AR226-1919

H18636: Slide Review of pancreas lesions from DuPont APFO Study

Date of Review: 28th November 2001-11-29

Reviewing Pathologists: Dr E E McConnell and Dr J R Foster

Study No: HN-18636

Study Title: Combined Chronic Toxicity/Oncogenicity Study with Linuron, C8 and Wy14,643.

Conclusion of the review:

The overall conclusion of the review of the two studies was that they were not inconsistent in their findings. The review confirmed the carcinogenic effect of APFO in the DuPont study and the most likely explanation for the lack of an oncogenetic effect of APFO in the 3M study was considered to be a decreased sensitivity for the development of pancreatic acinar effects, combined with an under-reporting of the acinar hyperplasia that was present. The DuPont study showed the full spectrum of APFO-induced acinar proliferations from hyperplasia through to carcinoma. It should be noted that the comment on under-reporting is not intended as a reflection of inadequacy in the original interpretation of the study but merely reflects the fact that knowledge, and discrimination of these subtle pancreatic lesions, has advanced in the years since the 3M study was reported. A final confirmation of this conclusion awaits a more extensive review of the pancreas slides from the 3M study to be carried out by Dr McConnell.

Summary of the review:

1. All of the neoplastic findings originally diagnosed on the DuPont study were confirmed.
2. Eleven of the hyperplasias originally diagnosed in group III on the DuPont study were down-graded so as not to be reported as hyperplasia.
3. Two of the hyperplasias originally diagnosed in group I on the DuPont study were down-graded so as not to be reported as hyperplasia.
4. An additional two acinar hyperplasias were diagnosed in group III during the review process which were not originally diagnosed as such.
5. In spite of these changes the overall conclusion for the DuPont study remained that APFO in this study had shown a carcinogenic effect for the male rat pancreas.
6. Following a limited combined review by Drs Foster and Frame, of the pancreas slides from approximately 30 animals (selected by Dr Frame), several acinar hyperplasias were confirmed in the 3M study and although all of the animals were not reviewed the preliminary conclusion of the limited review was that there did appear to be an APFO-induced increase in acinar hyperplasias on the 3M study. Dr McConnell has been requested to review all of the pancreas' from the 3M study.

Introduction:

The pathology review of the pancreas' from the two oncogenicity studies conducted in the rat on APFO was initiated because in the 3M study, which was carried out first, the compound was not carcinogenic to the pancreas while in the DuPont study, which was only conducted in the male rat, showed a clear oncogenic effect on the pancreatic acinar cells. The slide review was requested to confirm or refute the findings in the pancreas' from the two studies.

Site of Review:
The review took place at DuPont Haskell Laboratories, NewArk, Delaware on 28th November 2001.

Those Present:

Dr Randy Frame – Study Pathologist, DuPont Haskell Laboratories, Delaware, USA
Dr John Hansen – Head of Pathology, DuPont Haskell Laboratories, Delaware, USA
Dr G Kennedy – Head of Toxicology, DuPont Haskell Laboratories, Delaware, USA.
Dr C R Elcombe, Biochemical Toxicologist, Dundee University, UK.
Dr John Butenhoff, Toxicologist, 3M, Minnesota, USA
Dr John R Foster, Reviewing Pathologist, AstraZeneca Pharmaceuticals, Cheshire, UK
Dr E E McConnell, Reviewing Pathologist, PathLabs, North Carolina, USA

Conduct of Review:

1. The STP Guidelines for the diagnosis of Proliferative Lesions of the Exocrine Pancreas (1995) was the basis for the diagnostic criteria used in the review process.
2. Together with Dr Frame, on a two headed microscope, Dr Foster reviewed the pancreas' from approximately 30 animals from the 3M APFO study which included two animals from the control group and the remainder from the top dose group.
3. Dr McConnell was not able to review the 3M study on this occasion but has been given the slides from all of the animals on this study to review in the near future (report pending).
4. For the review of the DuPont APFO Study the reviewing pathologists (JRF and EEMcC) were given summary tables of the original diagnoses.
5. Dr McConnell initially reviewed the pancreas slides from only those group III animals where the presence of either acinar hyperplasia, adenoma or carcinoma had been recorded. In addition he reviewed the pancreas slides from all of the pair-fed control animals from group II. Pancreas slides from the group I control animals from the DuPont study were not reviewed.
6. Dr Foster then independently reviewed the same animals as Dr McConnell from group III but, in the interests of time, only reviewed those animals from group II that Dr McConnell had considered showed proliferative lesions and/or those deemed by the study pathologist to have shown lesions from the original report of the study.
7. The diagnosis from both Drs McConnell and Foster were independently recorded and then were compared.
8. Any disagreements between the reviewing pathologists were then reviewed together on a two-headed microscope and a consensus agreed in consideration of both the additional review of the slides, together with reference to the original diagnosis.

9. Drs McConnell, Foster, Hansen and Frame then met to discuss the findings of the review and were joined later by Drs Elcombe, Butenhoff and Kennedy for a final debrief.
10. It was agreed that Dr Frame would draft a single page report of the proceedings and circulate it to the attending members for comment after which the reviewing pathologists, and Drs Frame and Hansen would sign the final version as an accurate representation of the proceedings.

Table 1: Summary of JRF's review of the DuPont pancreas slides.

EEMcC/JRF Consensus	Agree/ Disagree	An. No	Review Diagnosis	Original Diagnosis
	√	R494669	Adenoma (nuclear atypia arising out of hyperplasia)	Adenoma
	√	R494673	Hyperplasia	Hyperplasia (3)
	√	R494674	Hyperplasia	Hyperplasia (4)
	√	R494675	Hyperplasia	Hyperplasia (1)
	√	R494677	Adenoma	Hyperplasia (2)
	√	R494683	NAD	Hyperplasia (2)
	√	R494685	Hyperplasia	Hyperplasia (2)
	√	R494689/4	NAD	
		R494689	Eosinophilic focus	Hyperplasia (2)
Adenoma	X	R494693	Hyperplasia-borderline adenoma	Adenoma (multiple)
NAD	X	R494702	Hyperplasia	Hyperplasia (1)
	√	R494706	Hyperplasia	Hyperplasia (3)
	√	R494707	Basophilic focus	Hyperplasia (2)
	√	R494711	Adenoma (autolysed)	Adenoma
	√	R494715	Adenoma (central autolysis)	Adenoma
	√	R494717	Adenoma (out of hyperplasia);l hyperplasia	Adenoma + Hyperplasia (4)
Adenoma	X	R494719	Adenoma (solid, no acini)	Hyperplasia (4)
	√	R494721	Basophilic focus	Hyperplasia (1)
NAD	X	R494724	Hyperplasia	Hyperplasia (1)
	√	R494725	Carcinoma (haemorrhage/nuclear atypia)	Hyperplasia (2) + carcinoma
	√	R494727	Diffuse change	Hyperplasia (1)
	√	R494734	Hyperplasia	Hyperplasia (3)
	√	R494748	Hyperplasia	Hyperplasia (2)
	√	R494754	Hyperplasia	Hyperplasia (2)
	√	R494762	Adenoma	Hyperplasia (3) + Adenoma (multiple)
	√	R494768	NAD	Hyperplasia (2)
	EEMc not reviewed	R494773	NAD	NAD
	√	R494775	NAD	Hyperplasia (1)
	√	R494781	Basophilic focus	Hyperplasia (1)
	EEMc not reviewed	R494790	Hyperplasia	Hyperplasia (2)
	EEMc not reviewed	R494793	NAD	Hyperplasia (1)
	EEMc not reviewed	R494800	Hyperplasia	Hyperplasia (2)
	EEMc not reviewed	R494803	Hyperplasia	Hyperplasia (1)

	EEMc not reviewed	R494808	Hyperplasia	NAD
	EEMc not reviewed	R494811	Hyperplasia	Hyperplasia (2)
	√	R494506	NAD	Hyperplasia (1)
Basophilic focus	X	R494509	Hyperplasia	Hyperplasia (1)
	√	R494513	Basophilic focus	Hyperplasia (1)
	√	R494514	Hyperplasia	Hyperplasia (2)
	√	R494547	Hyperplasia	Hyperplasia (2)
	√	R494552	Basophilic focus	Hyperplasia (1) + basophilic focus
	√	R494611	NAD	
	√	R494611-2	Hyperplasia	Hyperplasia (1)
	√	R494633	NAD	
Adenoma	X	R494633-2	Basophilic focus; Hyperplasia?	Adenoma
	√	R494638	NAD	
	√	R494638-2	Hyperplasia	Hyperplasia (2)

Table 2: Comparison of incidences of proliferative lesions in the acinar pancreas between original and review.

	Group 2	**Group 3**
Original Diagnosis		
Acinar hyperplasia	8	28
Acinar adenoma	1	6
Acinar carcinoma	0	1
Total	**9**	**35**
Reviewing Diagnosis		
Acinar hyperplasia	6	17
Acinar adenoma	1	8
Acinar carcinoma	0	1
Total	**7**	**25**
Total animals on study	79	76

J R Foster
1st December 2001