

US EPA ARCHIVE DOCUMENT

8-10-90

008368

(EXCERPT)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sulfosate - EPA File Symbols 10182-FTT and 10182-ETA
(PP#9F3796) - Sulfosate in/on Corn - Touchdown 4LC
and Touchdown Concentrate - Additional Toxicology
Information and Partial Evaluation of Data

Caswell No.: 893C
Project No.: 0-0523
Record Nos.: 162448, 162449,
250410

FROM: William Dykstra, Reviewer *William Dykstra 8/10/90*
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Roger Gardner, Acting Section Head
Review Section I *Roger Gardner 8-10-90*
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Requested Action

Review submitted toxicology data in support of tolerance
request for use of sulfosate in/on corn.

Conclusions and Recommendations

1. The supplemental information to the 2-year combined
chronic toxicity/oncogenicity studies in rats and mice
are adequate to upgrade the core-supplementary status
of those studies to core-guideline.

118

1/9

-2-

2. The 1-year dog study can be upgraded to core-minimum data and supports the registration.
3. The following submitted studies have been sent to Dynanac for review:

<u>Study</u>	<u>Review Hours</u>
1. 21-Day Dermal Pat	24
2. Acute Inhalation	4
3. Metabolism (rat)	24
4. 3-Month Dog	120
5. 3-Month Pat	120
Total	292

4. The company response to the review by Dr. Chen of the mouse micronucleus mutagenicity study has been transmitted to Dr. Chen for further comment.
5. Following resolution of items 2, 3, and 4, Toxicology Branch (TB) will evaluate the tolerance request for sulfosate in/on corn.

Review

I. TWO-YEAR COMBINED CHRONIC TOXICITY/ONCOGENICITY STUDIES IN RATS AND MICE

A. Supplemental Information

MRID Nos. 412099-07 and 412099-05; histopathology of individual animals with codes for individual animals.

1. T-11813; Addendum to Final Report of 2-Year Chronic Toxicity and Oncogenicity Dietary Study with SC-0224 in Mice; prepared by ICI Americas.
2. T-11082; Addendum to Final Report of 2-Year Chronic Toxicity and Oncogenicity Dietary Study with SC-0224 in Rats; prepared by ICI Americas.
3. Dictionary Codes for Histopathology Reports (hand carried on March 22, 1990 by Barbara Kaminski, ICI Americas) (attached).

B. Discussion

The January 5, 1988 review by W. Dykstra of the two 2-year chronic studies concluded the following:

"The 2-year rat feeding is considered a supplementary study. Evaluation of individual rat pathology sheets (Appendix N) did not provide a clear indication that tissue masses identified in the antemortem examination (Appendix I) and noted in the postmortem gross necropsy (Appendix L) were further evaluated microscopically. These deficiencies are required to be resolved." [End of quotation.]

"The 22-month mouse feeding study is considered a supplementary study. The tissue masses listed in Table I (clinical observations) and Table I (necropsy observations) were not clearly identified in the histopathology observations (Table V) as being histologically examined. This deficiency has to be resolved." [End of quotation.]

C. TR Conclusion

In the recent submission (MPID No. 412099-01), ICI stated that "in volumes 7 through 9, information will be submitted which we believe will greatly facilitate the tracking of tissue masses." [End of quotation.]

According to this submission:

"The following are being submitted for each study:

- "1. Trail for individual clinical mass observations.
- "2. Clarifications/annotations to trail.
- "3. Necropsy detail report by animal with codes.
- "4. Histopathology detail report by animal with codes.

"Necropsy and histopathology detail reports by animal were included in the original reports without codes. In the coded section to the extreme right of the enclose printouts, lesion numbers are listed which will clarify our tracking system. The Trail for Individual Clinical Mass Observation is an ancillary table prepared for EPA convenience." [End of quotation.]

-4-

The only data received by TP at this time is item 4: Histopathological detail report by animal with codes for each study.

Additionally, the dictionary code, which was hand delivered, provides codes only for the individual histopathological findings for each animal in the addenda. A check between the original histopathological report and the newly submitted histopathological addendum, by using the dictionary code, shows that the original histopathological findings and the histopathological findings in the addenda are the same. Therefore, the coded information in the histopathological addenda can be verified.

However, items 1, 2, and 3 listed above of ICI's present submission are required to be submitted to complete the evaluation of tracking the tissue masses. In response to this situation, telephone communication on August 1, 1990 with Dr. Ann Manley, Toxicologist with ICI, provided the correct MRID Numbers for completing the evaluation of the 2-year rat and mouse studies. The MRID Numbers are 412099-05 (Rats) and 412099-07 (Mice). These MRID Numbers contained the individual animal data for tissue masses and gross necropsy findings for all rats on the study.

Analysis of randomly selected individual male and female rats and mice for tracking of tissue masses to gross necropsy findings to histopathological findings showed that the tracking of tissue masses could be correctly accomplished. This issue is considered resolved and the 2-year rat and 2-year mouse studies can be upgraded to core-guideline.

II. TWELVE-MONTH DOG STUDY

A. HED Review

Classification of Data: Supplementary

Deficiencies: The MTD was not employed for this study. The volume of urine for all animals at the treatment intervals was missing in this study report. Historical control data are needed to evaluate the incidence of abnormal protrusion of pituitary and the incidences of hamartoma and dermal histiocytoma of pinna described in this study.

-5-

P. ICI Response to MTD Issue"Dose level selection in dog studies.

"Stauffer Chemical Co. performed three toxicology studies on SC-0224 in dog.

"In the 28-day gavage study (ICI Reference Vol. 6), 8 doses of the technical grade active ingredient of 150 mg ai/kg gave rise to death within 3 days. The highest dose which proved to be sustainable over a 28-day period was 75 mg ai/kg/day. Emesis was evident at this dose in many of the animals dosed probably resulting in a lower dose being actually received.

"The 90-day study (ICI Reference Vol. 4) used a slightly lower top dose of 50 mg/kg, one third of the dose at which deaths had occurred in the preliminary study and two thirds of the dose producing emesis over 28 days. Emesis was again recorded at 50 mg ai/kg in the early part of this study along with increased salivation. There were no other treatment-related effects of toxicological significance in the study and a NOEL was established as the middle dose of 10 mg ai/kg/day.

"The gavage dose levels were employed in the one year study (EPA MPID No. 40214005), probably in the expectation of increased toxicity over the extended dosing period. In the event, no signs of toxicity including no emesis was observed in the study.

"While it cannot be argued that 50 mg ai/kg/day was a maximum tolerated dose in the one-year study based on evidence of toxicity in that study, 50 mg ai/kg/day did produce emesis in the 90-day study. Furthermore, 75 mg ai/kg/day produced significant and sustained toxicity over the 28-day period of the first study.

"50 mg ai/kg/day is therefore very close to the MTD in the one year study and 75 mg ai/kg/day would probably have not been sustainable over one year."
[End of quotation.]

C. TB Conclusion Regarding the MTD

TB concurs with ICI that 50 mg/kg/day was appropriately selected based on preliminary findings and although the HDT did not produce chronic effects, TB concludes that the 1-year dog study is acceptable as core-minimum data on the basis of the MTD issue.

III. URINE VOLUME ABSENCE ISSUE

A. ICI Response

"Urine Volumes. Urine volumes were not measured in this study. Because of other normal findings in the study, there is no reason to believe that urine volumes would provide evidence for toxicity. Microscopic examination of kidneys showed no treatment-related changes in either sex. Normal background changes including presence of cysts, interstitial inflammation, mineralization and cytoplasmic vacuolization in proximal tubules were evident. Clinical laboratory parameters indicative of kidney function, including electrolyte levels, urinalyses, BUN and creatinine showed no consistent changes suggestive of a treatment effect." [End of quotation.]

B. TB Conclusion

TB concurs with the ICI explanation and concludes that the absence of urine volume measurement is of no toxicological significance in light of the available data.

IV. HISTORICAL CONTROL DATA ARE NEEDED TO EVALUATE THE INCIDENCES OF ABNORMAL PROTRUSION OF PITUITARY AND THE INCIDENCES OF HAMARTOMA AND DERMAL HISTIOCYTOMA OF PINNA

A. ICI Response

"Historical Control Data for Microscopic Findings. In this study, the diagnosis of mucocele in the pituitary was used to describe cyst or cyst-like spaces containing an amorphous, basophilic to lightly eosinophilic, often wispy material suggestive of mucus. Mucoceles were universally located in the anterior pituitary (pars distalis) and occasionally extended to the hypophyseal (Rathke's) cleft. They were lined by flattened to cuboidal/columnar, pseudostratified, focally ciliated epithelium (see photographs #1 and 2). Analogous terms (used in other studies at the Environmental Health Center) include: cyst, cystic change, cystic dilatation of craniopharyngeal duct remnants, craniopharyngeal duct remnant, mucus cysts of craniopharyngeal duct and dilatation craniopharyngeal duct. Cysts of embryologic craniopharyngeal duct origin are frequently found in the dog pituitary gland. They have been reported to have incidences as high as 53% (Jones et al., 1983;

-7-

Jubb et al., 1985). Their presence and dose group distribution in this study is misleading and has no relationship to administration of SC-0224.

"The following is a tabular summary of historical control data from dog studies conducted at this facility:

"Historical Control Incidences of Pituitary Lesions Analogous to Mucocele in Beagle Dog Studies Conducted at Stauffer Chemical's - Environmental Health Center.

<u>Study</u>	<u>Duration</u>	<u>Pathologist</u>	<u>Lesion Name</u>	<u>Incidence Males</u>	<u>Incidence Females</u>
T-11986	3 mo	Zwicker	cvst	0/4 ^a	1/4
T-11982	3 mo	Zwicker	cvstic change (used when cysts multiple) cyst	1/4	1/4
T-11002	3 mo	Thomassen	cystic dilatation of cranio- pharyngeal duct remnants	0/6	0/6
T-10125	3 mo	Thomassen	craniopharyngeal duct remnant	1/6	0/6
T-12625	1 yr	Taylor	mucus cyst craniopharyngeal duct (used when presence of mucus)	1/5	
			cyst pars distalis (used when no contents to cvst)		3/5
			dilatation, cranio- pharyngeal duct (used when ciliated epithelium present and not distended enough to be diagnosed cyst)		1/5

^aNumerator = # of animals with finding; denominator = # of animals in which pituitary gland was examined.

<u>Study</u>	<u>Duration</u>	<u>Pathologist</u>	<u>Lesion Name</u>	<u>Incidence Males</u>	<u>Incidence Females</u>
T-12723	1 yr	Taylor	cyst pars distalis	0/5	2/5
T-12969	6 mo	Zwicker	cystic change (used when cysts were multiple)	0/4	
			cyst	0/4	3/4
T-11872	3 mo	Turnier	cvst	1/4	0/4

"Canine cutaneous histiocytoma (see photographs #3 and 4) is a benign, non metastasizing tumor unique to the dog. It is relatively common and occurs approximately 50% of the time in dogs under 2 years of age with no sex predisposition. The pinna is the most frequently site of involvement followed by the skin of the distal forelegs and forefeet. The majority of histiocytomas spontaneously regress (Moulton, 1978). At the Environmental Health Center we have encountered it only once before in a low dose female dog of another study. This mass was also present on the pinna. The presence of two histiocytomas (on the pinna) both of which were in the high dose (50 mg/kg/day) (1 male, 1 female) animals in T-11075 were chance observations unrelated to SC-0224 administration.

"Hamartoma is a non-neoplastic malformation composed of an abnormal mixture of tissue elements or an abnormal proportion of a single element that is normally present in that site. In this study the term hamartoma was used to describe the focal, nodular presence of an abnormal number of follicular and adnexal structures in the skin of the ear of a 2 mg/kg/day male dog (see photograph #5). The term has not been previously used in a dog study conducted at this laboratory." [End of quotation.]

"References

Tumors in Domestic Animals
 Edited by Jack E. Moulton
 University of California Press
 Berkeley, Los Angeles, London 1978 pp. 24-26.
 Endocrine System
 Monographs on Pathology of Laboratory Animals sponsored
 by the International Life Sciences Institute
 Edited by T.C. Jones, U. Mohr, P.D. Hunt

7

Springer - Verlag New York 1983 pp. 115-117, 161-163.
Pathology of Domestic Animals III ed Volume 3
K.V.F. Jubb, Peter C. Kennedy, and Nigel Palmer
Academic Press, Inc., New York 1985 pp. 244-245."
[End of quotation.]

B. TB Conclusions

TB concurs with ICI and concludes that the lesions of concern were not compound-related based on the available information.

Summary: The 1-year dog study can be upgraded to core-minimum status.

Note: The five photographs referred to in the ICI response to these pathology issues are not included with this memorandum.

V. DYNAMAC REVIEW

Review Hours

A. 21-Day Dermal Rat	24
B. Acute Inhalation	4
C. Metabolism (rat)	24
D. 3-Month Dog	120
E. 3-Month Rat	120
	<u>120</u>
Total Tech Hours	292

The Dr. Chen review of the mouse micronucleus mutagenicity assay and the ICI Company response were sent to Dr. Chen on March 26, 1990 - 24 tech hours.

Attachment