Tox Rev 000262-OK

DATE: August 21, 1978

SUBJECT: Roundup - glyphosate; Evaluation of Validation of I.B.T. B-546: 2-year Chronic oral toxicity study with CP67573 in Albino Rats E.P.A. Reg.#524-30 Caswell #: 661A

FROM: William Dykstra, Ph.D. WHO 8/21/78
Toxicology Branch

TO: Robert Taylor (25)

THRU: Acting Deputy Chief E 8/21/78
Toxicology Branch

Recommendations:

1. Regarding I.B.T. B-564: 2 year chronic oral toxicity study with CP67573 in Albion rats, the chronic oral toxicological results from the validated report do not impact adversely on the original TB review which concluded that 100 ppm in the diet is the NOEL for glyphosate. The study is acceptable as core minimum data as a chronic toxicity study.

2. Since the validation does not include detailed histopathology for "concurrent controls" (why are they reported?), the small number of animals examined histologically in control and test groups and the loss of 70 animals from this study, TB cannot firmly conclude that glyphosate has or has not an oncogenic potential. The oncogenic aspect of the study is inadequate and does not support the registration. The oncogenic potential of glyphosate needs to be repeated according to protocols which require that all tumors and tissues of all animals of all groups be examined histologically.

3. If enough animals survived throughout the study they should be examined histologically for tumors and the results submitted together with the validation of the present results. This new information may provide valid information of the oncogenic potential of glyphosate.

Review:

1. Roundup; BTL 71-32, I.B.T. B-564: 2-year chronic Oral Toxicity Study with CP67573 in Albino Rats.

Note: The ADI & MPI for glyphosate are based on the NOEL of 100 ppm from this study.

a. Original Toxicology Branch Review; PP 5F1536; reviewed by D. Reisa, Ph.D. ; 1/22/75;

50 male and 50 female rats (Charles River Strain) were assigned to the control group and to each of 3 dose levels (30, 100 and 300 ppm). No abnormalities were noted in any of the following parameters which could be attributed to the ingestion of glyphosate: body weights, food consumption, mortality, behavioral reactions, hematology, blood chemistry,

urinanalysis, gross pathology and organ weights. Necropsies were performed on all post-mortem animals, on all sacrificed animals and all animals surviving the 24 month test period. Histological examination was conducted on 10 male and 10 female each from the control and highest dose level. Tumors and tissues with signs of possible tumor formation were submitted for histopathological examination and classification. In addition, the livers of animals in all dosages groups were examined, particularly for lipid.

Histological evaluation revealed a treatment-related increase in the incidence, in the degree of tabular involvement, and in the relative amount of lipid in the liver cells of the 300 ppm group. The amount of lipid in the livers of the 30 and 100 ppm groups appeared to be comparable to that of controls. No compound-related increase in tumor type or number was noted. Those tumors which were found were judged to be normal for rats of this age and strain and appeared in the control as well as the experimental groups. The NEL for the 2-year rat study is, 100 ppm. The effect at the next highest dose (300 ppm) is the presence of lipid vacuoles within liver cells.

b. Package of materials relating to validation of I.B.T. no. B-564 BTL-71-32, submitted in support of Registration no. 524-308, as follows.

1. Certification statement signed Monte C. Throdahl, Monsato company.

2. Exhibit A- Curriculum Vitae of G.L. Wesp, Ph.D.

3. Exhibit B- Curriculum Vitae of G.J. Levinskas, Ph.D.

4. Exhibit C- Audit Statement of G.L. Wesp, Dec. 15, 1977
   I. Animal Accountability and Mortality

In summary, there are 66 animals whose death dates can only be approximated by the dates of their disappearance from the individual body weight tables. The histopath logistics sheet in the raw data, which if complete and correct, would permit construction of an accurate mortality table are incomplete and contain a few errors, viz.

Number of animals
Not on sheets (sheets with death or necro dates)

Group	Male	Female
VC	5	11
T-I	12	8
T-II	6	6
I-III	8	9

64 Total +
2 death dates omitted on sheets

After resolving conflicting death dates or omitted death dates on the histopath Logistics sheets by referring to the body weight tables and some scattered observations in the notebooks, a frequency distribution of deaths was tabulated for comparison with that on page 17 of the lab report. The totals for numbers dead and tested were in agreement for all groups. However in 39 out of 64 entries the audit tabulation disagreed with the report on the number of deaths in a particular time period.

The customary Pathology observation sheets (one for each animal and containing both gross and micro observations as well as death dates) are not available except for two animals. Histopath Report sheets which give the micropathology for each animal so examined, but no death dates. Mortality Data to be re-evaluated by TB.

II. Body Weight Tables

Several errors were noted. Body weight data needs to be re-evaluated by TB.

III. Food Consumption

Several errors were noted. Food consumption data needs to be re-evaluated by TB.

IV. Hematologic DATA

Few errors were noted. Audit does not impact on original TB review. Check microfiche.

V. Clinical Blood Chemistry DATA

Few errors were noted. Audit does not impact on original TB review. Check microfiche.

VI. Urine Analysis DATA

Few errors were noted. Audit does not impact on original TB review.

VII. Organ Weight DATA

No errors were noted. Audit does not impact on original TB review.

VIII. Histopathologic Changes

Several added observations and changed observations in Audit require complete re-evaluation of histopathology by TB.

IX. Tumor Findings and Incidences

Several added observations and changed observations in Audit require a complete re-evaluation of tumor type and incidence

by TB. Compare to historical data for Charles River Strain albino rats.

5. Exhibit D- Validation statement of G.J. Levinskas
NOTE: Quoted from exhibited material.

Summary: Records exist to substantiate body weights, food consumption, hematology, clinical chemistry, urinalysis and organ weight data presented in the reports of this study. Of the 200 animals in this study, records document the date of death of 134 animals and indicate gross autopsies were performed on 130 animals.

Thus adequate data exist to suppport a tentative conclusion that this product does not induce a carcinogenic or tumorigenic response in rats even though the absence of some records procludes drawing a firm conclusion regarding the potential carginogencity of this product. TB needs to evaluate this summary.

Results of Audit

1. Animal Accountability and Mortality
It is not possible to verify that the subtotals are correct within each specified 3 month period according to Auditor.

2. Body Weights: Auditor states discrepancies were of no consequence.

3. Food Consumption: Auditor states rats fed test diets ate amounts of food comparable to those on a control diet.

4. Hematology: Auditor states hematologic data are supported by the records.

5. Clinical Chemistries: Auditor states clinical chemistries agree with raw data and report.

6. Urinalysis: Auditor ststes discrepancies were of no consequence

7. Organ Weight DATA: Auditor states raw data on computer printout agree with final report.

8. Gross and microscopic pathology: Auditor states that despite several changed observations and additions that raw data and report appears to be valid despite the changes made in the tabulation of microscopic findings. No records are available for 70 animals in the study to determine whether relevant gross autopsy findings were made and whether or not tissues were preserved. These animals fall into the following groups of the study:

Animals Not Listed Unaccounted Animals		Animal Number	Totals
Control	Males	(1-50)	5
28, 31, 37, 44, 46			
	Females	(51-100)	11
55, 62, 63, 64, 68, 75, 90, 91, 93, 95, 100			
T-I	Males	(101-150)	12
103, 105, 109, 115, 126, 130, 138, 140, 147, 149, 122, 135			
	Females	(151-200)	8
153, 159, 162, 169, 171, 179, 192, 199			
T-II	Males	(201-250)	6
202, 214, 236, 237, 247, 239			
	Females	(251-300)	6
262, 265, 268, 272, 263			
T-III	Males	(301-350)	8
318, 325, 331, 332, 335, 346, 336, 343			
	Females	(351-400)	9
359, 375, 381, 382, 384, 390, 392, 388, 395			

Animals not listed in Histopath Logistics.	65
Animals in Histopath Log but no necro date	2
Animals with no necro dates other than sometime after last body weight measurement.	
	67

NOTE: Audit states that total is 66

6. Exhibit E- Responses to E.P.A. questions are typed onto E.P.A. TDAP report.

7. Exhibit F- Stability Reports. Validation does not adversely impact on original TB review.

8. Marked copy of IBT Report No. B-564 showing descrepancies

9. Microfiche copy of data supplied by IBT.

10. Toxicology Branch Evaluation of Impact of Monsanto Validation to toxicological review of PP 5F1536 (D. Reisa, Ph.D. 1/22/75).

A. Body Weight DATA

Review of corrected Coalidated data does not adversely impact on original TB review.

B. Food Consumption DATA

Review of conected (Validated) data does not adversely impact on original TB review.

C. Histopathological DATA

1. Added observation * and changed observation **

SEE PAGE 5-A for chart.

Group	Sex	Animal number	Findings
control	M	5	lung-absecesses *
		12	No changes
		21	* Testis-degeneration
Tumor			* Testis-interstitial cell tumor
			** Kidney-focal lymphoid infiltration
Tumor			* Lung
Tumor			* Spleen
Tumor			* lymph node
Tumor			* Bone marrow
Tumor		22	Skin-Dermal fibroma
		29	No change
Tumor		30	* Lung-reticulum cell sarcoma
Tumor			* Liver-hepatoma
Tumor			* Testis-focal degeneration
Tumor			* Adrenal-medullary adenoma
			* Eye-retinal degeneration
		35	* Liver-focal necrosis
Tumor		43	Skin-fibroma
control	F	52	* Lung-chronic murine pneumonia
			* Pituitary-hyperplasia
		58	No changes
Tumor		66	* Skin-fibroademona in mammary
		67	* Pituitary-hyperplasia
Tumor		69	* Pituitary-adenoma
Tumor			Skin-fibroadenoma of mammary
		72	No change
Tumor		76	* Lung-reticulumcell sarcoma
		77	** Liver-fibroadenoma of mammary gland
control	F	85	* Liver-bile duct proliferation
Tumor		88	* Skin-fibroadenoma of mammary gland
		97	* Lung-chronic pneumonia
			* Lung-abscesses
			* Pituitary-hyperplasia
			* Adrenal-hypervolemia
		99	* Kidney-chronic nephritis
			pituitary-hyperplasia
T-I	M	110	* Abdomen-retroperitoneal abscess
		118	* kidney-nephritis
			* pituitary-adenoma
		127	* pituitary-hyperplasia
			* urinary bladder-hyperplasia
			* urinary bladder-cystitis
Tumor			* adrenal-medullary adenoma
			* testis-degeneration
		137	* Lung-chronic pneumonia
		123	* Kidney-chronic nephritis
Tumor			* pituitary-adenoma

Group	Sex	Animal Number	Findings
T-I	F	151	* Lung-chronic murine pneumonia
			* Lung-bronchiectatic abscesses
			* pituitary-hyperplasia
			* Adrenal-hypervolemia
Tumor			* Skin-mammary fibroadenoma
		152	* pituitary-hyperplasia
			* Adrenal-hypervolemia
		154	* Lung-chronic murine pneumonia
			* Lung-bronchiectatic abscesses
			* pituitary-hyperplasia
			* Adrenal-hypervolemia
T-I	F	155	* Lung-chronic pneumonia
			* Lung-bronchi absc.
			* pituitary-hyperplasia
Tumor		158	* pituitary-adenoma
			* adrenal-hypervolemia
Tumor		172	* Liver-hepatoma
			* pituitary-hyperplasia
			* adrenal-hypervolemia
Tumor			* Skin-mammary fibroadenoma
		174	* Adrenal-hypervolemia
		180	* lung-chronic mur. pneu.
			* pituitary-hyperplasia
			* adrenal-hypervolemia
		183	* pituitary-hyperplasia
			* adrenal-hypervolemia
		184	* lung-chron. mur. pneu.
			* lung-bronchiectatic abs.
			* Kidney-chronic nephritis
			* Stomach-edema
			* pituitary-hyperplasia
			* adrenal-hypervolemia
		186	* liver-chronic vacuolation
			* lung-chronic mur. pneu.
Tumor			* skin-mammary fibroid.
		187	* Kidney-chronic nephritis
			* pituitary-hyperplasia
		188	* Lung-chronic mur. pneu.
			* pituitary-hyperplasia
			* adrenal-hypervolemia
Tumor			* colon-fibroma
		193	* pituitary-hyperplasia
			* Adrenal-hypervolemia
Tumor			* Skin-mammary fibroadenoma

Group	Sex	Animal Number	Findings
T-I	F	195	* lung-chron mus. pneu.
			* lung-bronch. abs.
Tumor			* skin-mam. fibroad
T-II	M	210	* liver-focal cirrohis
			* lung-chron, mar. pneu.
			* lung-bronch. abs.
			* pituitary-hyperplas.
Tumor			* forestomach-papillomas
		223	* lung-chron, mur. pneu.
Tumor			* skin-mamm. adeno carcin.
T-II	F	253	* lung-chron. mur. pneu.
			* uterus-metritis
		254	* lung-chron. mur. pneu.
Tumor			* skin-mamm. fibroad
		270	* lung-chron. mur. pneu.
Tumor			* lymph nodes-retic sarc.
		276	* lung-chron. mur. pneu.
			* pituitary-hyperplasia
Tumor			* skin-fibromas
		280	* lung-chron. mur. pneu.
			* lung-bron. abs.
			* adrenal-hypervolemia
		285	* lung-chron. mur. pneu.
			* pituitary-hyperplasia
			* adrenal-hypervolemia
		286	* lung-chron. mur. pneu.
Tumor			* skin-mamm. fibroadenoma
		289	lung-chron. mur. pneu.
			pituitary-hyperplasia
			adrenal-hypervolemia
Tumor			skin-mamm. fibroaden
T-II	F	299	* skin-mamm. fibroad
T-III	M	303	* liver-hepatoma
			* thyroid-adenoma
Tumor		309	** lung-chron. mur. pneu.
			** kidney-chron. nephritis
		312	No changes
		326	No changes
		328	No changes
		329	No changes
		338	** Liver-fatty focal vacuolation
			** Liver-focal necrosis
		340	No changes
		344	No change
Tumor		345	* pituitary-adenoma

Group	Sex	Animal Number	Findings
T-III	F tumor	351	*Skin-mammary fibroadenoma
Tumor		352	*pituitary-adenoma
Tumor			*skin-mamm. fibroad.
		352	*lung-chron. mur. pneu.
			*liver-focal bile duct prolif.
			*pituitary-hyperplasia
		358	**lung-chron. mur. pneu.
		361	* lung-chron. mur. pneu.
			* liver-focal bile duct prolif.
			* liver-fatty cyto. vaculation
			* liver-cytoplas. vacuolation-hydrohic
			* pituitary-hyperplasia
Tumor		368	* skin-mamm. fibroadenoma
		377	* lung-chron. mur. pneu.
			* liver-cyt. vac. hydrophic
			* adrenal-hypervolemia
T-III	F	383	No change
		385	No change
Tumor		386	* adrenal-adenoma
Tumor			* skin-mamm. fibro.
Tumor			* skin-reticulum cell sar.
Tumor		389	* skin-mamm. fibroad.
Tumor		391	* skin-mamm. adenocar.
Tumor		396	* pancreas-islet cell adenoma

Conclusion from Histopathology Data (Validated) on impact of original toxicology review.

.Dose-related histopathology described as fatty cytoplasmis vacuolation of liver.

Control	Males	Females
T-I (30 ppm)	1/8 (.125)	5/13 (.38)
	1/5 .(.20)	5/15 (.33)
T-II (100 ppm)	0/2 (.00)	3/9 (.33)
T-III (300 ppm)	7/10 (.7)	10/13 (.76)

$$\frac{\text{* Number with lesion}}{\text{Number examined}} = \text{Frequency}$$

At 300 ppm, both sexes showed an increased occurrence of fatty cytoplasma vaculation of liver. However possible dose-related histopathological findings of this type may occurr in the low (T-F) and mid (T-II) dose groups if additional microscopic examination of all the liver tissue of all the animals available of all the dose groups is performed. No other histopathologic lesions were observed to occur at significant frequency in the high-dose group in comparison to the controls.

The memo of 6/29/77 from M. Quaife, Ph.D. states that the deficiency (lack of details of liver histopath findings) in T-I and T-II has been alleviated by the registrant. Therefore the validated data has not adversely impacted on the NOEL of 100 ppm. The I.R.T. No. B-564 is acceptable as core minimum data with respect to chronic effects. The NOEL is 100 ppm.

D. Tumor Findings and Incidence

Summary of Validated Tumor Findings and Incidence

	Males (Incidence)				
			(30ppm)	(100ppm)	(300ppm)
Type of Tumor	concurrent control	control	T-I	T-II	T-III
Reticulum cell sarcoma	0	1	0	0	0
Alveolar adenoma	0	1	0	0	0
papilloma (forestomach)	0	0	0	1	0
Islet cell adenoma (pancreas)	3	0	0	0	1
Chromophobe adenoma (pituitary)	2	0	0	0	0
Adenoma (pituitary)	0	0	1	0	1
Clear cell adenoma (thyroid)	2	0	0	0	0
Adenoma (thyroid)	0	0	0	0	1
Medullary adenoma (adrenal)	0	1	1	0	0
Interstitial cell tumor (testis)	0	1	0	0	0
Mammary and skin tumors	0	3	0	1	0
Hepatoma	0	1	0	0	1
Total Number of Tumors	7	8	2	2	4
Total Number of Animals Affected	7	6	2	2	2
Number of Animals examined	50	8	5	2	10

Summary of Validated Tumor Findings and Incidence
Females (Incidence)

Type of Tumor	concurrent control	control	T-I	T-II	T-III
Serosal Fibroma (cecum)	0	0	1	0	0
Cortical carcinoma (adrenal gland)	1	0	0	0	1
Islet cell tumor (pancreas)	2	0	0	0	1
Chromophobe adenoma (pituitary)	7	0	0	0	0
Adenoma (pituitary)	0	1	1	0	1
Adenoma (thyroid)	0	0	0	0	1
Hepatoma	1	0	1	0	0
Reticulum cell (sarcoma)	0	1	0	1	1
Uterine tumor	1	0	0	0	0
Mammary ans skin tumor	8	5	9	9	11
Total number of tumors	20	7	12	10	16
Total number of animals affected	16	5	7	6	8
Number of animals examined	50	13	15	9	13