John L. Butenhoff/US-Corporate /3M/US	To	Michael J. Falco/US-Corporate/3M/US@3M-Corporate
	cc	
09/27/2004 09:24 PM	bcc	
	Subject	Fw: Notes on Proposal to NTP

Mike,

I sent this before adding your name to the "list." Please pass on to anyone else you think could benefit.

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----- Forwarded by John L. Butenhoff/US-Corporate/3M/US on 09/27/04 03:23 PM -----

John L. Butenhoff/US-Corporate/3M/US	To	Michael A. Santoro/US-Corporate/3M/US, Thomas J. DiPasquale/US-Corporate/3M/US, Larry Zobel, krhyne@kslaw.com, BOB.SUSSMAN@LW.com, JULIA.HATCHER@LW.com
	cc	
09/27/04 03:23 PM	Subject	Notes on Proposal to NTP

There are no substantive issues associated with the NTP proposed work for the perfluroinated alkyl acids. I have annotated the PDF file, attached, and notes should show up as little notepad symbols in the text. You should see these by double clicking. If you have trouble, let me know.

I believe that a considerable amount of thought went into the proposal. It is my understanding that Jennifer Seed and Chris Lau were primary authors and thought leaders. Since we have carried on a dialog with them for several years, it is not surprising that there are no real issues with what is proposed.

Mike had asked me to reflect on the cancer study with exposure beginning in utero. This comes out of the Science Advisory Panel discussions last year on peroxisome proliferators (PPAR-alpha agonists) and the relevance of tumors to humans. I guess I would comment that, while I understand the rationale for the PFOA study and the general peroxisome proliferator mode-of-action discussion from which it arises, the study would investigate a general hypothesis, i.e., does in utero exposure to PPAR-alpha agonists increase cancer risk with continued exposure into adulthood? Testing that general hypothesis with PFOA makes some sense, because PFOA is a model moderate PPAR-alpha agonist in the rat and mouse. However, use of a non-responsive species or a PPAR-alpha null (genetically-transformed knock-out) model as well as the classic potent PPAR-alpha agonist, WY-14643, would improve the quality of the study by incuding a non-perfluorinated acid and a non-responsive (to PPAR-alpha agonists) species. Biomarkers of PPAR-alpha response should be followed, even in the PPAR-alpha knockout. These would include increases in hepatic peroxisomes, palmitoyl CoA oxidase activity, and others.

Tom and Mike had asked me to think about the "class" structure of this proposal, as well as inclusion of PFBS in the "class." Whether we like it or not, these materials are being regarded as constituting a class of structurally-related perfluorinated acids and telomer alcohols [I am surpirsed that the telomer sulfonates were not included.] The proposal does not make generalizations or characterizations that are inappropriate, rather, it seeks to develop the detailed knowledge base that will assist risk assessment and

risk management in making future decisions involving materials that fall into this broader group of related perfluorinated acids and telomer alcohols. We need to stay involved in this process and to do what we can to "command the science."

One way we can command the science is to initiate our own parallel programs in areas that NTP is unlikey to focus resources. My reading of the proposal suggests that NTP will be occupied with pharmacokinetics for some time. There is a steep learning curve for NTP as well a resource development. For example, analytical methods, internal stable-isotope-labelled standards, and test compounds need to be developed and standardized. All of this is likely to result in some delays before any major progress is made. By contrast, we are in a much better position to move forward with basic research programs at an academic level that will provide valuable insights on mode-of-action, as well as pharmacokinetic differences. 3M-sponsored research in the last few years has focused on descriptive studies that allowed us to characterize risk. Even though mode-of-action studies have been sponsored, these were difficult to focus without having the descriptive package of data in hand. We are now in a position to focus on quite specific questions with respect to mode of action. Now would be the ideal time to initiate these avenues of research; otherwise, as more time elapses, we will be spending our resources on reacting to the "studie du jour" as opposed to getting the meaningful research to the forefront.

PerfluorinatedCmpdsJLB.pdf

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