UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 26 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Dimethoate: Histopatahology Slide Inventory of Vascular Proliferative Lesions in Male Wistar Rats from Project 70C0326/8241

To: William Miller, PM# 15 Tox. Chem. No. 358
Insecticide/Rodenticide Branch
Registration Division (TS-767C)

From: Joycelyn E. Stewart, Ph.D. 4/27/88
Section VII, Toxicology Branch
HAzard Evaluation Division (TS-769C)

Thru: Albin B. Kocialski, Ph.D. ABK 4/22/88
Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C). 4/26/88

Dr. Lynnard J. Slaughter, consulting pathologist to the Toxicology Branch, has recently completed an inventory of the slides submitted for the subject and study referenced above in this memorandum. These slides were of spleens and mesenteric lymph nodes which had been prepared from rats administered dimethoate for two years, and had been reevaluated at the registrant's request by Dr. Robert Squire.

Dr. Slaughter concluded, after completing the inventory, that twelve (12) slides representing six animals were missing and not accounted for (see attached memorandum by Dr. Slaughter dated April 20, 1988). The missing slides were from the following: one(1) animal from the control group, three(3) animals from the 5 ppm group, and two(2) animals from the 25 ppm group. All slides from the high dose group were accounted for.

Dr. Slaughter indicated in his memorandum that the missing slides are of considerable importance and that he will refrain from making any microscopic evaluation of the slides submitted by American Cyanamid through Dr. Squire until all the slides are available for his review. In light of the Dr. Slaughter's memorandum, Toxicology Branch recommends that:

1. the registrant be informed about the missing slides and be asked to supply them, and/or

2. a qualified company representative be sent to Toxicology Branch to inventory the slides and discuss the current situation with Dr. Slaughter.

The current schedule projected by the Toxicology Branch (attached) should therefore be considered tentative pending the resolution of the inventory of the missing slides and receipt of the skin and kidney slides from Germany.

cc. Mr. Rick Tinsworth, Director, Registration Division (TS-767C)
Mrs. Anne Barton, Acting Director, Hazard Evaluation Division (TS 769C)
Dr. Reto Engler, Mission Support Staff, Toxicology Branch(TS-769C)
Dr. Theodore Farber, Chief, Toxicology Branch(TS-769C)

attachments (2)

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MEMORANDUM

SUBJECT: Histopathology Slide Inventory of Vascular Proliferative Lesions In Male Wistar Rats from Project 70C0326/8241

FROM: Lynnard J. Slaughter, D.V.M.
Consulting Pathologist L.J.S. 4/20/88
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Albin B. Kocialski, Ph.D., Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Joycelyn E. Stewart, Ph.D.
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Upon your request, I reviewed the documents and determined that it would be necessary for me to microscopically reevaluate certain slides where the tumor diagnosis opinions between the study pathologist and the consulting pathologist differed. On March 3, 1988, a parcel of slides was received from the consulting pathologist. In the presence of a witness, following our conversation about receipt of the parcel of slide boxes that were addressed to you, the box was opened and the contents were noted. This box contained an unsealed letter addressed to you, which I placed in your mailbox, and three slide boxes labeled 1, 2, and 3, which were sealed with tape. Immediately following opening of the slide boxes, an inventory of all slides in the boxes was conducted. The inventory was made on the basis of the appendix submitted to you by the consulting pathologist entitled "Blind Slide Reevaluation Key Male Rats/Dimethoate," pages 31-36, and "Appendix-Comparison of Slide Evaluations for Spleen and Mesenteric Lymph Nodes."

After reinventorying these slide boxes several times, it was determined that the boxes contained a total of 473 slides. Box #1 contained 194 slides; box #2 had 194 slides; and box #3 contained 85 slides. Thirty-two (32) animals had a tumor diagnosed by the study pathologist in either the animal's spleen or mesenteric lymph node, or in both of these organs. The consulting pathologist, after review of the same slides, differed from the study pathologist on at least 14 different occasions upon review of the same lesion. Therefore, in order to attempt to resolve the difference, at least 64 slides (2 slides per animal) are required for this reevaluation. However, it was determined that 12 of the expected 64 slides were missing, and only 52 slides of the animal tissues in question were received.

The 12 missing slides represent one (1) animal from the control group, three (3) animals from the low-dose group, 5 ppm, and two (2) animals from the median dose group, 25 ppm. None of the slides in the slide boxes was broken nor loose. Table 1 itemizes the slides found which had a tumor diagnosed of the type in question that had to be reevaluated, their location in the slide box slot in each of three slide boxes, missing slides, and their corresponding animal number.

Comments

Since the 12 missing slides are of considerable importance with respect to resolving the difference of tumor diagnosis between the two pathologists, I must refrain from making any microscropic evaluation of the slides until the missing slides are made available for my review.

Recommendations

1. Make another independent inventory of the slides forwarded to you by the consulting pathologist.

2. If the independent inventory confirms the missing slides, inquire about the missing slides.

If I can be of further service to you, contact me at your convenience.

Table 1

Box Number	Location of Slides Slide Slot	Animal Number	Dose Level	SP1/	CP2/
1	15	17	Control	Spleen HA	Prolif (1)
	Slides not found	46	Control	MLN -HA	Prolif (2)
	Slides not found	108	5 ppm	Spleen HS	Spleen HA
1	97	114	"	Spleen HS	Spleen HS
2	11	132	"	Spleen HS	Spleen HS
1	82	98	"	MLN-HA	Prolif (2)
	Slides not found	121	"	MLN-HA	Prolif (3)
2	6	125	"	MLN-HA	Prolif (5)
	Slides not found	126	"	MLN-HA	MLN-AS
1	83	100	"	MLN-HS	MLN-AS
2	4	122	"	MLN-HS	LN-HGE
2	5	123	"	MLN-HS	MLN-AS
2	12	133	"	MLN-HS	MLN-AS
2	68	195	25 ppm	Spleen HS	Spleen HS
	Slides not found	200	"	Spleen HS	Prolif (4)
2	25	151	"	MLN-HA	Prolif (5)
2	27	153	"	MLN-HA	Prolif (4)
2	32	159	"	MLN-HA	Prolif (3)
	Slides not found	187	"	MLN-HA	MLN-A
2	62	188	"	MLN-HA	Prolif (1)
2	34	161	"	MLN-HS	MLN-AS
2	35	162	"	MLN-HS	MLN-AS
2	38	165	"	LMN-HS	Prolif (5)
*3	1	231	100 ppm	Spleen HS	Spleen HS
3	2	232	"	Spleen HS	Prolif (5)
3	8	240	"	Spleen HS	Spleen HS
3	22	256	"	Spleen HS	Spleen HS
3	25	259	"	Spleen HS	Spleen HS
2	90	220	"	MLN-HA	Prolif (1)
*3	1	231	"	MLN-HA	Spleen HS
3	15	246	"	MLN-HA	Prolif (1)
2	94	225	"	MLN-HS	MLN-AS
2	95	226	"	MLN-HS	MLN-AS
3	24	258	"	MLN-HS	No finding

1/ SP = Study Pathologist
2/ CP = Consulting Pathologist
* = Same animal - slides in separate slots in slide box #3.

Reto Engler
Tox, HFD

NOTE TO DOUG CAMPT

FYI

This is to update you on the status of the Dimethoate FRSTR which is scheduled for issuance June 17, 1988 (the original date was January 8, 1988).

The Tox Branch has concerns with the rat oncogenicity study and has requested that the slides on the tissues of the spleen, the mesenteric lymph nodes, the kidney and the skin in the males only, be submitted for our review. American Cyanamid must obtain the slides from Germany. We expect they will be received by the Agency about the middle of May.

Reto Engler projects the following schedule:

- 6 weeks from receipt to read the slides
- 3 weeks to draft the reviewers Peer Review report
- 2 weeks to schedule Peer Review
- 6 weeks for Peer Review 1st and 2nd draft review

If SAP review is required:

- 3 months from final Peer Review for SAP
- 2 weeks for final EPA Review

A worse case scenario would project the issuance of the Dimethoate FRSTR into the 3rd or 4th quarter of FY'89. Even if SAP review was not needed, the FRSTR could not be completed in FY'88.

The alternative would be to issue the FRSTR without waiting for a resolution of the oncogenicity issue. This does not seem to be a viable option for a FRSTR.

I plan to postpone the FRSTR unless you believe otherwise.

Rick Tinsworth

cc: Reto Engler