US EPA ARCHIVE DOCUMENT

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

SEP 30 1988

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MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Glyphosate - EPA Registration No. 524-308 - Roundup - PP#8F3673 - Glyphosate in/on Corn - Tolerance Request and "Free Standing Summary"

Caswell No.: 661A
Project No.: 8-1090
Record No.: 229281/230208
Accession Nos.: 405594-01, 407671-01, 407671-02

FROM: William Dykstra, Reviewer William Dykstra 9/23/88
Review Section I
Toxicology Branch - Insecticide, Rodenticide Support
Health Effects Division (TS-769C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

THRU: Edwin Budd, Section Head
Review Section I
Toxicology Branch - Insecticide, Rodenticide Support
Health Effects Division (TS-769C)

Requested Action

Review 90-day rat feeding study, rat metabolism study, and request for tolerances for glyphosate in/on corn.

Conclusions and Recommendations

1. The 90-day rat feeding study is classified as "Acceptable (as a dose range-finding study)." The high-dose in the 90-day range finding study was 20,000 ppm. In the 9/11/87 memorandum of W. Dykstra to R. Taylor (attached), the high dose

of 20,000 ppm was accepted as the MTD for the 2-year chronic/oncogenic rat study.

2. The rat metabolism study is classified as Core Guideline data.

3. The requested tolerances may or may not be toxicologically supported (see below).

Background

Tolerances have been established for the combined residues of glyphosate (Roundup; N-[phosphonomethyl] glycine) and its metabolite aminomethyl phosphonic acid in several raw agricultural commodities (RACs) (40 CFR 180.364).

After review of all available evidence, the Agency decided to classify glyphosate as a "Class D Oncogen" and to request a repeat of the mouse oncogenicity study. Also, because of the large difference between the high-dose tested in the rat and mouse oncogenicity studies, the rat oncogenicity study was rereviewed. The rereview indicated that a maximum tolerated dose (MTD) may not have been reached in that study. Therefore, the Agency decided to also request a repeat of the rat oncogenicity study at doses high enough to reach an MTD.

The Agency's policy has been to establish new glyphosate tolerances if the resulting change in TMRC is < 1 percent. See item 3. on following page. However, any significant new registrations will be handled on a case-by-case basis and may not be granted until issues in the Glyphosate Registration Standard have been resolved. Monsanto Company has been notified of these conclusions and deficiencies.

Additionally, Toxicology Branch has concluded that the N-nitrosoglyphosate (NNG) content of glyphosate is not toxicologically significant (memorandum of W. Dykstra dated November 5, 1987) and that the levels of N-nitrososarcosine (NSAR) and N-nitro-N-methylaminomethyl phosphonic acid (NNMAMP) in Polado® are not of toxicological concern (memorandum of W. Dykstra dated April 26, 1988).

Review

1. Section F

Monsanto requests that the following tolerances be established for glyphosate in/on corn in 40 CFR 180.364.

Corn grain . . . . 1.0 ppm

Corn fodder . . . . 20 ppm

Corn forage . . . . 20 ppm

2. Calculation of the ADI

The ADI is based on the NOEL of 10 mg/kg/day in the 3-generation rat reproduction study. A hundredfold safety factor was used to calculate the ADI.

$$ADI = \frac{NOEL}{100} = 10 \text{ mg/kg/day} \times \frac{1}{100}$$

ADI = 0.10 mg/kg/day

The MPI is 6.0 mg/day for a 60 kg person.

3. The percent ADI utilized by published tolerances and the current tolerance and the percentage change in TMRC due to this request will be provided by a TAS analysis.

4. The formulation to be used is Roundup® Herbicide (EPA Registration No. 524-308). Inerts are cleared under §180.1001.

5. 90-Day Study of Glyphosate Administered in Feed to Sprague-Dawley Rats (Monsanto Laboratory Project I.D. ML-86-351/EHL 86128; November 30, 1987). MRID No. 405594-01.

Test Material - Glyphosate; lot XLG161; 95.21% purity; white powdery solid.

Methods - Randomized groups of 12 male and 12 female Sprague-Dawley rats (obtained from Charles River, Portage, MI) were administered, in the diet, concentrations of 0, 1000, 5000, and 20,000 ppm of test material for 3 months. The rats were 6 weeks old at initiation of dosing. The high-dose in the range finding study of 20,000 ppm was agreed to be the MTD for the chronic/oncogenic rat study as per memorandum of 9/11/87 (attached).

Food and water were available ad libitum. Fresh diets were prepared each week. Diet analyses were routinely performed to determine dietary concentrations.

All animals were observed twice a day for toxic signs and mortality. All animals were also given weekly detailed examinations for clinical signs and tissue masses. Body weights and food consumption were measured weekly. Ophthalmic examinations were performed on each animal at pretest and at termination of the study.

At the end of the study, the following clinical pathology determinations were performed on each animal:

Hematology - Red blood cell count, leukocyte count, platelet count, hematocrit, hemoglobin, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), leukocyte differential and reticulocyte count.

Blood Chemistry - Albumin, total protein, blood urea nitrogen, total bilirubin, direct bilirubin, chloride, globulin, glucose, glutamic pyruvic transaminase, alkaline phosphatase, glutamic oxaloacetate transaminase, inorganic phosphate, creatinine, cholesterol, calcium, sodium and potassium.

Urinalysis - pH, urine protein, blood, glucose, ketone, bilirubin, urobilinogen and specific gravity. Sediment from samples from control and high dose animals was examined microscopically.

All animals were necropsied and the kidney, liver, and testes (including epididymides) were weighed. The following organs and tissues were fixed in 10 percent neutral buffered formalin: adrenals, aorta, bone with marrow, brain, cecum, colon, duodenum, esophagus, eyes, Harderian gland, heart, ileum, jejunum, kidneys, lesions or masses, liver, lung (with mainstem bronchi), lymph node (mesenteric, submandibular), muscle (quadriceps femoris), nasal turbinates, nerve (sciatic), ovaries, pancreas, prostate, pituitary, rectum, salivary gland (submaxillary), seminal vesicles, skin (with mammary gland), spinal cord (cervical, thoracic and lumbar), spleen, stomach, testes with epididymides, thymus, thyroid/parathyroid, trachea, uterus (corpus and cervix), urinary bladder.

All tissues from the control and high-dose rats were examined microscopically. Additionally, the kidneys, livers, and lungs from the low- and mid-dose rats were also examined.

Statistical evaluation of the data were performed with $p < 0.05$ being significant.

Results - Diet analyses overall averaged 950, 4600, and 19,000 ppm for the low-, mid-, and high-doses, respectively. These levels corresponded to 63, 317 and 1,267 mg/kg/day for males and to 84, 404 and 1,623 mg/kg/day for females (based on actual body weights, food consumption and analyses of feed). There were no mortalities and no compound-related toxic signs. There were no compound-related effects in body weight for male and female rats during the study. Although body weight gain for mid-dose males was about 6 percent greater than controls, the increase was not statistically significant, nor dose-related, and was not considered compound-related.

Food consumption was comparable between control and treated groups of both sexes.

In males, there was a significant increase in mean number of WBC at 5000 ppm (mid-dose) in comparison to controls, but this finding was not dose-related and was not considered compound-related.

There was an increase in mean number of platelets at the high-dose in males in comparison to controls (867, 853, 906, and 932 in control, low-, mid-, and high-dose, respectively). Individual platelet values for high-dose males ranged from 582 to 1291 and were comparable to the range of controls (705 to 1152). The slight increased in platelet values for high-dose males were not considered compound-related.

In the absolute leukocyte data, there was an increase in the mean value of absolute neutrophils in the high-dose males (2.65) in comparison to controls (1.84), but examination of individual data showed that high-dose male rat #7 had a absolute neutrophil value of 15.0. In contrast, other high-dose male neutrophil values ranged from 0.6 to 4.1. These values were comparable to control male neutrophil values which ranged from 0.9 to 4.0. The slight increase in mean absolute neutrophil values in high-dose males was not considered compound-related.

The mean values of absolute lymphocytes were significantly increased in the low- and mid-dose

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levels of male rats (but were decreased at the high-dose) in comparison to controls. Individual lymphocyte values in males varied from 5.2 to 13.2 in controls, 6.9 to 13.7 in low-dose, 7.1 to 16.2 in mid-dose and 2.9 to 9.2 in high-dose. Since the individual values were comparable and the range for all groups were similar, the slight differences in the mean values were not considered toxicologically significant.

In female rats, there was a slight increase in the mean value of platelets in the high-dose in comparison to controls (809 in controls vs. 939 in high-dose). However, individual values in the controls varied from 575 to 1320 in comparison to the range of 659 to 1345 in the high-dose. Since the individual values in control and high-dose females were within a comparable range, the slight increase in mean value of platelets in the high-dose was not considered toxicologically significant. Other hematological findings between control and treated groups of both sexes were comparable.

With respect to clinical chemistry data, there was a statistically significant increase in mean glucose values for mid- and high-dose males in comparison to controls. Additionally, the low-dose males also had elevated mean glucose values in comparison to controls. The mean glucose values in males were 175, 184, 248, and 205 in the control, low-, mid-, and high-dose groups, respectively. The individual values for controls ranged from 147 to 200 mg/DL, the low-dose ranged from 154 to 214 mg/DL, the mid-dose ranged from 207 to 306 mg/DL and the high-dose ranged from 145 to 271 mg/DL. However, there was only one value above 200 mg/DL in controls, two values were above 200 mg/DL in the low-dose, all values were above 200 mg/DL in mid-dose and six values were above 200 mg/DL in the high-dose.

These findings may be possibly compound-related. In the absence of historical control data for comparison from Monsanto, historical control data from a different lab available to the reviewer shows glucose values in 3-month-old male rats ranging from 81 to 131 mg/DL. This historical range is somewhat lower than the concurrent control range from Monsanto.

Other possibly compound-related findings in male and female treated groups in comparison to their respective

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controls occurred in the mean phosphorus and potassium values. In males the mean values (mg/DL) for phosphorus were 8.4, 9.4*, 9.2, and 9.4* (*p < 0.05) in the control, low-, mid-, and high-dose levels, respectively.

In females, the mean values were 7.2, 9.2**, 9.1**, and 8.4** mg/DL in the control, low, mid, and high-dose levels, respectively (**p < 0.01).

With respect to potassium in males, the mean values were 6.9, 7.5, 8.2*, and 8.0* meq/L in the control, low-, mid-, and high-dose groups, respectively (*p < 0.05).

In females, the mean potassium values were 7.4, 8.4*, 8.4, and 8.1 meq/L in control, low-, mid-, and high-dose groups, respectively (*p < 0.05). As expected, there was a shift to higher individual potassium and phosphorus values in treated male and female rats in comparison to controls.

On the basis of historical controls available to the reviewer (not from Monsanto), the mean for phosphorus was 7.7 mg/DL for males and 6.8 mg/DL for females. The means for potassium were 7.0 meq/L for males and 6.4 meq/L for females.

It can be seen that the mean values for phosphorus in males and females from the glyphosate study (including controls) are higher than these historical controls. With respect to potassium, the mean values for the treated males and females also exceed the historical controls.

Additionally, high-dose males had an elevated mean BUN and alkaline phosphatase value in comparison to mean control values. Evaluation of individual data showed that high-dose male rat #7 had a BUN value of 193 mg/DL. In comparison to other high-dose male values ranging from 10.9 to 18.3 mg/DL, the increased high-dose BUN mean was due to this single male value.

Similarly, this same rat had an alkaline phosphatase value of 752 Iu/L. In contrast, the range of alkaline phosphatase values for other high-dose males was 134 to 345 Iu/L. Therefore, the elevated mean alkaline phosphatase in the high-dose males was due to a single animal.

There were no compound-related effects observed in individual urinalysis data of male and female rats.

Glyphosate toxicology review

Page_____ is not included in this copy.

Pages 8 through 9 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

There were no compound-related ophthalmic findings. There were no compound-related effects in gross findings or organ weights in male or female rats.

Histologically, three high-dose male rats (#2, #8, and #10) had mild to moderate acute inflammation of the pancreatic islets which extended into the acinar parenchyma in two of the rats. No lesions of this type were observed in the controls. The blood glucose levels of these three high-dose rats were 145, 215, and 180 mg/DL. Therefore, a relationship of glucose levels and pancreatic lesions was not apparent.

Conclusion - Possibly compound-related findings in male rats are increased serum phosphorous and potassium values at 1000, 5000, and 20,000 ppm; increased serum glucose values at 5000 and 20,000 ppm; and increased serum BUN and alkaline phosphatase values at 20,000 ppm. In addition, histopathologic lesions observed in the pancreas of 20,000 ppm male rats may have been compound-related. The pancreas of male rats was not examined at lower dosage levels. Possibly compound-related findings in female rats are increased serum phosphorous and potassium values at 1000, 5000, and 20,000 ppm.

In as much as clinical chemistries were performed only once during the entire study and on a small number of animals, and since the pancreas was not histologically examined in the low- and mid-dosage levels groups, it is difficult to conclude whether or not these findings are truly attributable to the test material on the basis of this study alone. Since this study was intended to be a dose range-finding study for a subsequent chronic feeding/oncogenicity study (which the registrant has already agreed to perform), it is not necessary at this time to make firm conclusions about the results in the 90-day study. When the results of the chronic study become available, data from both studies will be used to make conclusions regarding compound-related effects following subchronic and chronic oral administration of glyphosate to rats.

Classification - Acceptable (as a dose range-finding study).

6. The Metabolism of Glyphosate in Sprague-Dawley Rats; Part I. Excretion and Tissue Distribution of Glyphosate and Its Metabolites Following Intravenous and Oral Administration.

Part II - Identification, Characterization and Quantitation of Glyphosate and Its Metabolites After Intravenous and Oral Administration.

[Monsanto Project No. 86139; Study No. MSL-7215; March 23, 1988 (Part I); Monsanto Project No. 9-23-760.20-206376; Study No. MSL-7206; February 1988 (Part II).] MRID Nos. 407671-01 and 407671-02.
Test Material - "The test material for this study was a mixture of unlabeled ^{12}C and labeled ^{14}C glyphosate [N-(phosphonomethyl)glycine]. The ^{14}C glyphosate, labeled in the phosphonomethyl carbon, possessed a radiochemical purity of greater than 99%. The unlabeled ^{12}C glyphosate had a chemical purity of 99.8%.

"The radiochemical specific activities of the glyphosate samples used for dosing were as follows:" [End of quotation.]

	dpm/ug
Groups 1 and 2	5.285×10^4
Group 3	5.292×10^4
Group 4	5.263×10^2
Group 5	5.285×10^4
Group 6	5.294×10^4
Group 7	5.289×10^4

Methods - Seven groups of Sprague-Dawley rats (3 to 5/sex/group) were given a single oral or intravenous dose of C-14 glyphosate (radiochemical purity > 99%). Expired air, blood, urine, and feces were collected during a 7-day postdosing period for analysis of radiolabeled content by liquid scintillation counting (LSC). Urine and feces (Group 3 to 6) were also specifically analyzed for glyphosate and its metabolites using two different high pressure liquid chromatography (HPLC) techniques and LSC. Dosing regimens and sample collection for each group are shown below:

Group	Dose (mg/kg)	Route	Samples Collected
1	10	Oral	Urine, feces, and expired air at 6, 12, and 24 hours
2	10	Oral	Blood at .25, .5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours
7	10	Intravenous	Same as above
3	10	Intravenous	Urine and feces at 6, 12, and 24 hours
Group	Dose (mg/kg)	Route	Samples Collected
			and daily thereafter; organs, tissues, and carcass at day 7
4	1000	Oral	Same as above
5	10	Oral	Same as above
6	10[a]	Oral	Same as above

[a]Animals were preconditioned with unlabeled glyphosate (10 mg/kg/day) for 14 days prior to the single dose of labeled glyphosate.

Results

a. Elimination of Glyphosate

As can be seen in Table I, feces was the major route of elimination of the oral dose of groups 1, 4, 5, and 6. Urine was, as expected, the major route of elimination for the intravenous dose of group 3.

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Table I

Percent of Administered Radioactivity in Excreta[a]

Group	Dose (mg/kg)	Route	Feces		Urine	
			Male	Female	Male	Female
1	10	Oral	68.6	70.4	12.2	11.1
3	10	Intravenous	4.5	8.3	79.0	74.5
4	1000	Oral	68.9	69.4	17.8	14.3
5	10	Oral	62.4	69.4	28.6	22.5
6	10[b]	Oral	61.0	70.9	30.9	23.1

[a]Not corrected for total recoveries.
[b]Animals were preconditioned with unlabeled glyphosate (10 mg/kg/day) for 14 days prior to the single dose of labeled glyphosate.

The overall recoveries of radioactivity for the males and females of the different groups are shown in Table II.

Table II

Overall Recovery of Excreted Radioactivity

Group	Percent	
	Males	Females
1	81.4	82.2
3	86.0	85.3
4	90.9	92.1
5	92.8	94.2
6	93.3	96.3

The overall recovery of excreted radioactivity in the various groups was comparable between sexes as shown in Table II.

b. Radioactivity in Organs, Tissues, and Carcass

Results from group 3 (intravenous) showed that males retained more radioactivity (0.09%, than females (0.05%), although both sexes were quite low. The highest levels of radioactivity were bone > tail > carcass > liver > lung.

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In group 4 (high dose, oral), a very small amount of radioactivity remained in the stomach and small intestine, carcass, bone and organs at 168 hours after dosing. Bone had the highest radioactivity (30.6 and 19.7 ppm, for males and females, respectively), followed by spleen, liver, kidney, stomach, small intestine, lung and thyroid. The levels were higher in males than females.

In group 5 (low dose, oral), the results were similar to group 4. Very little radioactivity remained in the organs and tissues after the 168-hour elimination period.

Bone had the highest level of radioactivity (0.552 and 0.313 ppm, for males and females, respectively). Males had higher levels of radioactivity than females.

In group 6 (14 daily doses at 10 mg/kg/day followed by one C^{14}-dose at 10 mg/kg), glyphosate was cleared from the body effectively and only a small amount of the dose (0.49% and 0.32% for males and females, respectively) remained in the tissues. The highest level was found in bone (0.748 ppm and 0.462 ppm in males and females, respectively).

c. Percent Absorption by Oral and Intravenous Routes

Based on analysis of radioactivity in whole blood after oral (group 2) and intravenous (group 7) administration, the oral absorption of glyphosate was 30.3% for males and 35.4% for females. By intravenous methods, the absorption of glyphosate was 36.2% for males and 30.2% for females.

d. Rates of Elimination of Radioactivity

Based on analysis of radioactivity in urine and feces and using the "sigma-minus" plotting method, males and females of groups 3 to 6 had alpha half-lives of 2.11 to 7.52 hours and 5.00 to 6.44 hours, respectively. The beta half-lives of males and females in these groups ranged from 69.0 to 181 hours for males and 79.9 to 337 hours for females.

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e. Metabolism of Glyphosate (Part II)

Data from group 1 rats showed that less than 0.27 percent of the dose was expired as CO_2 within 24 hours. Glyphosate, per se, was the highest radiolabeled material found in the urine and feces of groups 3 to 6. The minimum level of glyphosate extracted from urine and feces was 97.5 percent. Aminomethylphosphonic acid (AMPA) was found in the excreta of animals from group 5 and 6 at levels of 0.2 to 0.3 percent and 0.2 to 0.4 percent, respectively. No detectable AMPA metabolite was found in group 3 (intravenous) and group 4 (high dose, oral). There were no other metabolites of glyphosate formed.

Conclusions - The results show that 30 to 36 percent of orally administered glyphosate is absorbed. Glyphosate is excreted unchanged in the feces and urine (97.5%, minimum). The only metabolite formed is AMPA, in the excreta, at low levels ($\leq$ 0.4%). Less than 1 percent of the absorbed dose remains in tissues and organs, primarily bone. Repeated dosing with glyphosate at 10 mg/kg does not significantly change the metabolism, distribution, or excretion of glyphosate.

Classification - Core-Guideline

g. "Free Standing Summary"

1) The data available in considering the tolerances include:

o Rat Oral LD_{50}	4320 mg/kg (M+F)
o Rabbit Teratology	Negative - 350 mg/kg (HDT)
o Rat Teratology	Negative - 3500 mg/kg (HDT)
o 3-Generation Rat Reproduction	NOEL = 10 mg/kg/day
o 26-Month Rat Feeding Study*	Oncogenic potential: Negative at 31 mg/kg/day; NOEL = 31 mg/kg/day (HDT)

o 2-Year Oncogenic Mouse Feeding Study*	Oncogenic potential: Indeterminate at 30,000 ppm (HDT)
o Multitest Mutagenic Studies	Negative
o 1-Year Dog Study	NOEL = 500 mg/kg/day

*Studies to be repeated.

2) No data are currently lacking. However, the Agency has requested a repeat of the mouse oncogenicity study. The Agency has also requested a repeat of the rat oncogenicity study at doses high enough to reach an MTD.

3) The registrant has been informed of these repeat studies.

4) Tolerances have been established for the combined residues of glyphosate and its metabolite aminomethyl phosphonic acid in several RACs (40 CFR 180.364).

5) The percent ADI utilized by published tolerances and the current tolerance will be provided by a TAS analysis.

6) The ADI is based on the NOEL of 10 mg/kg/day in the 3-generation rat reproduction study. A hundredfold safety factor was used to calculate the ADI.

$$ADI = \frac{NOEL}{100}$$

$$ADI = 10 \text{ mg/kg/day} \times \frac{1}{100}$$

$$ADI = 0.10 \text{ mg/kg/day}$$

The MPI for a 6.0 mg/day for a 60 kg person.

7) There are no pending regulatory actions against registration of the pesticide.

8) After review of all available evidence, the Agency decided to classify glyphosate as a "Class D Oncogen" and to request a repeat of the mouse oncogenicity study. Also, because of the large difference between

the high dose tested in the rat and mouse oncogenicity studies, the rat oncogenicity study was rereviewed. The rereview indicated that an MTD may not have been reached in the study. Therefore, the Agency decided to also request a repeat of the rat oncogenicity study at doses high enough to reach an MTD. The Agency's policy has been to issue new glyphosate registrations in which the resulting change in TMRC is < 1 percent. However, any significant new registrations will be handled on a case-by-case basis until issues in the Glyphosate Registration Standard have been resolved. Monsanto Company has been notified of these conclusions and deficiencies. Additionally, TB has concluded that the N-nitroso-glyphosate (NNG) content of glyphosate is not toxicologically significant. Also, the levels of N-nitrososarcosine (NSAR) and N-nitro-N-methylaminomethyl phosphonic acid (NNMAMP) in Polado® are not of toxicological concern.

R:53371:Dykstra:C.Disk:KENCO:9/10/88:CT:
R:53390:Dykstra:C.Disk:KENCO:9/26/88:CT:AW:PSR:CL

CASWELL FILE

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C 20460

SEP 11 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate - EPA Registration No. 524-333 - Memorandum of Understanding Regarding Toxicology Discussion

Caswell No.: 661A
Project No.: 7-0973
Record No.: 201837

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769C)

William Dykstra 9/3/87

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

THRU: Edwin R. Budd, Section Head
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Budd 9/9/87

9/9/87

Requested Action

Review the letter that reports the toxicology discussion on the 90-day rat feeding study with glyphosate.

Conclusions and Recommendations

1. The letter (attached) of June 5, 1987 from T. Long of Monsanto to W. Dykstra summarizes the toxicology discussion of the preliminary results of the 90-day rat feeding study with glyphosate.

   The dosage levels in the 90-day rat study were 1000, 5000, and 20,000 ppm.

2. The full report of the rat study was not submitted to the Agency for review. However, based on the brief discussion, Monsanto proposed that 20,000 ppm glyphosate should be the high-dose level for the 2-year chronic study.

3. In light of the discussion of the data, Dr. Dykstra stated that 20,000 ppm would be consistent with the Agency's position paper on the maximum tolerated dose (MTD) and the seemingly lack of dose-related effects in the 90-day study.

   Dr. Dykstra added, however, that a low-dose had to be used that would establish the NOEL for the study.

   In the June 5, 1987 letter, Monsanto states:

   > "Therefore, based upon our discussions on June 3rd, the following dose levels have been chosen for the chronic rat study: 0, 2000, 8000, and 20,000 ppm glyphosate."

It should be emphasized at this point that the Agency only concurred, based on the data under discussion, that the high-dose (the MTD) should be 20,000 ppm. The mid- and low-dose levels were selected by Monsanto without Agency concurrence.

Attachment

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7-09-3

Monsanto

MONSANTO AGRICULTURAL COMPANY
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167
Phone (314) 694-1000

June 5, 1987

William Dykstra, Ph.D.
Hazard Evaluation Division (TS-769C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall #2, Room 824-C
Arlington, Virginia 22202

Dear Dr. Dykstra:

This letter is to confirm the discussions held between Monsanto (T. Long, T. Amrstrong and L. Gingerich) and EPA (W. Dykstra and R. Taylor) on June 3, 1987. At this meeting we presented preliminary results of a 90-day feeding study with glyphosate in rats. A copy of the data which we discussed is attached for your records. The purpose of our meeting was to reach agreement on a high dosage level for the chronic rat feeding study scheduled for initiation in July, 1987. The following summarizes Monsanto's understanding of our discussions.

The dosage levels in the 90-day rat study were 1000, 5000 and 20,000 ppm glyphosate. No treatment-related effects were observed upon the following parameters at any of the dosage levels: body weight, food consumption, physical observations, organ weights, and hematological parameters. Slight, statistically significant increases in plasma phosphorous and potassium concentrations were observed in some dosage groups of both sexes. In addition, plasma glucose concentration was elevated slightly in mid and high dose males. Since all of these values were within historical control ranges (historical data attached) and since the changes were not dose-related, these slight alterations in clinical chemistry parameters were not considered to be treatment-related.

Based upon these results and the principles set forth in the Agency's position paper on maximum tolerated dose[1], Monsanto proposed that 20,000 ppm glyphosate should be the high dose level for the 2-year chronic rat study. The Agency concurred that the high dose level should be 20,000 ppm.

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Therefore, based upon our discussions on June 3rd, the following dose levels have been chosen for the chronic rat study: 0, 2000, 8000, and 20,000 ppm glyphosate.

We appreciate the time you spent with us reviewing the 90-day results. Please notify us if any of the above information needs to be modified.

Sincerely,

T. J. Long

Timothy J. Long, Ph.D.
Product Toxicology Specialist

/jb