DuPont Central Research
and Development
Haskell Laboratory for Toxicology
and Industrial Medicine
P.O. Box 50, Elkton Road
Newark, DE 19714-0050
Fax: (302) 366-5207

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TECHNICAL FILE
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[redacted]
3M Center Bldg 270-3S-05
St. Paul, MN55144-1000

Dear [redacted]

The pertinent results from my review of the pancreases of high-dose males from the 3M two-year study with FC143 (C8) are attached. I also had selected lesions reviewed by two other pathologist here at Haskell (Ted Slone and John Hansen). I have included a draft of the Society of Toxicologic Pathologists nomenclature/criteria document for the exocrine pancreas, of which John Hansen is the primary author. The criteria set forth in that document was used in this review. I should note that the criteria used to differentiate adenoma from hyperplasia was primarily size--lesions greater than 3 mm were diagnosed as adenomas. This seems arbitrary but is nonetheless the published criteria. Basophilic foci were not tracked since they are not considered relevant to acinar cell carcinogenicity. Further, non-proliferative lesions were not considered in this review.

Based upon our review of the 3M study, the incidence of acinar cell adenomas/carcinomas in 300 ppm males was 3/48 (6.2%)(for comparative purposes, both 3M data and Haskell data refer to animals necropsied after one year on study). In the Haskell study, the incidence of pancreatic adenomas and carcinomas combined was 8/71 (11.3%). Thus, as was the case for liver and testicular neoplasms, the incidences of pancreatic neoplasms in the two studies were somewhat similar.

In contrast to the above, the incidence of acinar cell hyperplasia in 300 ppm males was greater in the Haskell study (29/71 or 40.8%) than in the 3M study (7/48 or 14.6%). In fact, the ad libitum control incidence of acinar hyperplasia in the Haskell study (14/73 or 19.2%) was greater than the incidence in 300 ppm males in the 3M study. I can think of no explanatory variables for this discrepancy since body weights relative to controls were similar for both studies, and in both studies survival was good. Indeed, survival was greater in the 3M study, which would tend to result in a higher incidence of age-associated proliferative lesions.

The finding of 3/48 pancreatic adenomas/carcinomas in the 3M study is slightly outside the historical control range for feeding studies in SD rats for both our laboratory (0-5%; cumulative incidence of 2.6%) and for Charles River (1.3-2.0%). However, this finding is equivocal at best; the low tumor incidence along with the absence of an associated increase in hyperplasia doesn't argue strongly for a compound-related effect. Of course more definitive conclusions about causality, if attainable at all, would require a

review of study controls, evaluation of historical controls at the contracting laboratory, and perhaps evaluation of the intermediate group for the presence or absence of a dose-response (which, given the low lesion incidences, would be difficult to discern). In my view, such efforts would most likely provide little additional clarification and are thus not warranted, and the conclusions of the study pathologist relative to the pancreas should stand.

I appreciate the opportunity to review these lesions. If you have any questions please give me a call [redacted].

Sincerely,

[redacted]

cc: [redacted]