Facts/Observations	Significance/Possible Interpretation	Questions/Knowledge Gaps	Approaches/Recommendations
PFOS is basis for large number of chemistries and applications	Potential for human and environmental exposure, direct or indirect, is high		
PFOS is persistent in the environment	Does not degrade; may gradually accumulate, either in dispersed fashion or through concentration	1) PFOS bioconcentration; 2) environmental fate; 3) current prevalence in environment	
PFOS is readily absorbed form the GI and is toxic with cumulative toxicity higher than acute toxicity and subchronic cumulative toxicity dose-response curve is quite steep: 90-day oral studies in rats and monkeys resulted in deaths at 6 mg/kg/d in rats via feed and 4.5 mg/kg/d in monkeys via water; however rats survived 1.8 mg/kg/d and monkeys survived 1.5 mg/kg/d :: All pregnant f. rats died within five days after 20 mg/kg/d for 10 days (days 6-15 of gestation); however, they survived less than 10 mg/kg/d under same circumstances (1 and 5 mg/kg/d) with NOAEL at 1.0 mg/kg/d	Cumulative tox coupled with lack of elimination presents a true concern for lifetime cumulative dose/body burden; 2) good interspecies comparison on subchronic basis with regard to lethality, suggesting common mechanism of action; 3) seldom see sub-chronic study dose response curves as steep; 4) a critical threshold body burden appears to be reached over time	1) Biological exposure guideline is needed; 2) what are the biologicaly relevant endpoints which determine the critical toxic response; 3) what is the threshold body burden	1) Develop biological exposure guideline; 2) investigate plasma concentration vs. liver concentration; 3) do an acute and subchronic study to look at lethal body burdens; 4) study blood concentrations in workers; 5) discover primary mechanism of toxicity
PFOS is accumulative in mammals and is concentrated in the liver (10 x other tissues) and is not eliminated	1) potential for drug interactions and other competitive effects; 2) may provide clue to mechanism; 3) potential for reaching critical toxic body burden is high; 3) may be resorbed in proximal tubule; 4) may undergo enterohepatic circulation; 5) may bioaccumulate	1) what is bioaccumulation potential; 2) are there potential drug interactions; 3) what is the potential for dermal absorption (may have been answered); 4) why is accumulation in liver preferential over other tissues; 5) excretion mechanisms	1) bioaccumulation study; 2) protein binding in plasma; 3) membrane accumulation; 4) L-FABP; 5) impaired transport; 6) differential accumulation in tissue; 7) dermal absorption; 8) ADME with specific reference to enterohepatic circulation, carrier protein and renal clearance
Biochemical effects/interactions:			
1) decreased body weights, all species: a) male mice (m.m) 0.05% of diet, 5 days; b) male rats (m.r.) 0.02% of diet, 7-14 days; c) monkeys 1.5 mg/kg/d 90 days; d) rats 1.8 mg/kg/d 90 days; f. rats 10 mg/kg/d 10 days	Severe metabolic effect		
2) increased liver weights in (rats and (m.m. but not monkeys)	Species differences, rodent to primate, possibly due to lack of primate responsiveness to PP effect; however, very similar toxic response with respect to lethality; therefore, PP may be secondary to prime toxic mechanism		

3) increased mitochondrial protein (m.m.)		Morphometry	
4) increased beta oxidation (m.m. & i.h.)	Biomarker of PP		
5) increased catalase in mitochondria and cytosol (m.m.)	Biomarker of oxidative stress which could reflect uncoupling of oxidative phosphorylation with concommitant increase in superoxide and peroxyradicals or impairment of other antioxidant mechanisms	1) is SOD activity elevated; 2) are other antioxidant pathways impaired	
6) increased glutathione transferase (m.m.)			
7) increased epoxide hydrolase (m.m.)			
8) increased DT-diaphorase (m.m.)			
9) increased omega- & omega-1-hydroxylation (m.m.)	1) microsomal FA oxidation pathway stimulated; 2) leads to increased dicarboxylates which stimulate PP		
10) increased liver triacylglycerol (m.r.)			
11) increased liver free cholesterol (m.r.)	Could represent increase in mitochondrial FA oxidation leading to decrease in phosphatidate phosphohydralase activity, thus stimulating CTP:phosphocholine cytidyltransferase leading to increased phospholipid and decreased triglyceride which could affect formation of cholesterol esters		
12) decreased liver cholesterol esters (m.r.)	d.o. above		
13) decreased serum cholesterol (rats & monkeys)	d.o. above		
14) decreased serum triacylglycerols (m.r.)	d.o. above		
15) decreased synthesis of cholesterol from pyruvate, acetate & 3-hydroxy-3-methyl-glutarate but not mevalonate (i.h.)	Cholesterol biosynthetic pathway is impaired prior to mevalonate and may reflect low activity of HMG CoA reductase		

16) decreased F.A. synthesis (i. h.)	1) Could be from substrate depletion as result of mitochondrial FA oxidation; 2) could result from acetyl CoA carboxylase inhibition (common with long-chain FA which are PP) which would result in decreased malonyl CoA (an inhibitor of carnitine palmitoyl transferase) leading to increased activity of carnitine palmitoyl transferase leading to increased mitochondrial FA oxidation, which in turn could lead to increased dicarboxylic acids and PP as well as decreased triacylglycerols, cholesterol esters and phosphoglycerides; 3) could result from inactivation of L-FABP???		
17) decreased activity of HMG CoA reductase			
18) decreased activity of acyl CoA:cholesterol acyl transferase			
19) peroxisome proliferation delayed several days	PP may be secondary to PFOS toxicity	1) What is time course of biochemical events; 2) is P450 IVA1 induced; 3) is essential substrate depleted and why/how	
20) PFOS not activated to CoA thioesters	Most PP are activate to CoA thioesters, which again suggests PP is secondary to toxicity		
A segment I reproductive study was previously recommended	N-ethyl PFOSulfonamide causes reversible testicular atrophy; however, PFOS is not eliminated & don't know mechanism of testicular atrophy	Would PFOS cause a reproductive effect	Support seg I reproduction study
Immunotoxicity studies were previously recommended	Effects occur at high dose but more subtle	Are there meaningful assays	Research and propose testing plan
A 2-year bioassay was previously recommended	We don't have chronic dosing data; however, there is no evident direct genotoxicity; would expect tumors in rats related to PP (liver, pancreas, testes); a 2-year swtudy of cumulative body burden and tox would help establish biological EG	Are there better surrogates	Await results of mechanistic studies and/or design chronic cumulative tox study and incorporate mechanistic endpoints in two species
NOAEL for maternal tox and embro/fetotox and developmental effects is 1.0 mg/kg/d in rats			