



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

003435

MEMORANDUM

12/14/83

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: R. Mountfort (PM#23)
Registration Division (TS-767C)
and
J. McCann, Chief
Lab Audit Program, BFS (TS-768)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

SUBJECT: Review of Chronic Rat Study of Metolachlor
Accession Nos.: 250369-250375 CASWELL#188DD

Registrant: Ciba-Geigy Corp.
Agricultural Division
Greensboro, N.C.

Recommendation: It is recommended that this study be core classified as Supplementary Data. The NOEL is 30 ppm, based on atrophy of the testes with degeneration of the tubular epithelium in the mid and high dose groups. An increase in primary liver tumors is observed in the male and female high dose groups. A risk assessment may eventually be required based on this study; however, it is first recommended that a laboratory audit be conducted on this study. This is triggered by conflicting reports of the incidence of liver tumors emanating from a preliminary report and the Final Report of the study. Depending upon the results of the audit, this study may be upgraded to Core Minimum Data.

Review of Data:

Chronic Feeding, Rats. Conducted by Hazelton Raltech, Inc., Madison, WI, Study No. 80030 and submitted by Ciba-Geigy, May 2, 1983.

CD-Crl:CD(SD)BR rats were obtained from Charles River Breeding Laboratories and were acclimated for two weeks prior to testing. Seventy rats per sex were assigned to groups which were to receive either 0 or 3000 ppm. Sixty rats per sex were assigned to groups which would receive either 30 or 300 ppm. Test diet was offered ad libitum for 104 weeks of testing and was formulated with metolachlor technical. Water was available ad libitum.

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All animals were individually housed in a room with a temperature of $72^{\circ} \pm 3$ and 30 to 70% relative humidity.

Animals were examined twice daily within their cages. Once per week animals were removed and carefully examined. Starting at week 14, animals were palpated weekly for tissue masses.

Body weights were recorded weekly from weeks 0-13 and biweekly after week 16. Food consumption was recorded weekly for weeks 0-13 and biweekly after week 16 for 10 animals per group. In addition, food consumption was recorded for all animals in all groups at weeks 40, 52, 66, 78, 92 and 104.

Clinical studies were conducted on eight animals per group after 3, 6, 12, 18 and 24 months on test. At the 18th month of testing, an additional 10 animals per group were selected. Hematology consisted of RBC, WBC and leucocyte counts, hematocrit, hemoglobin and platelet counts. Clinical chemistry consisted of LDH, AST, ALT, AP, BUN, glucose, total protein, total cholesterol, direct and total bilirubin, Ca and K. Urinalysis consisted of "Ames multistix", specific gravity and microscopic examination.

All animals on test were necropsied. A total of 31 organs had tissues taken and all gross lesions and tissue masses were preserved. The following tissues were examined as reported by the registrant:

Adrenal glands
Bone marrow section (femur)
Brain (cerebrum, cerebellum, and pons)
Cecum
Colon
Esophagus
Eyes
Gonads
Heart
Kidneys
Liver (at least two lobes)
Lungs (two coronal sections including all lobes and mainstem bronchii)
Lymph nodes (cervical and mesenteric)
Mammary gland
Muscle (skeletal)
Urinary bladders
Uterus

Optic nerve
Pancreas
Parathyroid glands
Pituitary gland (fixed in situ)
Prostate
Salivary glands (sub-maxillary)
Sciatic nerve
Skin
Small intestine (duodenum, jejunum, and ileum)
Spinal cord (two levels)
Spleen
Stomach (cardiac, fundus, pylorus)
Thymus
Thyroid glands

All animals on test had tissues microscopically examined. The following organs were weighed prior to fixation: heart, liver, spleen, kidney, gonads and brain.

Ten males and 10 females from the control and high dose groups were randomly selected after 12 months for a recovery study. Five of these animals were sacrificed immediately and 5 were placed on control diet (absent test compound) for 4 weeks. Clinical studies, organ weight determinations, gross and histopathology determinations for recovery animals were identical to those that continued on test. Statistical comparisons were conducted by the registrant on all parameters (this reviewer independently conducted statistical analysis for the liver tumor incidences using the Fisher's Exact Test).

Results:

Diet analyses were conducted for all dose levels at weeks 1-4 and for randomly selected test diets on a weekly basis for the remainder of the test period. No metolachlor (< 5.0 ppm) was found in control diets, time-weighted averages of 29.1, 273, and 2851 ppm were found in the diet.

Survival over the course of the study was adequate with 54, 57, 42 and 57% of the control, 30, 300 and 3000 ppm dose groups surviving until study termination at 24 months. It did not appear that the survival rate was influenced by test compound administration.

At week 9, animals in all groups began to show clinical symptoms indicative of sialodacryoadenitis virus. These symptoms included "palpable enlargement of the submaxillary salivary glands, a generalized edema in the cervical and mandibular areas, and red-tinged (porphyrin) discharges in the nasal and ocular areas."

The symptoms persisted for only 2-3 days and animals showed no further indication of disease. In addition to the above described clinical signs, animals lost weight (approximately 5 grams) during the time of infection. No animals died during this period. The disease outbreak is considered by this reviewer to be of little consequence to the interpretation of the study.

Mean body weights of females in the high dose group were consistently less than controls from week 2 until study termination. For 26 of the 59 intervals at which animals were weighed, this difference was significant at the $p < .01$ level. Neither male body weights nor low or mid dose female dose groups were affected by treatment. Food consumption in high dose females was slightly less than controls and the difference was statistically significant ($p < .05$) at 10 of 59 intervals with seven of these intervals between weeks 5 and 18. Male food consumption appeared unaffected by treatment.

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Organ weights and organ to body weight ratios were similar among all dose groups.

A variety of differences in the clinical pathology measurements were found between control and dosed groups at various intervals but no consistent dose-related effects were apparent with one exception. Aspartate aminotransferase activity was less than controls in both sexes at 3000 ppm at 12 months and the decrease was significant ($p < .01$) in males. Nonstatistically significant decreases in AST activity were noted at 3000 ppm; at other intervals for both sexes and in females at the 300 ppm dose level at 18 and 24 months. It should be noted that the recovery study found that AST values in high group, which were depressed at 12 months, increased after one month recovery period to a level that was not statistically significant. The recovery study also suggests that body weight depression in the 3000 ppm dose level also is reversible with most of the difference between control and high dose body weights disappearing through the one month recovery period.

Gross pathology findings of the scheduled sacrifice, moribund sacrifice and "died on test" animals were unremarkable.

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The incidence of neoplastic nodules and hepatocellular carcinomas reported in the Final Report was as follows:

Males

	Dose			
	0 ppm	30 ppm	300 ppm	3000 ppm
Neoplastic nodules	0	0	0	4
Hepatocellular Carcinomas	2	1	3	2
Total Examined	59	59	60	60

Females

	Dose			
	0 ppm	30 ppm	300 ppm	3000 ppm
Neoplastic Nodules	0	0	1	4
Hepatocellular Carcinomas	0	0	0	2
Total Examined	60	60	60	60
Total Examined After the Observation of the First Animal with Tumor	45	43	42	50

The numbers of animals examined after the observation of the first of females dying with tumors (a high dose animal observed at week 90) were 45, 43, 42 and 50 for the control, 30, 300 and 3000 ppm dose level females, respectively. Although the registrant asserts that the incidence of these tumors in high dose females is not statistically significant compared to the control group, this reviewer found statistical significance with $p = .0183$ (Fisher's Exact test, 0/45 vs. 6/50 for the control vs. high dose groups).

The incidence of these tumors in female rats at this laboratory can only be assessed from a single other study as indicated on p. 36 of Vol. 1 of the registrants submission. Apparently two control groups were used in the historical study and the incidence of these tumors were 0/47 and 1/46 for females of the two groups.

The incidence of other tumor types was unremarkable and did not appear to be related to treatment.

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It should be noted that the increased incidence of these tumors is consistent with IBT Study No. 622-07926, conducted with the same doses and classified as "Supplementary Data". It should also be noted that a letter from the registrants dated December 9, 1983 (Attachment A) reported a different incidence of liver tumors in this study than was subsequently reported by the registrants in the Final Report. The incidence of liver tumors originally reported as 2, 2, 2 and 9 for control, low, mid and high dose males and 0, 1, 2, and 7 for control, low, mid and high dose females. This reviewer has requested an explanation for the differing incidences of primary liver tumors in the two reports of the the same study and the response from the registrant was received on November 2, 1983 (Attachment B). The response states that "Subsequently, liver sections were reviewed during the examination of all other protocol tissues and it became apparent that some of the "original diagnoses" would have to be changed. Primarily this was because the presence or absence of "compression of surrounding parenchyma" had not been given uniform consideration during the original examination...The primary difference in the two sets of data was that some of the lesions originally classified as proliferative foci (neoplastic nodules) were ultimately classified as foci of cellular change due to a lack of compression of surrounding parenchyma."

Microscopically, atrophy of the testes with degeneration of the tubular epithelium was found to a greater extent in mid and high dose animals than in the control group, with 6/60, 6/60, 10/60 and 12/60 animals affected in the control, low, mid, and high dose groups, respectively. Although the severity of this finding appeared similar in all groups the time of observation of the atrophy was sooner in the treated groups, with 0/27, 5/26, 7/35 and 10/26 of those animals that died-on-test animals having this finding. An increased incidence of eosinophilic foci were observed in the livers of high dose males and females with 10/59, 15/59, 14/60, 21/60 (males) and 4/60, 7/60, 5/60 and 23/60 (females) affected in the control, low, mid and high dose groups, respectively. Other pathological findings are considered by this reviewer to be incidental to test compound administration.

Classification: Supplementary Data.

The NOEL for non-neoplastic effects is 30 ppm based on testicular atrophy with degeneration of the tubular epithelium. An increased incidence of neoplastic nodules/hepatocellular carcinomas were observed in this study. Due to a difference in the incidence of liver tumor reported in a preliminary report and the Final Report of the study, the conduct of a laboratory audit is recommended.

Gary J. Burin

Gary J. Burin, Toxicologist
Toxicology Branch
Hazard Evaluation Division (TS-769C)

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CIBA-GEIGY

Agricultural Division
CIBA-GEIGY Corporation
P.O. Box 11422
Greensboro, North Carolina 27409
Telephone 919 292 7100

Attachment A

December 9, 1982

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Mr. Richard F. Mountfort
Product Manager (23)
Registration Division (TS-767C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Mr. Mountfort:

SUBJECT: METOLACHLOR HERBICIDE
RISK ASSESSMENT BASED ON THE REPEAT
2-YEAR RAT STUDY

As you are aware, CIBA-GEIGY agreed to repeat a 2-year rat study on metolachlor when agency scientists determined that the original IBTL study did not meet the core minimum classification. The in-life phase of that study was completed earlier this year and the histopathology evaluation of the livers on the repeat 2-year rat study on metolachlor technical performed at Hazelton-Raltech, Inc., Madison, Wisconsin has been recently completed. In the repeat study, as in the original IBTL study, certain liver lesions appeared to result from the administration of metolachlor. Additional evaluations are planned in this study.

A repeat 2-year mouse study recently submitted to EPA did not indicate any oncogenic potential of metolachlor, as with the initial mouse study. Therefore, the rat liver response is considered a very weak species-specific lesion.

At this time, low dose extrapolation to evaluate the potential risk to humans with respect to these findings is considered inappropriate. If it were essential to perform risk assessment after all evaluations are completed with respect to the repeat rat study, the data employed should be the number of animals bearing proliferative lesions of the hepatocytes. These data are presented on the following page.

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Incidence

Lesion	Sex	0	Feeding Level (PPM)		
			30	300	3000
Proliferative Foci (Neoplastic Nodule)	M	0 0	2 0	0 0	6 4
	F	0 0	1 0	1 1	5 4
Hepatocellular (Carcinoma)	M	2 2	0 1	2 3	3 2
	F	0 0	0 0	1 0	2 2
Total Animals with Lesions	M	2 2	2 1	2 3	9 6
	F	0 0	1 0	2 1	7 6
Total Animals Examined	M	60 54	57 54	60 60	60 60
	F	59 60	60 60	59 60	60 60

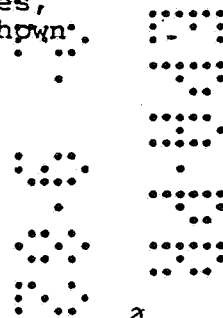
Based upon the computer model of Crump, the coefficients of the polynomials that best fit the data for the multi-stage model are:

Male Data: $Q(0) = 3.444 \times 10^{-2}$
 $Q(1) = 0$
 $Q(2) = 0$
 $Q(3) = 4.743 \times 10^{-12}$

Female Data: $Q(0) = 9.916 \times 10^{-3}$
 $Q(1) = 4.081 \times 10^{-5}$
 $Q(2) = 0$
 $Q(3) = 0$

Exposure

Potential Theoretical Maximum Residue Concentration (TMRC) for established and proposed tolerances are based on tolerances, percent of diet and percent acreage treated. These are shown below for metolachlor.



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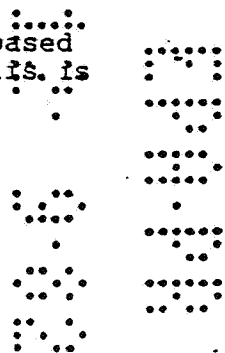
Established Tolerances

<u>Consumed Commodities</u>	<u>Tolerances</u>	<u>% of Diet</u>	<u>% of Acreage Treated*</u>	<u>TMRC mg/day/ 1.5 kg food</u>
Sorghum	0.30	0.03	24.2	3.29×10^{-5}
Corn, Grain	0.10	1.00	18.9	2.84×10^{-4}
Peanuts	0.10	0.36	2.7	1.46×10^{-5}
Soybeans	0.10	0.92	8.6	1.19×10^{-4}
Eggs	0.02	2.77	18.9**	1.57×10^{-4}
Meat: Inc. Poultry	0.02	13.85	18.9**	7.86×10^{-4}
Milk & Dairy Products	0.02	28.62	18.9**	1.62×10^{-3}
Cottonseed	0.10	0.15	0.6	1.38×10^{-6}
Potatoes	0.20	5.43	3.8	6.19×10^{-4}
Corn: Pop	0.10	0.08	18.9	2.27×10^{-5}
Corn: Sweet	0.10	1.43	18.9	4.06×10^{-4}
Seed and Pod Veg.	0.30	3.66	2.3	3.79×10^{-4}
Safflower	0.1	0.03	10	4.50×10^{-6}
Barley (Rotational)	0.1	0.03	2	9.00×10^{-5}
Buckwheat (Rotational)	0.1	0.03	< 1	4.50×10^{-7}
Millet Forage (Rotational)	0.1	0.03	< 1	4.50×10^{-7}
Milo (Rotational)	0.1	0.03	< 1	4.50×10^{-7}
Oat (Rotational)	0.1	0.36	3	1.62×10^{-5}
Rice (Rotational)	0.1	0.55	3	2.48×10^{-5}
Rye (Rotational)	0.1	0.03	< 1	4.50×10^{-7}
Wheat (Rotational)	0.1	10.36	5	7.77×10^{-4}

Total TMRC = 5.36×10^{-3} mg/1.5 kg food
or 3.57 ppb in the diet.

*Based upon 1983 projected sales figures, these are larger figures than the 1982 projections so they represent maximal values.

**The acreage used is that for corn. This assumption is based on corn as the major seed component and the fact that this is one of the larger percentages of acreage treated.



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<u>Consumed Commodities</u>	<u>Pending Tolerances</u>			<u>TMRC mg/day/ 1.5 kg food</u>
	<u>Tolerance</u>	<u>% of Diet</u>	<u>% of Acreage Treated*</u>	
Flax Seed	0.20	0.03	1.3	1.17×10^{-6}
Sunflower	0.30	0.03	1.3	1.82×10^{-6}
Peanuts (High Rate)	0.50	0.36	2.7	7.29×10^{-5}
Soybeans (High Rate)	0.20	0.92	8.6	2.37×10^{-4}

Subtotal TMRC - 3.10×10^{-4} mg/1.5 kg food
or 0.21 ppb in the diet.

The TMRC for all established tolerances plus proposed tolerances would be the combination of the 2 numbers minus the TMRC for low rate peanuts and soybeans:

$$5.36 \times 10^{-3} + 3.10 \times 10^{-4} - 1.04 \times 10^{-4}$$

$$= 5.57 \times 10^{-3} \text{ mg/1.5 kg food}$$

or

$$= 3.71 \text{ ppb in the diet}$$

Applicator Exposure has been established by R. Honeycutt. These data are presented below:

Mixer/Loader Exposure:

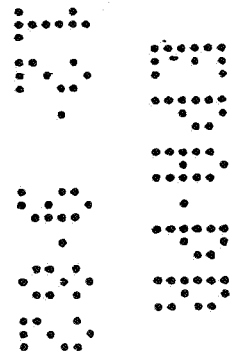
0.515 mg/yr. X 10% absorbed: 365 days/yr X 40 yrs./70 yrs.
= 0.000806 mg/day averaged over a lifetime.

This is equivalent to 0.054 ppb in the diet.

Applicator Exposure:

38.1 mg/yr. X 10% absorbed: 365 days/yr. X 40 yrs./70 yrs.
= 0.005965 mg/day average over a lifetime.

This is equivalent to 4.00 ppb in the diet.



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Risk Calculations (Based on Repeat Rat Study)

Risk calculations are then based on the modile parameters of worst case (female data) and exposure estimate are presented below:

Present dietary exposure including market share:

Dose .00357 Response: 1.44×10^{-7}
Risk $1/6.93 \times 10^6$

Dietary risk for established and pending tolerances including market share:

Dose .00371 Response: 1.50×10^{-7}
Risk $1/6.67 \times 10^6$

Mixer loader including dietary (10% dermal absorption):

Dose .003764 Response: 1.52×10^{-7}
Risk $1/6.57 \times 10^6$

Applicator including dietary (10% dermal absorption):

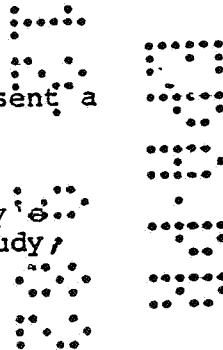
Dose .00771 Response: 3.12×10^{-7}
Risk $1/3.21 \times 10^6$

Risk based on mixer loader, applicator and dietary exposure:

Dose .007764 Response: 3.14×10^{-7}
Risk $1/3.19 \times 10^6$

These values indicate that even if metolachlor were to present a potential risk to humans, the risk is not unreasonable.

Risk calculations, based on the original IBTL study, were submitted to you on November 11, 1981. Based on the Agency's subsequent internal risk assessment of the original rat study,



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tolerances were established for metolachlor residues in cotton, potatoes, seed, and pod vegetables, sweet corn and popcorn, which permitted the March 5, 1982 registration of Dual® 8E for use on these crops. The risk calculations above are substantially the same as those based on the IBTL Study. Therefore, we conclude that the results of the risk assessment on the repeat rat study support the continued usage of metolachlor herbicides as currently registered, as well as proposed expanded usage on corn, soybeans, peanuts, sunflowers and flax.

Further evaluation of these data continue. We expect the final report to be available on or before the September 1983 date agreed upon.

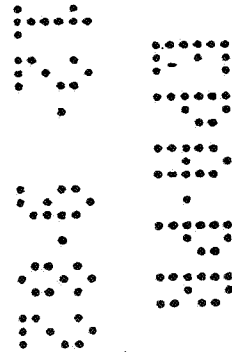
If you have any questions, please call me.

Sincerely,

Gene Holt

Gene Holt, Ph.D.
Senior Regulatory Specialist
Government Affairs

GH/ms/0201



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CIBA-GEIGY

Agricultural Division
CIBA-GEIGY Corporation
P.O. Box 18300
Greensboro, North Carolina 27419
Telephone 919 292 7100

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November 2, 1983

Mr. Richard F. Mountfort
Product Manager (23)
Registration Division (TS-767C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Mr. Mountfort:

SUBJECT: METOLACHLOR HERBICIDE
REPEAT 2-YEAR RAT CHRONIC FEEDING STUDY
EXPLANATION OF CHANGE IN DIAGNOSES OF
LIVER PATHOLOGY BETWEEN PRELIMINARY
REPORT AND FINAL REPORT

On October 25, 1983 you relayed to CIBA-GEIGY a question from Dr. Gary Burin concerning the difference in diagnoses of liver pathology in the preliminary report on the subject study submitted on December 9, 1982, and the final report submitted on May 20, 1983.

We have contacted the laboratory which conducted the study, Hazleton Raltech, Inc., for an answer to your question. We are enclosing three (3) copies of their signed explanation for EPA's files.

Would you please transmit a copy of this report to Dr. Burin as soon as possible, in order that he may conclude his review of this study.

Thank you for handling this matter.

Sincerely,

Gene Holt

Gene Holt, Ph.D.
Senior Regulatory Specialist
Government Affairs

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Enclosures

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**HAZLETON** LABORATORIES AMERICA, INC.

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3301 KINSMAN BLVD. • P.O. BOX 7545 • MADISON, WI 53707 • (608) 241-4471 • TUX 703956 HAZRAL MDS LTD

NOV 2 1983

November 1, 1983

James T. Stevens, PhD
Manager of Toxicology
CIBA-GEIGY Corporation
Agricultural Division
P. O. Box 18300
Greensboro NC 27419

Dear Jim:

Enclosed is a memo from Dr. Terry Jackson to me concerning the liver histopathology for Study No. 80030, "Two-Year Toxicity and Oncogenicity Study With Metolachlor Technical in Albino Rats." In it he discusses the foci of cellular change and primary neoplasms in the draft expedited liver pathology data and his subsequent review and reclassification of the lesions in some of the animals prior to issuance of the final report.

I trust this explanatory memo will help link the draft data to that presented in the final report.

Sincerely,

Myerall

Merrill Tisdell
Study Director, Toxicology

MT/-t

Enclosure

cc: T. Jackson
Toxicology

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TO: Merrill Tisdell

FROM: T. Jackson

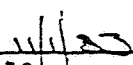
RE: Draft vs. final data for liver,
Study No. 80030

DATE: 10/31/83

Sections of liver from all animals in this study were examined during October, 1982 following a special request by CIBA-GEIGY. Draft data, subject to a more timely and thorough examination of the liver sections, were prepared and submitted. This data indicated that a greater number of foci of cellular change and primary liver neoplasms were present in the treated groups, especially the high dose level, than in control groups.

Subsequently, liver sections were reviewed during the examination of all other protocol tissues and it became apparent that some of the "original diagnoses" would have to be changed. Primarily this was because the presence or absence of "compression of surrounding parenchyma" by foci of cells had not been given uniform consideration during the original examination. Where appropriate diagnoses were changed and subsequent data were submitted in the final report. The primary difference in the two sets of data was that some of the lesions originally classified as proliferative foci (neoplastic nodules) were ultimately classified as foci of cellular change due to lack of compression of surrounding parenchyma.


Terry A. Jackson, DVM, PhD
Diplomate, American College of
Veterinary Pathologists


Date

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