft Risk Assessment in general appropriately discusses the uncertainties and limitations of the data that support the postulated mode of action for PFOA-induced liver tumors in adult rats, it fails to consider two important issues in sufficient detail. First, studies of PPAR-alpha null mice by Yang *et al.* (2002) cited in the report in the context of the receptor dependence of PFOA immunotoxicity, exhibited increased liver weight, but not acyl CoA oxidase induction in response to PFOA treatment. This fact was not mentioned in the draft risk assessment. This finding is of uncertain significance, due to the lack of histopathology. However, it should be noted that the well-characterized PPAR-alpha agonist, WY-14,643, did not induce an increased liver weight in this study, leaving open the possibility that PFOA may induce some of its effects in mouse liver by a PPAR-alpha-independent pathway.

The second critical issue not discussed in the PFOA Draft Risk Assessment is whether arguments about the relevance to humans of the PPAR-alpha agonist mode of action for induction of liver tumors in adults may be extended to exposed infants and children. Humans are refractory to some but not all PPAR-alpha activation effects. Data from studies using PPAR-alpha receptor knockout mice have shown that these receptors are essential for the rapid induction of liver neoplasms after exposure to WY-14,643. However, humans have functional PPAR-alpha receptors, leaving unanswered the question as to why they respond so differently from rats and mice to PPAR-alpha agonists. Available data suggests that the difference between humans and rats or mice may be a consequence of a lower number of PPAR-alpha receptors. Thus, the PPAR-alpha mode of action is not considered likely to yield a similar hepatic cancer response in adult humans. However, exposures of neonates and children to PFOA remain a potential concern. Rodent studies suggest PPAR-alpha receptors in neonates and adults are similar, but because adult humans have so few, and information in neonates and children is minimal, this same extrapolation cannot be made in humans. Given that human exposures to PFOA and related chemicals appear ubiquitous, uncertainties and limitations of the data for children have not been adequately characterized in order to conclude that the PPAR-alpha mode of action is not operative in this young age group.

Finally, two aspects of the PPAR-alpha mode of action as presented in the report should receive further consideration. First, the current PFOA Draft Risk Assessment states (page 76 lines 15-16) that the "[a]ctivation of PPAR-alpha leads to an increase in cell proliferation and a decrease in apoptosis, which in turn leads to preneoplastic cells ..." There is no experimental evidence that the induction of PPAR-alpha results in an increase in the number of preneoplastic foci. The effect of the PPAR-alpha activation appears to be at level of focal lesion clonal expansion (Klaunig et al., 2003).

Second, Kupffer cell activities are considered to be associative events (shown in Figure 1, page 78), but are not discussed in the text of the PFOA risk assessment. There is an extensive literature on the essential role of Kupffer cells in signaling peroxisome proliferator-induced hepatocyte proliferation. Studies have shown that hepatocyte proliferation and peroxisome proliferation occur by different mechanisms. Parzefall et al. (2001) and Hasmall et al. (2001) demonstrated that peroxisome proliferators had no effect on DNA synthesis but still induced peroxisomal acyl CoA oxidase activity in cultured rat and mouse hepatocytes that had been purified to remove contaminating Kupffer cells. Kupffer cells, which are resident macrophages in the liver, are a major source of growth factors (tumor necrosis factor alpha, interleukins) that induce DNA synthesis or suppress apoptosis in purified hepatocytes. A key finding relevant to the proposed MOA is that Kupffer cells do not express PPAR-alpha (Peters et al., 2000), but are activated by peroxisome proliferators. Prevention of Kupffer cell activation by glycine inhibited, although not completely, the development of liver tumors by the potent peroxisome proliferator, WY-14,643 (Rose et al., 1999). There are no data available on the effects of peroxisome proliferators in human Kupffer cells. Recognizing the role of Kupffer cell activation in the induction of DNA synthesis and subsequent neoplastic development by PPAR-alpha agonists, some members of the FIFRA Science Advisory Panel (2003) [SAP Minutes No. 2003-05] noted that the interplay between PPAR-alpha agonism and Kupffer cells has not been characterized and thus results from the PPAR-alpha null mouse are not directly applicable to the human situation in which PPAR-alpha is present and can be activated.

Issue 2: Descriptor for Carcinogenic Potential

Question 2. *Please comment on the proposed descriptor for the carcinogenic potential of PFOA.*

The PFOA Draft Risk Assessment proposes that the PFOA cancer data may be best described as providing "*suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential*" under the interim 1999 EPA Guidelines for Carcinogen Risk Assessment (US EPA, 1999), as well as the 2003 draft EPA Guidelines for Carcinogen Risk Assessment (US EPA, 2003). This opinion is based on the absence of adequate human studies on PFOA and carcinogenicity as well as the quantitative differences between rats and humans that OPPT believes raises uncertainties about the human relevance of the "tumor triad" response (liver tumors, Leydig cell tumors, and pancreatic acinar cell tumors) of PPAR-alpha agonist activation in rats.

The determination of an appropriate descriptor for the carcinogenic potential of PFOA requires an examination of the available carcinogenicity data, an evaluation of mechanistic or mode-of-action (MOA) data, and guidance on how EPA applies various descriptors for summarizing weight of evidence data.

Cancer studies on PFOA

Carcinogenicity studies in Sprague-Dawley rats have shown that PFOA induces neoplasms at multiple sites. In male rats exposed to 0 or 300 ppm ammonium perfluorooctanoate (APFO) in the feed for 2 years, increased incidences of testicular Leydig cell tumors (LCT) (0% vs. 11%), pancreatic acinar cell tumors (PACT) (0% vs. 11%), and liver adenomas (3% vs. 13%) were observed in treated animals compared to controls (Biegel et al., 2001). In a 2-year study in which male and female Sprague-Dawley rats were fed diets containing 0, 30 or 300 ppm APFO, a dose-related increase in LCT was observed (0% in controls, 4% at 30 ppm, 14% at 300 ppm) (Sibinski et al., 1987). The PFOA Draft Risk Assessment document does not address the carcinogenic effects in the liver reported in the Sibinski study. In that study, the incidences of hepatocellular carcinoma in male rats were 6%, 2%, and 10%, and although no adenomas were diagnosed, the incidences of hyperplastic nodules in the liver were 0%, 0%, and 6%. Because hyperplastic nodules may be part of the continuum of proliferative lesions in the liver carcinogenic process, the incidence of hepatoproliferative lesions in the three groups in this study is 6%, 2%, and 16% (hepatocellular carcinoma and hyperplastic nodules), assuming no animals in the 300 ppm dose group were diagnosed with both lesions. The livers in the Sibinski study should be reevaluated for a potential carcinogenic effect.

In female rats, a dose-related increase in mammary gland fibroadenomas was reported (22% in controls, 42% at 30 ppm, and 48% at 300 ppm) (Sibinski et al., 1987). In addition, the incidence of mammary gland adenocarcinomas was greater in the low dose group than in controls (15% in controls, 31% at 30 ppm, and 11% at 300 ppm). The PFOA Draft Risk Assessment did not consider the mammary gland neoplasms to represent a compound-related effect because of high background rates reported for fibroadenomas in Sprague-Dawley rats in other laboratory studies. However, in the historical database of Chandra et al. (1992), the incidence of mammary gland fibroadenomas in controls was 19.0% and the incidence of adenocarcinomas in controls was 8.8% in female Sprague-Dawley rats. A neoplastic effect in the mammary gland is apparent in the Sibinski study when tumor rates are compared to the historical control database of Chandra et al. For historical controls to be useful in interpreting potential treatment related effects, the conditions of studies in the historical database must be similar with each other and with the study under evaluation. Because of interlaboratory differences in tumor response due to factors such as differences in diet, differences in animal age at the start and termination of studies, different animal supply sources and breeding practices, different environmental conditions, different vehicles and routes of administration, differences in animal care procedures that may affect weight gain and survival, and the use of different substrains, the concurrent control group is the most appropriate group for evaluations of chemical-related effects. Thus, most panel members believe that the elevated tumor rates observed in female rats in the Sibinski study raise concerns for neoplastic effects induced by PFOA in the mammary gland that should not be dismissed.

Mode-of-action analysis, uncertainties, and human relevance

The PFOA Draft Risk Assessment proposes that there is sufficient evidence to conclude that liver tumors induced by PFOA are due to a proposed PPAR-alpha agonist MOA (Klaunig et al., 2003), and that this MOA is unlikely to occur in humans based on quantitative differences between rodents and humans. In addition, the PFOA Draft Risk Assessment proposes that the Leydig cell tumors (LCT) and pancreatic acinar cell tumors (PACT) induced in the rat by PFOA probably do not represent a significant cancer hazard for humans because of quantitative toxicodynamic differences between the rat and the human. Thus, the panel examined issues related to our understanding of the MOA for the multiple tumor types induced by PFOA in rats and the impact of available information on determining the human relevance of the animal tumor responses.

Liver adenomas.

As noted under Issue 1, PFOA is a PPAR-alpha *agonist* that induces peroxisomal β-oxidation activity, increases in absolute and relative liver weight, and liver tumors in Sprague-Dawley rats. Issues to be considered are whether a PPAR-alpha agonists MOA for liver tumor induction in rats might occur in humans and/or whether additional MOAs might be involved.

Lack of data on key events in the PPAR-alpha agonist MOA.

The PFOA risk assessment did not identify dose-response data showing increases in hepatocyte proliferation and suppression of apoptosis in rats exposed to PFOA. This is a critical deficiency because these are key events in the proposed MOA linking activation of PPAR-alpha to the liver tumor response. The increase in liver weight in rats exposed to PFOA and the return to control levels following an 8-week recovery period (Palazzolo, 1993) is consistent with an increase in cell proliferation and suppression of apoptosis by PFOA during the exposure period. The lack of an increase in hepatic cell proliferation in rats after 1 month or more exposure to PFOA (Biegel et al., 2001) is consistent with observations of a transient increase in hepatocyte proliferation with other peroxisome proliferators.

However, important to understanding the potential human relevance of the response in rats is the observation that the same early effects occur in monkeys exposed to PFOA, namely induction of peroxisomal β-oxidation activity (2.6 fold), significant increases and positive dose-response trends for absolute and relative liver weights (1.6 fold), and the return of relative liver weight to control levels after a 13-week recovery period. Cell proliferation was evaluated in monkeys only after 6 months of exposure. Unfortunately, neither the rat nor the monkey studies provided data on hepatocyte proliferation during the first 1-2 weeks of exposure, or direct measurements of apoptotic cells after exposure to PFOA was stopped. The lack of data on cell proliferation and apoptosis in animals exposed to PFOA makes it impossible to analyze dose-response concordance between these key events and tumor induction for PFOA in relation to other PPAR-alpha agonists. Because the available data for PFOA in rats and monkeys indicate similar responses in the livers of rodents and primates, human relevance for liver effects induced by PFOA by a PPAR-alpha agonist MOA cannot be discounted.

PPAR-alpha -independent liver effects.

In a comparative study of PFOA and Wy-14,643 in PPAR-alpha null mice, at doses of each chemical that produced increases in liver weight and peroxisomal fatty acid acyl-CoA oxidase activity in wild-type mice, only PFOA caused a similar increase in liver weight (but no increase in acyl-CoA oxidase activity) in the PPAR-alpha null mice (Yang et al., 2002). This study confirms that PFOA is a PPAR-alpha agonist for peroxisomal enzyme induction, but also shows that liver changes induced by PFOA in rodents can occur by a MOA that is independent of PPAR-alpha activation. The lack of liver enlargement or tumor response in PPAR-alpha null mice exposed to Wy-14,643 for 11 months has been cited frequently as evidence that liver cancer induction by peroxisome proliferators is mediated by PPAR-alpha activation (Peters et al., 1997); however, the study of Yang et al., (2002) shows that results with Wy-14,643 in PPAR-alpha null mice do not predict all of the potential liver effects of PFOA. As noted under Issue 1, PPAR-alpha independent stimulation of hepatocyte growth factor production in Kupffer cells appears to be central to the mechanism of hepatocyte replicative DNA synthesis, suppression of apoptosis, and liver tumor development by peroxisome proliferators. Until the interplay between PPAR-alpha agonism and Kupffer cell activation are characterized, negative results from the PPAR-alpha null mouse may not be relevant to the human situation in which Kupffer cells and hepatocellular PPAR-alpha are present and can be activated. Thus, significant uncertainties exist in the predictability of the PPAR-alpha agonist MOA for human cancer risk associated with exposure to PFOA.

LCTs, PACTs, and mammary neoplasms.

The Panel concluded that available data are insufficient to characterize the MOA for PFOA-induced LCTS and PACTs; for the mammary tumor response no MOA data are available. Further, placing the liver tumors, LCTs, and PACTs into a triad MOA is not justified; available evidence is inadequate to support a PPAR-alpha agonist MOA for the induction of LCTs and PACTs (Klaunig et al., 2003). A specific MOA needs to be worked out for each tumor type. As discussed in EPA's Cancer Guidelines, in the absence of sufficient data to establish a MOA, the animal tumor responses are presumed to be relevant to humans.

Application of cancer descriptors

The meaning of terms such as "suggestive evidence of carcinogenic potential" or "likely to be carcinogenic to humans" may differ among some in the general public and the EPA because of differences in perception and intent. Hence, EPA recommends a weight-of-evidence narrative that explains the complexity of issues influencing an agent's carcinogenic potential in humans. Descriptors are applied to provide consistency across agents that are evaluated for their carcinogenic potential. In developing their cancer risk assessment guidelines (US EPA 1999, 2003), EPA has not provided definitive criteria for choosing a descriptor; however, examples of the types of evidence that would be covered by a descriptor are listed. EPA also cautions that terms such as "likely," when used as a weight-of-evidence descriptor, does not correspond to a quantifiable probability.

Human cancer data on PFOA are inadequate to support a conclusion of the presence or absence of a causal association. However, data from two separate feeding studies demonstrate that PFOA is a multisite carcinogen in rats. Significant increases in tumor incidence and dose-response trends were observed in male and female rats. Some of the tumor responses were observed at sites with low background rates; the incidence of PACTs and LCTs in control rats was 0% at both sites. Following the examples provided in EPA's Cancer Guidelines, because available data are insufficient to characterize the MOA for PFOA-induced LCTS, PACTs, or mammary tumors, the responses at these sites are presumed to be relevant to humans. Uncertainties also exist for the MOA(s) for liver tumors induced by PFOA.

The available animal data indicate a carcinogenic potential for PFOA in humans. The animal data are much stronger than the examples summarized in the EPA's Cancer Guidelines under the descriptor "suggestive evidence of carcinogenic potential." That descriptor is typically applied to agents that show a marginal increase in tumors only in a single animal study or a slight increase in a tumor response at a site with a high background rate.

The animal data for PFOA are consistent with the examples listed by EPA under the descriptor "likely to be carcinogenic to humans." That descriptor is typically applied to agents that tested positive in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans; or a positive study that indicates a highly significant result and where the response is assumed to be relevant to humans.

While the majority of panel members opted for the descriptor "likely to be carcinogenic to humans" they noted that there was insufficient data available to estimate a likelihood of PFOA causing cancer in humans. The panel concluded that a cancer risk assessment for each of the PFOA-induced tumors is appropriate. The risk characterization narrative should address the state of knowledge and uncertainties in the MOA for each tumor site and a range of approaches should be considered in the cancer dose-response assessment.

Issue 3: Selection of Endpoints

Question 3. *Please comment on the selection of these toxicity endpoints for the risk assessment.*

The Panel agreed with the Agency approach of considering multiple endpoints and developing multiple margin of exposure (MOE) values at this stage in the assessment of potential human health effects associated with PFOA. With regard to the selection of endpoints, the initial overall philosophy should be one of inclusivity. That is, endpoints should be considered unless evidence for an effect by PFOA is equivocal or the dose associated with the effect is sufficiently high that other effects will clearly be of greater concern. The reason for being inclusive is not to generate an exhaustive catalog of PFOA effects, but rather to insure that sensitive effects (i.e., effects occurring at relatively low doses) are not overlooked or prematurely excluded from the assessment.

The Panel agreed with inclusion of all of the endpoints in the current draft of the risk assessment. None were recommended for deletion. However, caveats regarding the use of organ and body weights as endpoints were offered. Organ and body weights are often among the least sensitive endpoints for chemicals that exert specific effects on physiological or developmental systems. Nevertheless, in the absence of information with which to select more specific endpoints (e.g., biochemical or histological changes), body and organ weight changes are likely to be indicative of toxicity.

The Panel recommended consideration of additional endpoints in the risk assessment:

- Based on discussion in response to Question 2, the Panel considered PFOA to possess the potential for carcinogenic effects in humans. In view of this, cancer endpoints (liver, testicular, pancreatic acinar, and mammary) should be added to the risk assessment.
- Liver histopathology, other than cancer, should be considered as an endpoint. The Panel could not conclude with confidence that all liver effects are mediated through PPAR-alpha agonism (see response to Question 1), and therefore liver histopathology from PFOA may be relevant to humans. The Panel recognized that interpretation of some liver changes as adverse effects may not always be apparent (e.g., liver enlargement with no other pathology), and this should be discussed in the risk assessment.
- Other than ataxia, no data on neurotoxicity endpoints for PFOA are available. Neurotoxicity endpoints, including behavioral measures, should be added to the risk assessment. PPAR-alpha receptors, as well as other PPAR receptors, are found in both neurons and glia, and are found in multiple brain regions (frontal cortex, basal ganglia, reticular formation). It has been proposed that, in addition to their roles common to other tissues, these receptors in brain may have specific functions in the regulation of genes involved in neurotransmission (Moreno et al., 2004). This would likewise suggest their importance in behavioral function. The Panel recognizes that little or no information presently exist on these endpoints. The Panel considered this to be a significant data gap for PFOA.

- Immunotoxicity should be added as an endpoint addressed quantitatively in the risk assessment. The Panel recognizes that in order to be incorporated into the risk assessment, immunotoxicity data will need to be derived in rats, or approaches developed for the estimation of serum PFOA concentrations in mice.

- The two-generation rat study (Butenhoff et al., 2004) involved both perinatal PFOA exposure and direct PFOA dosing of the F1 offspring beginning at weaning. The Panel recognized that this approach is consistent with U.S. EPA guidance regarding developmental studies. However, consideration should be given to using developmental endpoints in F1 generation animals prior to initiation of direct dosing so that potential effects associated with perinatal exposure can be more clearly identified.

- Consideration should be given to addition of endpoints related to lipid metabolism.

- Current data suggest that PFOA might produce hormonal effects that would be important to consider, but in most cases the significance of the observations are unclear. For example, in a 26-week study of PFOA administration to cynomolgus monkeys, serum TSH was slightly but significantly elevated in all treatment groups on the final day of the experiment, and serum thyroxin was slightly but significantly reduced (Butenhoff, 2002). It is not clear whether these observations are physiologically meaningful or that they were strictly dependent upon treatment per se, since hormone levels appeared to change in the control animals during the course of the experiment as well. The analysis of Butenhoff data did not include a repeated measures ANOVA, so interactions were never pursued. Even that, however, would not have revealed why hormone levels changed over the course of the experiment in control animals. One study found decreased pituitary weight in F1 generation female rats, but the functional significance of this observation is unclear. Overall, the Panel thought that Margins of Exposure (MOEs) should not be calculated for hormonal endpoints at this time, but that additional research to clarify the hormonal effects of PFOA should be encouraged.

The Panel encouraged exploration of methods to identify critical targets for PFOA beyond a PPAR-alpha model of action. Consistent with that recommendation, adult male rats exhibited a much slower elimination of the ammonium salt of PFOA, i.e., ammonium perfluorooctanoate (APFO or C8), than did females. This appears to be due to gonadal hormones inasmuch as castration increased APFO elimination and testosterone replacement returned the elimination rate toward normal levels. Importantly, renal elimination was blocked by probenecid, a selective antagonist of organic anion transporters (OATPs) (Shitara, 2004). Thus, gender differences in renal OATPs may account for the gender differences in renal clearance of APFO. Likewise, the slower clearance of APFO in males may account for the observation that lower doses of APFO produced adverse effects in males compared to females. For example, the NOAEL for APFO in a 13-week study of male CD rats was 0.56 mg/kg-day whereas females exhibited a NOAEL of 22.4 mg/kg-day. These results suggest that specific organs (e.g., liver, kidney, and perhaps adrenals) are targets of APFO because of the pattern of expression of the OATPs that transport it across the cells (OATP1-4 in rat). Research to identify the relationship between OATP and PFOA toxicity may offer insight into the most important targets for PFOA effects and the best endpoints for evaluation.

Question 4. *Given the available data to date, please comment on the most appropriate lifestage/gender/species for assessing human risk.*

In general, there was consensus that at this stage in the risk assessment process, no lifestage/gender/species should be excluded from consideration in predicting human risk. Moreover, absence of information identifying a "critical period" in development during which PFOA may exert adverse effects on development requires inclusion of all life stages. Biomonitoring data indicate children and adults alike exhibit measurable levels of PFOA in serum, and the half-life of PFOA appears to be around 4 years. Therefore, there is no reason to exclude any developmental period from examination. Finally, the inclusion of data on internal dose is an important element of the dataset for PFOA which should ameliorate concerns about the use of female rats, discussed below.

There are two considerations in evaluating the current dataset for use in assessing human risk. There was general agreement that the most appropriate criterion for assessing human risk is one that produces the lowest margin of exposure (e.g., 90^{th}, 95^{th}, or 99^{th} percentile) based on a LOAEL, including the animal models. The second consideration is that the most appropriate animal is the non human primate because it is considered to be most comparable to humans.

In articulating the first view, the emphasis is on having data based on the internal dose relationships (i.e., serum PFOA levels) in some of the animal studies so that interspecies differences in metabolism and clearance are taken into account. In addition, these data also allow using both males and females despite a dramatic difference in clearance rate. Also, considering empirical measures of exposures in children and adults, this view emphasizes a concern that both developmental and adult endpoints be captured, and these endpoints have not been evaluated in non human primates. Therefore, the findings from adult male rats including the 13 week study by Goldenthal (1978) in which liver weight was significantly increased, and the F1 males in the two-generation reproductive toxicity study (Butenhoff et al., 2004) in which body weight was reduced should be considered in further analysis of human health risk.

The second view emphasizes the biological similarities between non human primates and humans for risk assessment. This is particularly important in the case of PFOA because there are a number of issues with a rodent model for PFOA exposure; e.g., sexual dimorphism with respect to elimination of PFOA, and differences in sensitivity to PPAR-alpha signaling between rat and human. However, monkeys also exhibit a different half-life of PFOA than do humans. Moreover, information about the potential toxicity of PFOA on non-human primates are derived primarily from adults. Because there are measurements of internal dose in monkeys (serum levels) that can be compared to humans, differences in half-life may not be that important. In addition, the evidence from the rat studies suggest that there are not large differences in sensitivity to PFOA during different life stages; therefore, the fact that information about PFOA toxicity in monkeys is derived solely from adults may not be so important. Clearly, these data should be confirmed in other rodent models and in other species.

Question 5. *Please comment on the appropriateness of the available animal models. Please comment on whether additional animal models should be investigated, and if so, what information would better enable us to ascertain potential human risks.*

The available animal models are useful, but all are considered uncertain matches for humans with respect to PFOA toxicity. Thus, the majority of Panel members supported continued use of multiple animal models and the need for additional models. As previously noted, some endpoints appear to respond to PFOA via modes of action not related to PPAR-alpha. Without knowing how these PPAR-alpha independent effects are mediated, the ability to identify the specific animal models that would be most useful is limited.

Some Panel members suggested the development and use of additional animal models without PPAR-alpha, such as transgenic or siRNA rats. Use of these animal models would be of assistance for more clearly identifying PPAR-alpha independent effects of PFOA.

Overall, the Panel thought that results obtained in models using female rats were informative because they currently provide the only indication of potential effects on endpoints specific to females (e.g., reproduction and developmental effects, mammary tumors). However, some concerns were noted regarding the difference in toxicokinetics of PFOA in female rats versus male rats and monkeys.

As part of a discussion of additional sources of information to help ascertain potential human risks, the Panel considered observations from studies in humans. The Panel makes the following specific observations in regard to inclusion of the epidemiologic data as informative regarding endpoints.

- The Draft declined to consider the occupational biomonitoring data because "data are not available for specific occupation exposures." The Panel points out that neither are data available for "specific environmental exposures." The further claim that information on "critical factors" like gender, sampling methods and occupation are not available for the worker populations does not seem relevant. Gender differences are not considered in the PFOA Draft Risk Assessment document's MOE calculations (combined male and female values are used) because, unlike in rats, there are no apparent gender differences in PFOA elimination in humans, at least in the sparse published data available at the time of this review.

- In the PFOA Draft Risk Assessment document, review of the epidemiological studies, limitations of epidemiological studies are emphasized, while reports of certain adverse effects (cancer, heart disease, blood chemistries) are discounted, based on small numbers and the consequent sensitivity of the results. It is undeniable that the epidemiology studies, like the toxicological ones, have some limitations, not the least of which are uncertainties regarding exposure. However, there is little doubt that these workers are more highly exposed than the general population. A special strength of epidemiological studies is that no cross-species extrapolation is needed. We are dealing directly with the species of interest, human beings. Moreover, many of the animal studies have serious limitations that have not disqualified them. Is also true that there may be multiple exposures in the occupational studies, but this fact alone cannot disqualify them without simultaneously disqualifying virtually all epidemiological studies, which doesn't seem to be appropriate. If the question addressed by an MOE analysis is "how far" are existing human exposures from exposures that can cause a health effect, any health effects in the epidemiological studies imply the answer is "zero distance," *regardless of the actual serum values.*

The panel concedes the small numbers and short follow-up in the available epidemiological studies make the positive results less than compelling. But neither are they reassuring. In the context of animal evidence regarding carcinogenicity, and considering that increases in cholesterol and triglyceride values have shown up in several worker cohorts along with some indications of increased risk of cardiovascular disease mortality. In addition to cancer and lipid metabolism, inclusion of occupational biomonitoring data seems appropriate when considering other endpoints including cardiovascular disease.

The Panel believes these points should be reflected in the final PFOA Draft Risk Assessment document. There was not a consensus among the Panel as to whether this meant that occupational biomonitoring data should be included in MOE calculations.

Issue 4: Risk Assessment Approach
4a: Pharmacokinetic Modeling and Use of AUC as a Measure of Internal Dose

Question 6. *Please comment on use of the one-compartment pharmacokinetic model.*

The purpose of developing a mathematical model to fit the serum PFOA time course data from the single dose rat oral dosing studies PFOA Draft Risk Assessment document was to estimate the AUC and C_{max} values during the longer term toxicology studies with daily dosing. The internal dose metrics calculated with this model were then compared with human serum concentrations to establish an MOE. The equations used to describe these data sets are the same as those usually employed in one-compartment models for uptake and elimination and were referred to throughout the document as a one-compartment model.

However, Panel members are concerned that using the "one-compartment" nomenclature without caveats and qualifications will give readers of the Risk Assessment Document the impression that PFOA pharmacokinetics follow a one-compartment description when in fact they are much more complex. In a one-compartment model, the chemical distributes evenly throughout a volume of distribution that is itself in rapid equilibrium with blood. Elimination kinetics are first-order and do not change with dose level or with time. However, the data indicate that it is clearly inappropriate to describe the observed kinetics of PFOA in rats or monkeys as following a simple one-compartment model. The relatively complex pharmacokinetic behavior of PFOA is reflected in several of the pharmacokinetic data sets. For example, blood elimination after iv dosing and tissue distribution kinetics after oral dosing are poorly characterized by the one-compartment model. In both rats and monkeys, blood levels are related in a complex manner to dosage and the duration of treatment.

Although the one-compartment model is not appropriate, the empirical model used in the document and referred to as a 'one compartment model' is adequate for predicting blood levels resulting from repeated dosing. However, the document needs to make it clear that the fitting procedure is specific to this limited data set and useful for this one application. It is strongly recommended that the terminology 'one-compartment' model should be stricken from the document unless carefully defined.

Question 7. *Please comment on the use of the AUC as a measure of internal dose for rats and humans for calculation of the MOE.*

Calculating the 'blood' AUC (as a measure of average daily concentration of PFOA) is an appropriate method of estimating the internal dose, although it is not the only possible measure. In the absence of clear understanding of modes of action (MOA), it is also possible that the Cmax, the integrated dose above a minimum concentration, or some other quantity may be a more plausible measure of internal dose. For example, if the MOA was receptor based as might be expected for interactions of PFOA with PPAR or other receptor proteins, one of these other measures of dose might also be appropriate. These alternatives include receptor occupancy or the concentration above some minimum concentration (Cmin) where Cmin is the concentration required to initiate activation of the receptor-mediated signaling pathway. In this latter case, the MOE would be based on the integral of (Ct-Cmin) rather than just the integral of concentration (Ct).

In light of these other possible internal dose measures, the EPA document would be strengthened if a clear rationale for the choice of the AUC were included. Since the inclusion of this explanation may involve a detailed discussion of toxicokinetic and toxicodynamic issues, such a discussion would best be included as an appendix. While the report does provide an example of how the MOE differs when based on the Cmax as compared to the AUC, it would be helpful if the impact on the magnitude of the MOE of using each of these other internal dose measures was explored in more detail. Calculations of MOEs based on these other measures would provide a better idea of the extent of possible variability introduced by different internal dose measures that may reflect a variety of possible MOAs.

When estimating an AUC, it is important to note the sample that is being analyzed in the various studies. AUCs can be calculated for serum, plasma or whole blood. These are very different biological matrices. The document should clearly specify the biological media measured in each study in which AUCs are reported.

Another issue to be considered is that the analyses of serum time course in the document are based on the assumption that the analyte in serum is in the same form and the proportion of free compound in blood is constant throughout the period of observation. This assumption does not always hold true. For example, with some siloxanes, the blood concentrations during and after inhalation exposure are primarily free siloxanes that are available for exhalation and metabolism. After a period of time in the body, the siloxanes in blood appear to reside in the lipid pool within the blood and although they are easily analyzed are no longer available for these other clearance processes (see Andersen et al., 2001; Reddy et al., 2003). A situation where the PFOA in blood at much longer times after exposure is in a distinctly different biological pool would lead to difficulties in comparing rat AUC and human AUC values to obtain a MOE.

General Recommendations:

The direct use of internal measures of dose by US EPA in this document represents a promising and relatively innovative approach for risk assessments of environmental compounds compared to the more usual practice based on comparing daily dose rates by various routes of administration. This new approach reduces the need to include uncertainties introduced by the use of administered or ambient doses as measures of exposure. This type of risk assessment methodology is likely to become much more widespread due to advances in analytical chemistry and the rapid expansion of human biomonitoring activities throughout the world. Because this risk assessment is likely to serve as a prototype for future tissue-dose based risk assessments, some important issues raised by this tissue-dose based approach need to be more fully considered and adequately contrasted with the more common assessments based on comparisons of administered doses.

To address these issues, the EPA should develop documentation explaining their rationale guiding these tissue-dose based risk assessment approaches. Due to the complexities of such a rationale, it would be more appropriate to include the documentation as an appendix to the PFOA draft risk assessment. Such documentation should compare current methods based on daily intakes with these alternative, 'tissue-based' approaches to more explicitly address the risk characterization issues that arise in moving to this new approach. The appendix might include discussion of (1) the choices of tissue dose measures based on serum concentrations and the risk implications of each choice; (2) the impacts of utilizing direct measures of tissue dose on the magnitudes of interspecies and interindividual uncertainty factors; (3) the implications of different metrics for characterizing distributions of human tissue dose measures on estimates of

MOEs; and (4) the importance of routine analysis of appropriate blood concentrations; e.g., serum, plasma, etc. in providing the information for most appropriately applying the tissue dose approach.

Issue 4b: Cross Species Extrapolation

Question 8. *Please comment on the need to use or modify the default value of 10 for cross species extrapolation given the pharmacokinetic analysis.*

The internal dose analysis used in this document is considered by the panel to be a significant step toward reducing uncertainty related to cross species extrapolation. Although reduced, cross species toxicokinetic uncertainty is not eliminated. Sources of uncertainty remain, including the lack of information about the measured internal dose that best predicts adverse effect in human and other species, and the bias inherent in measurement/modeling error. While it is difficult to assign a quantitative value to the magnitude of this uncertainty reduction, it can be stated that the toxicokinetic uncertainty value for PFOA would fall within the range of one to three, based on the customary scale of a value 3 for each aspect of cross species extrapolation, pharmacokinetics and pharmacodynamics. Pharmacodynamics aspects of PFOA cross species scaling are not addressed in a sufficient manner to alleviate the application of some type of uncertainty factor/s (addressing toxicodynamic equivalence across species). The additional complexity of multiple C-8 environmental exposures in humans versus animal experiments involving exposures to PFOA specifically further cloud the overall uncertainty analysis.

In addressing the question of whether USEPA needs *to use or modify the default value of 10 for cross species extrapolation given the pharmacokinetic analysis* employed in the draft RA for PFOA (and the subsequent materials presented to the Panel), the USEPA Cancer Guidelines of 2003 serve as a compass in this matter stating, "Toxicokinetic modeling is the preferred approach for estimating dose. Toxicokinetic models generally consider a dose profile over time. More complex models can reflect sources of intrinsic variation, such as polymorphisms in metabolism and clearance rates.

While the pharmacokinetic modeling that is presented in the PFOA risk assessment is useful, a more comprehensive way to account for biological processes that determine internal dose as with the development of a physiologically based toxicokinetic model would be needed to reduce the uncertainty. These models are based on blood flow between physiological compartments and simulate the relationship between applied dose and internal dose. Toxicokinetic models generally need data on absorption, distribution, metabolism, and elimination of the administered agent and its metabolites.

The panel encourages EPA to continue to develop toxicokinetic models as they can improve dose-response assessment by revealing and describing nonlinear relationships between applied and internal dose. Nonlinearity observed in a dose-response curve often can be attributed to toxicokinetics (Hoel et al., 1983; Gaylor et al., 1994), involving, for example, saturation or induction of enzymatic processes at high doses. Toxicokinetic processes tend to become linear at low doses (Hattis, 1990).

A discussion of confidence should always accompany the presentation of model results and include consideration of model validation and sensitivity analysis, stressing the predictive performance of the model. Quantitative uncertainty analysis is important for evaluating the performance of a model. The uncertainty analysis covers questions of model uncertainty (Is the model based on the appropriate dose metrics?) and parameter uncertainty (Do the data support unbiased and stable estimates of the model parameters?). Toxicokinetic modeling results may be presented as the preferred method of estimating equivalent human doses or in parallel with default procedures (see Section 3.1.3), depending on the confidence in the modeling.

Standard cross-species scaling procedures are available when the data are not sufficient to support a toxicokinetic model or when the purpose of the assessment does not warrant developing one. The aim is to define dose levels for humans and animals that are expected to produce the same degree of effect (U.S. EPA, 1992b), taking into account differences in scale between test animals and humans in size and in lifespan.

The aim of these cross-species scaling procedures is to estimate administered dose in animals and humans that result in equal lifetime risks. It is useful to recognize two components of this equivalence: toxicokinetic equivalence, which determines administered doses in animals, and humans that yield equal tissue doses, and toxicodynamic equivalence, which determines tissue doses in animals and humans that yield equal lifetime risks (U.S. EPA, 1992b). Toxicokinetic modeling (see Section 3.1.2) addresses factors associated with toxicokinetic equivalence, and toxicodynamic modeling (see Section 3.2.2) addresses factors associated with toxicodynamic equivalence. When toxicokinetic modeling is used without toxicodynamic modeling, the dose-response assessment develops and supports an approach for addressing toxicodynamic equivalence, perhaps by retaining some of the cross-species scaling factor (e.g., using the square root of the cross-species scaling factor or using a factor of 3 to cover toxicodynamic differences between animals and humans, as is done in deriving inhalation reference concentrations (EPA 1994))."

It is equally important to note that pharmacodynamics aspects of PFOA cross species scaling are not addressed in a sufficient manner to alleviate the application of some type of uncertainty factor/s (addressing toxicodynamic equivalence across species). These factors may be different for each species extrapolated. By the language used in the USEPA Cancer Guidelines it seems evident that standard default values were never intended to act as complex scaling factors when internal doses in human serum are compared to animal internal doses across multiple pathways, genders, steady-state serum levels with long human half-lives and/or different life stages. The additional complexity of multiple C-8 environmental exposures in humans versus animal experiments involving exposures to PFOA specifically further cloud the overall uncertainty analysis.

In the case of PFOA the strong reliance on LOAEL-driven MOE calculations instead of more appropriate Bench Mark Dose methodologies, and the absence of probabilistic approaches to assessing human exposure and risk, was considered by most panel members as another source of dynamic uncertainty.

The use of an uncertainty factor/s based on data variability may be an alternative to the traditional scaling factors given the kinetics analysis strength and in light of the larger concerns of overall uncertainties related to dynamic analysis (as reflected in the MOE approach). This may prove more productive when comparing relatively robust toxicokinetic dose response models involving serum concentrations and/or their surrogates.

In conclusion, whereas toxicokinetic uncertainty is possibly reduced in this analysis, care must be exercised in the estimation of the overall cross species uncertainty, which further dynamic analyses may show falls below or above 10.

4c: Human Biomonitoring Data

Question 9. *Please comment on the adequacy of the human exposure data for use in calculating a MOE.*

The charge question relates to the use of the human exposure data for a specific purpose, calculating a Margin of Exposure (MOE) for PFOA. Thus, it also involves the question as to the appropriateness of the MOE measure as an indicator of the potential for human health risk. The Panel notes that if MOE is not appropriate, then the human exposure data are inadequate when applied to that purpose, if the purpose is to "assess potential human health risks associated with exposure to PFOA and its salts."

Populations used for MOE calculations

In addition to the occupational biomonitoring data, the PFOA Draft Risk Assessment document described three separate study populations from the United States with available individual serum PFOA levels. One consists of samples from six American Red Cross blood banks, another from a study of Streptococcal A infection in children, and a third from elderly volunteers from Seattle who participated in a study of cognitive function. Only the first two study populations were used in calculating the MOE for the risk assessment.

There are a variety of possible problems with using these data to represent the general population, but the Panel felt that they were likely to be reasonably representative and are better than data often available for exercises of this nature.

One Panel member raised the question about reliance on the female blood bank donor population for calculating prenatal MOEs, because the influence of pregnancy on serum PFOA levels is not known. Likewise, use of the samples obtained from the children for the age span of 2-12 years for the postweaning period MOE may not be appropriate. Half-life issues in humans, especially when considering the impact of age at exposure (or the critical windows of exposure model), contribute to the questions about adequacy of using these samples (Pryor et al., 2000; Selevan et al., 2000).

The Panel notes there may be several distributions of exposed populations, some with much higher levels than indicated in the blood donor and pediatric populations. Besides the occupationally exposed (a group of unknown size) data presented at the meeting indicate high levels of PFOA have been detected in the serum of neighbors of the DuPont plant in West Virginia. The levels approach or at times exceed those found in worker populations. Thus, the appropriateness of relying solely on the blood bank and pediatric samples for MOE calculations depends strongly on the purpose of the MOE exercise, i.e., whether it is to assess the likelihood that any people could be suffering health effects from PFOA or only the "general population." If the latter case, the biomonitoring data that were used may be appropriate, but the sizes of more highly exposed populations remains unknown and this should be acknowledged.

Occupational biomonitoring data

In responding to charge question #3, the Panel recommends that human cancer and alterations in lipid metabolism be included in the relevant endpoints for consideration. This implies that the rich data base of occupational exposures be added to the occupational biomonitoring data to be considered. They are not now included in the PFOA Draft Risk Assessment document because the worker epidemiological studies were not considered suitable for quantitative risk assessment. The Panel comments further on this in charge question 5.

Depiction of the biomonitoring data

The tables and summary statistics that were used in the PFOA Draft Risk Assessment document are somewhat uninformative and unsatisfactory. It is difficult to determine from these the distribution of population exposures given the method of data presentation. A preferable approach would be to use a non-parametric data-driven method to display the data (including the occupational data), using, for example, some density estimation procedure or smoother. Inclusion of the worker data in these displays would allow a clearer understanding of the relationships. Even side-by-side box plots would have been preferable to what was provided. This requires having access to the raw data, however. Because such a request is easy to satisfy, the Panel recommends that EPA provide more informative displays of the biomonitoring data.

Appropriate summary measures for MOE calculations

At least three summary statistics are mentioned in the Draft, the geometric mean, the arithmetic mean, and the 90th percentile.

The rationale for the use of "means" should be explained, especially the use of the geometric means which seems the least satisfactory, since it is about 25% lower than the arithmetic mean in these data. Use of a geometric mean for population inference (to transform a lognormal to a normal distribution, for example) might be justified, but not for the purpose of calculating an MOE. Moreover, the distribution does not even seem to be lognormal, as judged by the Shapiro-Wilk test. The idea that a few censored data points are responsible for failing this test seems highly unlikely, and could have been accounted for in the test itself.

Means of any kind don't seem appropriate for a ubiquitous exposure. Of the three choices, the

90^{th} percentile seems the most appropriate in that case. At least one Panel member wondered why some even higher percentile, say 95^{th} or even a maximum value wouldn't be better. The maximum value in any of the samples is still an underestimate of the maximum value in the population. Even the upper 99.99^{th} percentile represents 30,000 people in the US.

In summary, the Panel finds that:

- Use of the blood donor and pediatric biomonitoring data may be acceptable if the purpose is to assess whether there is a potential health effect to the "general" population, although there is some question as to the size of other populations that might be more highly exposed;

- Including the occupational biomonitoring data in the MOE calculations, especially regarding additional endpoints such as cancer or alterations in lipid metabolism, should be considered if these endpoints are included (see charge question 5);

- The biomonitoring data should be presented in a more informative manner, for example, through side-by-side box plots or some other method that would better depict the range of values and distributions;

- Thought should be given to what appropriate summary statistic for the biomonitoring datasets used in MOE calculations should be. Some panelists believe that 90^{th} percentiles or higher, perhaps even maximum values might be most appropriate. In any event, justification for use of the chosen summary measure should be made and related to the explicit objective of the MOE analysis.

References

Andersen, M.E., Sarangapani, Reitz, R.H., Gallavan, R.H., Dobrev, I.D. and Plotzke, K.P. 2001. Physiological Modeling Reveals Novel Pharmacokinetic behavior of Inhaled Octamethylcyclotetrasiloxane. Toxicological Sciences, 60:214-231.

Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook JC. 2001. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. Toxicological Sciences, 60:44-55.

Butenhoff, J., Costa, G., Elcombe, C., Farrar, D., Hansen, K., Iwai, H., Jung, R., Kennedy, G. Jr., Lieder, P., Olsen, G. and Thomford, P. 2002. Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. Toxicological Sciences, 69: 244-257.

Butenhoff, T., Kennedy, G.L. Jr., Frame, S.R., O'Connor, J.C. and York, R.G. 2004. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. Toxicology, 196:95-116.

Chandra M, Riley MG, and Johnson DE. 1992. Spontaneous neoplasms in aged Sprague-Dawley rats. Archives of Toxicology, 66:496-502.

Gaylor, D.W., Kodell, R.L., Chen, J.J., Springer,J.A., Lorentzen, R.J., Scheuplein, R.J. 1994. Point estimates of cancer risk at low doses. Risk Analysis, 14:843-850.

Goldenthal, E.I. Final report, ninety day subacute rat toxicity study on Flourad® Fluorochemical FC-143, International Research and Development Corporation, Study No. 137-089, 3M Reference No. T-3141, November 6, 1978. US EPA AR226-0441.

Hasmall S, James N, Hedley K, Olsen K, Roberts R. 2001. Mouse hepatocyte response to peroxisome proliferators: dependency on hepatic nonparenchymal cells and peroxisome proliferator activated receptor alpha. Archives of Toxicology, 75:357-61,

Hattis, D. 1990. Pharmacokinetic principles for dose-rate extrapolation of carcinogenic risk from genetically active agents. Risk Analysis, 10:303-316.

Hoel, D.G., Kaplan, N.L. and Anderson, M.W. 1983. Implication of nonlinear kinetics on risk estimation in carcinogenesis. Science, 219 (4588):1032-1037.

Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, DeLuca JG, Lai DY, McKee RH, Peters JM, Roberts RA, Fenner-Crisp PA. 2003. PPAR-alpha agonist-induced rodent tumors: modes of action and human relevance. Critical Reviews in Toxicology, 33:655-780,

Moreno, S., Farioli-Vecchioli, and Ceru, M.P. 2004. Immunolocalization of peroxisome proliferators activated receptrs and retinoid X receptors in the adult rat CNS. Neuroscience, 123:131-145.

Palazzolo, MJ. 1993. 13-Week dietary toxicity study with T-5180 ammonium perfluorooctanoate (CAS No. 3825-26-1) in male rats. Laboratory Project Identification HWI 6329-100. Hazelton Wisconsin, Inc. US EPA AR226-0449.

Parzefall W, Berger W, Kainzbauer E, Teufelhofer O, Schulte-Hermann R, Thurman RG. 2001. Peroxisome proliferators do not increase DNA synthesis in purified rat hepatocytes. Carcinogenesis, 22:519-23,

Peters JM, Cattley RC, Gonzalez FJ. 1997. Role of PPAR-alpha in the mechanism of action of the nongenotoxic carcinogen and peroxisome proliferator Wy-14,643. Carcinogenesis, 18:2029-2033.

Peters JM, Rusyn I, Rose ML, Gonzalez FJ, Thurman RG. 2000. Peroxisome proliferator-activated receptor alpha is restricted to hepatic parenchymal cells, not Kupffer cells: implications for the mechanism of action of peroxisome proliferators in hepatocarcinogenesis. Carcinogenesis, 21:823-826.

Pryor, J.L., Hughes, C., Foster, W., Hales, B.F. and Robaire, B. 2000. Critical windows of exposure for children's health: the reproductive system in animals and humans. Environmental Health Perspectives, 108 (Suppl 3):491-503.

Reddy, M.B., Dobrev, I.D., Plotzke, K.P., Andersen, M.E., Reitz, R.H., Morrow, P., and Utell, M. 2003. A Physiologically Based Pharmacokinetic model for inhalation of octamethylcyclotetrasiloxane (D4) in humans during rest and exercise. Toxicological.Sciences, 72:3-18.

Rose ML, Rusyn I, Bojes HK, Germolec DR, Luster M, Thurman RG. 1999. Role of Kupffer cells in peroxisome proliferator-induced hepatocyte proliferation. Drug Metabolism Reviews, 31:87-116.

SAP minutes 2003-05, USEPA, December 9, 2003, A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Proposed Science Policy: PPAR-alpha Agonist-Mediated Hepatocarcinogenesis in Rodents and Relevance to Human Health Risk Assessment.

Selevan, S.G., Kimmel, C.A. and Mendola, P. 2000. Identifying critical windows of exposure for children's health. Environmental Health Perspectives, 108 (Suppl 3):451-455.

Shitaray, Y., Sato, H. and Sugiyama, Y. 2004. Evaluation of drug-drug interaction in the hepatobiliary and renal transport of drugs. Annual Review of Pharmacology and Toxicology, 2004, in press.

Sibinski, LJ. 1987. Two year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats. Vol. 1-4, 3M Company/Riker Exp. No.0281CR0012.

US EPA. 1999. Draft Revised Guidelines for Carcinogen Risk Assessment (External Draft, July 1999). U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.

US EPA. 2003. Draft final guidelines for carcinogen risk assessment. EPA/630/P-03/001A. NCEA-F-0644A. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.

US EPA. 2005. Guidelines for Carcinogen Risk Assessment . EPA/630/P-03/001F. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC,

Yang Q, Xie Y, Alexson SE, Nelson BD, DePierre JW. 2002. Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. Biochemical Pharmacology, 63:1893-1900.