

3M MEDICAL DEPARTMENT

CORPORATE TOXICOLOGY

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Subject: Pathology Review

Date: 22 July 1999

On 19 July 1999 during my visit at Covance, Madison, I did a slide review of selected tissue sections on the PFOS six-month monkey toxicity study (Study 6329-223).

Lung sections from the high dose males which died late in the study were examined microscopically.

Animal IO5506 (moribund sacrifice) lung sections were normal and thus, there was no histologic evidence of an intubation error.

Animal IO5509 (died post dosing) lung sections showed a large area of acute inflammation (pneumonia) with considerable necrosis in part of one lung section. In other areas of the lung, including directly adjacent to the acute reaction, a chronic inflammation with fibrosis was present. At necropsy multiple adhesions were noted involving all lobes of the right lung. A review of the clinical observations revealed that 7 days before death the animal was recorded as being normal. Three days before death few feces were noted and no feces was recorded two days before death – animal off feed. Labored respiration was noted the day of death. Overall, the picture was one of an acute flare of an old chronic pneumonia. Although a possible intubation error could not be absolutely ruled out, the picture fits much better that as compound toxicity weakened the animal the chronic pneumonia, which had been present for some time, had an acute flare.

My conclusion is that both high dose male monkey deaths should be considered as compound related.

I also reviewed the liver tissue slides from all the animals (male and female) in all dose groups. Microscopic examination revealed no compound related changes in the low and mid dose animals. The high dose animal showed hepatocyte hypertrophy with various degrees of vacuolation. On Thursday, 15 July, before my Covance visit I had received from PAI the final electron microscopic report on these monkey livers. Electron microscopic examination revealed the same results. Namely, no compound related changes in low and mid dose animals but at high dose there was hepatocellular fat vacuolation and hypertrophy. Semi-quantitation of peroxisomes did not indicate any differences between control livers and high dose livers.

The electron microscopic report was reviewed with Covance's reading pathologist, Bob Leedle. He and I also looked at various liver slides together on the multi-headed microscope. Dr. Leedle agreed that compound related liver changes were present only in the high dose monkeys. His pathology report will reflect this conclusion.

From a morphological perspective, the NOEL for liver changes is the mid dose – 0.15 mg/kg/day.

Final notes regarding the electron microscopic report:

The copy received from PAI with original prints of the electron micrographs was put in the study file behind Melinda desk. **When final report documents on this study are put into Corporate Toxicology record files, this report should be included. Also Covance will not include this report as part of their final report. Therefore, 3M needs to prepare a overall study summary which includes the em findings.**

A copy of the electron microscopic report was left with Bob Leedle as he asked for one for informational purposes.

Andrew Seacat and Marv Case also have a copy of the electron microscopic report.