NS

Exhibit
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3M CONFIDENTIAL

Toxicology Contribution to White Paper

Prepared by:

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3M sells products which contain the series of chemical compounds built from the parent molecule, perfluorooctanesulfonyl fluoride (POSF), as either intentional components or residual contaminants. These chemicals include, in order of increasing molecular size, Perfluorooctane Sulfonate (PFOS), N-Ethyl Perfluorooctane Sulfonamide (N-Et FOSamide), N-Ethyl Perfluorooctane Sulfonamidoethanol (N-Et FOSE), and the mixture of Mono-, Di- and Tri[N-Ethyl Perfluorooctane Sulfonamidoethyl] Phosphates (Monoester, Diester, and Triester, respectively). All of these molecules incorporate the PFOS structure, which is not known to degrade metabolically.

Risk is related to exposure and bioavailability as well as toxicity. The data suggest that, with the exception of diester and triester, all of these molecules are appreciably absorbed form the digestive system. Specific absorption studies show that absorption from the digestive system decreases with molecular weight. In other words, PFOS is > 95% absorbed, N-Et FOSE is > 75 % absorbed, Monoester is approximately 40 % absorbed, and Diester and Triester do not have appreciable absorption. While we have no specific data n the N-Et FOSamide, its significant sub-chronic oral toxicity suggests that it is well absorbed.

After absorption of N-Et FOSE or N-Et FOSamide, PFOS can be found in various tissues, with the largest relative amounts found in liver and blood. Based on an intravenous injection study using PFOS, it appears that 25 % of the dose can be found in the liver after 89 days, and 3 % in the plasma. There is little concentration in fat. Evidence suggests that PFOS is highly protein bound, and it has a high affinity for fatty acid carrier proteins. Other evidence suggests that it can incorporate into membranes and increase membrane fluidity.

All of these molecules could be expected to degrade metabolically in some proportion to the PFOS structure as an end-stage metabolite. Other metabolites are known, such as the N-Ethyl Perfluorooctane Sulfonamido Acetate (for example). We do know that the N-Et FOSE, Monoester and the N-Et FOSamide will form PFOS metabolically. There is also evidence to suggest that N-Et FOSE and Monoester will form the N-Et FOSamide as well as other metabolites.

PFOS is very effective at ion pairing with proteins, and has a high affinity for fatty acid carrier proteins such as albumin and L-FABP. PFOS also has an amphoteric nature which would suggest an affinity for incorporation in membranes. Because of these properties, it is not surprising that PFOS is slowly eliminated from the body, once absorbed. In rats, approximately 60 % of a given dose was still present after 89 days. With good absorption (> 95 %) and slow clearance from the body, chronic ingestion can significantly contribute to observed biological effects due to accumulation of PFOS.

With the exception of the Monoester, Diester, and Triester, which have not been studied as pure compounds, these molecules appear to share the similar toxic effect of severe weight loss and anorexia. In the case of PFOS, N-Et FOSE, N-Et FOSamide and Monoester, there is potential for cumulative toxicity over time. The similar values of the product of dose x time with respect to total dose (mg/kg/d x days) would be expected to and does appear to lead to a similar degree of toxicity. The primary toxic effect appears to be metabolic stimulation or metabolic wasting. This is hypothesized to be due to an effect on fatty acid metabolism, membrane function, protein synthesis and/or mitochondrial bioenergetics. These compounds lack genotoxicity but have NOAELs or LOAELS generally in the range of 0.1-1 mg/kg/d. Cumulative toxicity and toxic endpoint will certainly affect the value of the LOAEL or NOAEL.

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Restricted

Overview Assessment of Information Adequacy

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February 28, 1998
At the direction of Larry Zobel, MD

Note bene: This table should not be construed to suggest that all areas not noted as adequate should require specific studies in those areas. For example, a better understanding of monoester metabolism may preclude specific studies on monoester, if studies are adequate for known metabolites. This table is meant as a framework for the prioritization process.

Information	Information Adequacy by Molecule (Adequate means no additional work warranted)				
	[redacted]	[redacted]	[redacted]	N-EtFOS Amide	[redacted]
GI Absorption	Good	Good	Fair (toxic)	Fair (toxic)	Fair (impurity)
Distribution	Good	Good	None	Poor	Good
Metabolism	Good	Fair	None	Fair	Fair
Excretion	Good	Good	None	Unknown	Good
Acute Toxicity	Adequate	Adequate	Good	Adequate	Poor
Sub-Chronic	Adequate	Adequate	None	Adequate	None or Poor (to extent that monoester is a component of FC-807)
Chronic	None or Poor (to extent that amide is metabolite of N-EtFose)	Fair (impurity)	None	None or Poor (to extent that amide is metabolite of N-EtFose)	None
Reproductive	None	None	None	Adequate	None
Developmental	Adequate	Adequate	None	Adequate	None
Genotoxicity	Adequate	Adequate	Adequate	Adequate	None
Immunotox.	None	None	None	Unknown	None
Protein Bind.	Good	Good	None	Good	None
Bioenergetics	Good	Good	None	Good	None
Peroxis. Prolif.	Good	None	None	None	None
Food Transfer	Poor	Adequate	Poor to Good	Poor	Poor
Milk Transfer	Poor	Poor	None	Poor	None
Placental Trans	None	None	None	None	None

Other areas of investigation to be considered:

- Additional mechanistic work
- Sources of exposure other than Scotchban
- Preferential partitioning, distribution, metabolism based on branched vs. linear isomer structure
- Multisource risk assessment

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			

FX-12 or N-Ethyl PFOSulfonamide

Facts/Observations	Significance/Possible Interpretation	Questions/Knowledge Gaps	Approaches/Recommendations
PFOS and PFOSulfonamide are found as products of metabolism and formation of PFOSulfonamide is known to occur readily *in vitro*; also find PFOSulfonamidoethanol and PFOSulfonamidoacetate as metabolites; prior studies of ADME failed to quantitate PFOS, PFOSulfonamide, PFOSulfonamidoethanol or PFOSulfonamidoacetate, since they looked primarily at ^{14}C labeled ethyl moeity.	N-EtPFOSulfonamide toxicity may be due, in part, to PFOSulfonamide and/or PFOS; PFOSulfonamidoethanol and PFOSulfonamidoacetate may be readily excreted *in vivo*; current ADME data is incomplete and does not form adequate basis on which to assess risk	To what extent is N-EtPFOSulfonamide toxicity due to PFOSulfonamide or PFOS; what is extent of in vivo conversion; what is half-life of elimination	
The metabolite, PFOSulfonamide, uncouples oxidative phosphorylation in isolated kidney proximal tubules and cortical mitochondria	May be primary mechanism of toxicity which could be common to other members of PFOSulfonamide class		
Acute toxicity is low and has some dependence on isomeric mixture and sex (wide range LD50 rat < 5g/kg (7/10) and NOAEL of 500 mg/kg rat in cottenseed oil; narrow range NOAEL rat 5g/kg aqueous solution; 72.2% linear LD50 rat 2549 mg/kg male 1580 mg/kg female; 31.7 % linear LD50 rat 772 male 1571 female)	Branched and linear may have different tox patterns, with branched being more toxic, particularly to male rats	What is basis for male/female difference in sensitivity to branched material	
Sub-chronic dermal toxicity is low (3-week dermal in rabbits resulted in 8/10 dead at 1000 mg/kg/d and NOAEL of 100 mg/kg/d, males and females) with emaciation, decreased food consumption and body weight, testicular atropy, kidney and ovary weight increases, and effects on GI, lung, liver, testes)			

Sub-chronic oral tox more serious (female rats survived 17 mg/kg/d for ten days with NOAEL of 8.5 mg/kg/d; male rats survived 5.7 mg/kg/d for 8 weeks with no change in food consumption but a 7% change in body weight; NOAEL for 90-day feeding study in male and female rats was approx. 1 mg/kg/d with deaths at approx. 9 mg/kg/d (10/30) and emaciation, weight loss, decreased food consumption, increased liver weight, decreased spleen, lung, heart and kidney weights, hematological and serum chemistry changes [what???], morphologic changes in liver, GI, lung, testes, histopath changes in liver and kidney, no effect on sperm number or motility - NOAEL 0.6 mg/kg/d; 4/8 dogs died during two-weeks at 375 mg/kg/d - NOAEL of 25 mg/kg/d females and 8 mg/kg/d males, signs of weight loss, testicular atrophy, decreased sperm number and motility, shown in a later study to be reversible	Possible sign of uncoupling of oxidative phosphorylation	What were clinical chemistry changes	
PFOSulfonamidoethane fits common wasting pattern seen in other members of class	May be able to approach toxicity of entire class at structure activity level	Common intermediate metabolite	
EtPFOSulfonamide is residual in many applications	Perhaps a primary toxic form	Purity of products	
Maternal and fetal NOAEL in rats = 1 and 4 mg/kg/d, respectively; maternal and fetal NOAEL in rabbits = 0.1 and 1.5 mg/kg/d, respectively			

FC-807 or Phosphate Esters of EtFOSE

Facts/Observations	Significance/Possible Interpretation	Questions/Knowledge Gaps	Approaches/Recommendations
Used in high volume for indirect food contact	Widespread exposure and regulatory scrutiny	Current uses other than food packaging; current and projected production volumes	Assign research into non-food-packaging uses and production volumes to PRL
Thorough risk analysis on dietary exposure to EtFOSE residues completed by ENVIRON and 3M	Food use risk from EtFOSE exposure well understood; however, dietary exposure to other components less clearly understood	Adequacy of food transfer data for PO_4^- esters, amides and other components; 2) adequacy of current information on FC-807 be considered adequate by current FDA review practice; 3) are mechanistic, segment II, 90-day dog, repro/dev and 2-year feeding studies necessary	1) Assign team of toxicology, lab, and PRL to review adequacy of transfer data and determine what additional work may be needed; 2) verify ADI based on FDA current FDA approach; 3) have ENVIRON review issue; 4) await results on metabolism and risk assessment as issue may be tied to review of FC-95 and EtFOSE reproductive and chronic toxicity
ADME data contradictory, old, and based on radiolabel of perfluorinated chain	Doubts concerning ADME characteristics of components of FC-807	Knowledge of the overall ADME characteristics of FC-807 as a complex mixture	1) Complete SRI/ABS in vitro comparative metabolism study; 2) verify results in vivo; 3) identify suitable human surrogate species
Differences observed in feeding studies based on species and length of study: 1) 33-day rat NOEL was 60 mg/kg/d; 2) 90-day rat LOEL was 30 mg/kg/d; 3) 90-day dog NOEL was 125 mg/kg/d (high dose)	Definite species differences (rat to dog); initial response is that this is not a concern; however, if cumulative (see above) it may be a concern	Whether or not there is a concern for cumulative toxicity based on food transfer data and ADME data	Refer to approaches above
Corneal opacity observed in PEI study	Possible metabolic effect	See above	See above
Irritation/sensitization potential is low	Low contact hazard	---	---
Genotoxicity studies are negative (Ames and Yeast, with and without activation, and mouse micronucleus)	Supports low genotoxicity potential	---	---
Dermal absoption/persistence shows no transport	Supports low contact hazard	---	---
Limited evidence from comparative metabolism shows extensive metabolism in rat and potential rat/human difference	Potential rat/human metabolic differences may support observation of rat/dog toxicity differences	Full understanding of ADME	Complete comparative ADME studies

FC-143 or PFOA

Facts/Observations	Significance/Possible Interpretation	Questions/Knowledge Gaps	Approaches/Recommendations
Hepatocellular adenoma in long-term feeding studies in rts which can be explained to relate more specifically to rat model based on PP mechanism	"Cancer" implication is most likely not valid for humans; however, with respect to food use, would be interpreted as presenting human cancer risk based on FDA interpretive policy re contaminants of products in contact with food; ACGIH lists as A3 carcinogen;	Is it possible to revert ACGIH opinion based on mechanistic data	Support through EPA guidelines for cancer risk assessment, and/or have consultant make case; e.g., Mel Anderson or Joe Rodricks
Main use of FC-143 is as emulsifier for TEFLON	Potential food and device exposure; exposure in numerous compounding and processing operations	What are residues in applications for TEFLON, particularily, food and device applications; what is extent of exposure based on compounding	Ask DuPont for information on uses and residues; have PRL investigate current production volumes
In rats, dose dependent elevation in Leydig cell adenoma, explained by elevation of E2 by induction of aromatase	Possible "cancer" effect which could relate to humans if E2 elevated; however, workers with > 30 ppm in plasma have only 10% increase in E2, which represents a threshold	Does aromatase induction occur in higher species; are there other possible mechanisms; can we argue that a 10% increase in E2 within normal range is insignificant, especially since we do not obsere an increase in testicular cancer	Mechanistic studies and consultation
Exposed workers have 10% E2 increase if plasma FC-143 > 30 ppm	Appear to be at a threshold of response in these workers which compares well to rat and monkey data (approx. 50 ppm serum FC-143 is a threshold); if FC-143 accumulates in humans, not much margin of safety	Of high dose workers, how long exposed and what is risk of exceeding threshold	Analyze work histories on these employees and estblish EG based on plasma level rather than air concentration
FC-143 is being re-engineered/phased out	May disappear as product	What is current/future value	Assign to PRL to gather data
Some equivalence between where rat, monkey and human serum PFOA levels are associated with elevation of E2	Can relate human serum levels closely to other species data		
Female rats excrete PFOA 10 X more rapidly than males rats, but no sex difference is seen in mice, rabbits, dogs, monkeys	Is renal elimination controlled by E2 in rat		
Humans have very long elimination half-life	May impede extrapolation of data between rats and humans	Does DuPont have more data on elimination in humans; need ADME data; potential for cumulative effect in humans; do we have all data relative to tissue concentration and dose; are there specific carrier proteins for PFOA	Develop PBPK model, rat::human
3M exposed workers have significantly less cardiovascular disease	May be PFOA related, since PP reduce serum cholesterol and suppress HMG CoA reductase		

Pancreatic acinar cell tumors in rats				May be relevant to humans if cholestasis	Is this relevant to humans; what is mechanism; what are responses of pancreas; duodenal synthesis and excretion of CCK; bile acids; P450 induction	
Spec.	Dose mg/kg/d	ppm PFOA	E2			
rat	0.64	55	=			
rat	1.94	104	+			
rat	6.50	159	+			
monkey	3.0	54	?			
monkey	*10.0*	*67*	*?*			
monkey	*30.0*	*145*	*?*			
human	?	>30	+			

FC-120 or Ammonium Perfluorodecane Sulfonate

Facts/Observations	Significance/Possible Interpretation	Questions/Knowledge Gaps	Approaches/Recommendations
High to extreme acute oral toxicity	High acute toxicity risk	Unsure about dosing and symptoms in study	Have toxicologist: 1) correct summary; 2) check symptoms relative to morbidity and time in study; 3) check reference to cholinesterase inhibition; 4) check preparation of sample and dosing
Lower production volume and fewer use applications are assumed	Limits potential risk	Current production volumes and applications and do these justify recommendations for: 1) acute inhalation; 2) PP; 3) 90-day feeding study	Assign PRL to collect data on current production volumes and use applications and have toxicologist review
Estimated acute dermal toxicity is >250 mg/kg with one death at 14 days with GI symptoms prevalent	Skin is significant route for systemic exposure	What were results of dermal absorption/persistence	Assign toxicologist to find out
Negative genotoxicity assays (Ames c & c/o activation and mouse micronucleus)	Low risk of genotoxicity	---	---
Minimal contact irritation, eyes and skin	---	---	---
Ha recommended Seg II and 90-day feeding study	---	Should these be done	Check to see if 90-day study may have been done and await results of production volume and uses to determine nee for additional testing

FC-10 or EtFOSE

Facts/Observations	Significance/Possible Interpretation	Questions/Knowledge Gaps	Approaches/Recommendations
McFOSE currently regulated based on EtFOSE data and MeFOSE is basis for new products; e.g., FX-845	McFOSE is considered a carcinogenic contaminant by FDA Food Branch and is restricted by a risk level and little data exists on McFOSE	The extent to which McFOSE can be considered similarity toxic to EtFOSE based on: 1) metabolic profile; 2) toxicity profile	Support the development of a separate metabolic and toxicity profile for EtFOSE
EtFOSE is an important intermediate in production of various SMD/SCD materials	Widespread exposure to population and environment	1) Knowledge of current production volumes and uses of EtFOSE; 2) what is contribution to exposure from metabolism of FC-807 (see FC-807 review)	1) Assign PRL to collect data on production volumes and uses of EtFOSE; 2) Support comparative ADME study to more thoroughly understand exposure/dose relationships
Wide-range and narrow-range EtFOSE produced and degree of branching may vary	EtFOSE is comprised of a mixture of unique chemical components and isomers which could have individual influences on toxicity	Are there significant differences in toxicity based on "range" and branching	Support: 1) a series of comparative in vitro studies looking at specific toxic endpoints (e.g., cytotox, cell proliferation, peroxisome proliferation, mitochondrial function); 2) comparative ADME in vitro
Narrow range EtFOSE has always been used to produce FC-807	See above, and should there be more concern to investigate narrow range	See above, and is wide range reflective of narrow range, i.e., are there differences	See above
Tox data is split between narrow range and wide range	Information base may lead to incorrect conclusions regarding risk if similarity in between wide and narrow range is assumed	See two rows above, and should data be developed on narrow range material to support regulatory issues	See two rows above and support: 1) two-year feeding study on narrow range EtFOSE
FDA considers EtFOSE a carcinogenic contaminant of FC-807 and applies a risk factor of 5 ug/day	1) EtFOSE exposure acceptable to FDA if limited to 5 ug/day; 2) "cancer" label can only be removed if supporting data is developed	Does SCD want to spend resources to develop data to remove FDA "cancer" label	Business must decide regulatory strategy, and, if removing FDA "cancer" label is considered desirable, SCD must commit resources for two-year feeding study
Wide range EtFOSE contains carboxamides	May be responsible for toxicity through metabolism to acids we know to be PP	Do other materials contain carboxamides; if so, how toxic are they and how are they metabolized	Assign Toxicology/PRL team to collect information and propose research plan to study contribution of carboxamides to EtFOSE toxicity
Dermal absorption/persistence study was recommended	May represent a significant route of exposure	What was outcome	Assign toxicologist to discover outcome
Mouse micronucleus was negative	Genotoxic potential is low	Was UDS done	Assign toxicologist to discover if UDS
Linear sulfuramide, a possible metabolite of EtFOSE, produced decreased sperm count and motility in dogs and rats with effect being reversible in dogs based on Griffin study, and preliminary comparative metabolic data shows conversion to sulfuramide (rat & man)	1) May be able to apply sulfuramide data to EtFOSE if sulfuramide is metabolite of EtFOSE; 2) potential exists for reproductive effects; 3) there has been a past action against S. C. Johnson Wax by EPA with repro effect potential at basis of concern	To what extent is EtFOSE metabolized to sulfuramide and is there a risk of testicular effects	1) suppport completion of comparative metabolism studies; 2) have toxicologist review sulfuramide studies for testicular effect and compare to available data on EtFOSE
EtFOSE fetotoxic and equivocally teratogenic in rats without NOEL	Cannot assess developmental effects risk without NOEL	Dose representing NOEL for fetotoxicity/teratogenicity	Support Seg II reproduction study with appropriate species after elucidating comparative metabolism

Sex difference in hepatic response (rat)	May explain species differences	Hormonal? PP? Sex diff other species?	Ovarectomized rats & sex study inGP/Rbt