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

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: 12-SEP-2016

SUBJECT: **Glyphosate.** Completion and submission of toxicology data evaluation records.

PC Code: 417300
Decision No.: 521111
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0057497

MRID No.: See Table

DP Barcode: D435650
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 41071-83-6; 38641-94-0; 70393-85-0; 114370-14-8; 40465-76-7; 69254-40-6; 34494-04-7; 70901-12-1
40 CFR: §180.364

FROM: Anwar Y. Dunbar, Ph.D.
Pharmacologist, Risk Assessment Branch 1
Health Effects Division (HED) (7509P)

THROUGH: Kelly Lowe, Acting Branch Chief
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED; 7509P)

TO: Khue Nguyen, Risk Manager Reviewer
Neil Anderson, Risk Manager
Pesticide Registration Division (RD; 7508P)

I. CONCLUSIONS

RAB1 has reviewed the submitted cancer and metabolism studies for the active ingredient Glyphosate. The study types and classifications are listed in the table below.

II. ACTION REQUESTED

Please review the submitted cancer studies for Glyphosate.

ED_001560_00000092-00001

Table 1. Submitted Toxicology Studies for Glyphosate		
Guideline Toxicology Studies		
Study Type	**MRID**	**Classification**
Carcinogenicity Study in Mice 870.4200b	50017108, 50017109 (1997)	Acceptable/Guideline
Chronic/Carcinogenicity Study in Rats 870.4300	50017104, 50017105, 50017103 (1997)	Acceptable/Guideline

ED_001560_00000092-00002

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anw Y. Dunbar
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-12-16
EPA Secondary Reviewer: Greg Akerman, Ph.D. **Signature:** [illegible]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 09-12-16

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057497

STUDY TYPE: 24-Month Oral Chronic Toxicity and Carcinogenicity Study in Rats – Rat (83-5)

DP BARCODE: D435650

P.C.CODE.: 417300

MRID NO.: 50017104, 50017105, 50017103

TEST MATERIAL (Purity): Glyphosate (94.61-97.56%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Enemoto, K. (1997), HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 1. The Institute of Environmental Toxicology, Kodaira-shi, Tokyo, Japan, Arysta Life Sciences, Study No.:IET 94-0150. MRID 50017104. Unpublished.

Enemoto, K. (1997), HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 2. The Institute of Environmental Toxicology, Kodaira-shi, Tokyo, Japan, Arysta Life Sciences, Study No.:IET 94-0150. MRID 50017105. Unpublished.

Enemoto, K. (1997), HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Appendix. The Institute of Environmental Toxicology, Kodaira-shi, Tokyo, Japan, Arysta Life Sciences, Study No.:IET 94-0150. MRID 50017103. Unpublished.

SPONSOR: Sankyo Col, Ltd., 7-12, Ginza 2-Chome, Chuo-ku, Tokyo 104, Japan

E XECUTIVE SUMMARY:

In a combined chronic toxicity/carcinogenicity study (MRID 50017104), glyphosate (94.61-97.56% a.i.) was administered to groups of 50 Sprague–Dawley (ctj:CD) rats/sex/dose in the diet at doses of 0, 3000, 10000, and 30000 ppm (0, 104/115, 354/393 and 1127/1247

mg/kg/day) for 104 weeks. In addition, 30 rats/sex/group were included for interim sacrifices at 26, 52, and 78 weeks. Mortality, body weight, body weight gain, and food consumption were monitored throughout the study. Tissue weights, gross necropsy and histopathological analysis were determined throughout the study and at study termination.

At 3000 ppm, there were no treatment-related abnormalities in either sex.

At 10000 ppm, males showed a decreased body weight gain with low food efficiency during the first weeks of treatment, and their growth remained slightly retarded compared to the control thereafter. Females showed an increased incidence of thickened area (s) of the skin in the tail at necropsy. Absolute and relative weights of the cecum were increased in both sexes at almost all examination intervals with occasional statistical significance. Histopathologically, follicular hyperkeratosis and/or folliculitis/follicular abscess corresponding to the thickened area (s) in the tail skin were observed in females.

At 30000 ppm, loose stool was observed in all cages of both sexes with soiled fur in the perianal region in some individual males. An increase in incidence of tail mass was also observed in males. Neither sex showed an increase in mortality, although mortality in males was lower than the control during the last half of the treatment period with statistical significance in most of the weeks. Significant decreases or decreasing trends in absolute body weights were observed in both sexes throughout the treatment period along with a decreasing trend in food consumption in males during the first few weeks (~9%); decreased food efficiency was also observed in both sexes. Ophthalmological examinations, urinalysis, and hematological and blood biochemical analyses did not reveal apparent toxicity of the test substance in either sex. At necropsy, significant increases in incidence of distention of the cecum were observed in both sexes. This effect was accompanied by soiled fur in the perianal region in males and significant increases in absolute and relative weights of the cecum in both sexes, but not associated with histopathological abnormalities. The incidences of thickened area (s) in the skin of the tail, corresponding to the tail mass in clinical observation, were diagnosed as follicular hyperkeratosis and/or folliculitis/follicular abscess histopathologically. An increased incidence of hair loss was also observed in females, but it lacked corresponding histopathological changes.

There were no tumor datasets (54 male and 40 female) that were significant ($p<0.05$) in the Fisher exact test. This determination was made following a thorough search and examination of the study's pathology report.

Based upon the effect in this study, the LOAEL is 10000 ppm (354/393 mg/kg/day) based upon retarded growth in males throughout the study. The NOAEL is 3000 ppm (104/115 mg/kg/day).

There was no evidence of treatment-related neoplastic lesions in this study.

CLASSIFICATION

This chronic/carcinogenicity study in rats is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic/carcinogenicity study [OCSPP 870.4300; OECD 451] in rats.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided. A Data Confidentiality statement was not located in the study report.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** [signature]
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-12-16
EPA Secondary Reviewer: Greg Akerman, Ph.D. **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 09-12-16

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057497

STUDY TYPE: Carcinogenicity Study in Mice – Mouse (82-1)

DP BARCODE: D435650

P.C.CODE.: 417300

MRID NO.: 50017108, 50017109

TEST MATERIAL (Purity): Glyphosate (94.61-97.56%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Sugimoto, K. (1997), HR-001: 18-Month Oral Oncogenicity Study in Mice, Vol. 1. The Institute of Environmental Toxicology, 2-772, Suzuki-cho, Kodaira-shi, Tokyo, 187, Japan, Study No.:IET 94-0151. MRID 50017108. Unpublished.

Sugimoto, K. (1997), HR-001: 18-Month Oral Oncogenicity Study in Mice, Vol. 2. The Institute of Environmental Toxicology, 2-772, Suzuki-cho, Kodaira-shi, Tokyo, 187, Japan, Study No.:IET 94-0151. MRID 50017109. Unpublished.

SPONSOR: Sankyo Col, Ltd., 7-12, Ginza 2-Chome, Chuo-ku, Tokyo 104, Japan

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID 50017108), glyphosate (94.61-97.56% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 1600, 8000, and 40000 ppm (0, 165/153.2, 838.1/786.8, or 4348/4116 mg/kg bw/day) for 78 weeks. In addition, 30 mice/sex/group were included for interim sacrifices at 26, 52, and 78 weeks. Mortality, body weight, body weight gain, and food consumption were monitored throughout the study. Tissue weights, gross necropsy and histopathological analysis were determined and observed throughout the study and at study termination.

At 1600 ppm, there were no treatment-related abnormalities seen in either sex in any parameter.

At 8000 ppm, retarded growth was observed in females with statistically significant decreases in absolute body weights at week 6 and weeks 9-24. No treatment-related changes were seen in males.

At 30000 ppm, the incidence of pale-colored skin was increased in males. In addition, loose stool was observed in all cages beginning at week 21 in males and at week 20 in females. Retarded growth was persistently observed during the treatment period showing statistically significant differences in weight from week 16 to 36 in males and from week 6 to the end of the treatment in females. These changes were associated with the depressed food consumption and food efficiency. At necropsy, the increased incidences of distension of the cecum were noted in males and females at terminal kill and in all animals examined, which were consistent with an increase in absolute and relative weights of the cecum. However, no abnormalities were recorded in the cecum histopathologically. In males, a significant increase was noted for the overall incidence of anal prolapse which corresponded to erosion/ulcer of the anus histopathologically.

The agency performed a search of the pathology report and performed a statistical analysis of the hemangiomas in females where there was a potential monotonic dose response. The tumor incidences for hemangiomas in females are presented in Table 1. A statistically significant trend was observed for hemangiomas. Regarding the tumor incidence at the high-dose, there was a statistical significance with the raw (unadjusted) p-value as compared to concurrent controls; however, with an adjustment for multiple comparisons, the high dose tumors were not statistically significant (p=0.055). Based on a weight-of-evidence for this study, the agency does not consider these increases in hemangiomas in female rats to be treatment-related. Other than the hemangiomas, there were no tumor datasets (25 male and 31 female) that were significant (p<0.05) in the Fisher exact test.

Table 1. Hemangioma Incidences
Fisher's Exact Test and Cochran-Armitage Trend Test Results

Tumor Type	0 mg/kg/day	153.2 mg/kg/day	786.8 mg/kg/day	4116 mg/kg/day
Hemangioma Incidence (%)	0/50 (0)	0/50 (0)	2/50 (4)	5/50 (10)
Raw p-value =	0.002**	1.000	0.247	0.028*
Sidak p-value =	--	1.000	0.434	0.055

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01.

In males, the LOAEL is 40000 ppm (4116 mg/kg/day [M]) based on a significant increase was noted for the overall incidence of anal prolapse which was correspondent to erosion/ulcer of the anus histopathologically. The NOAEL is 8000 (838.1 mg/kg/day [M]).

In females, the LOAEL is 8000 ppm (838.1 mg/kg/day [F]) based upon retarded growth with statistically significant decreases in weight at 6 and weeks 9-24. The NOAEL is 1600 ppm (153.2 mg/kg/day [F]).

The neoplastic lesions seen in this study are not considered to be treatment-related.

CLASSIFICATION

This carcinogenicity study in CD-1 mice is **Acceptable/Guideline** and satisfies the guideline requirement for a carcinogenicity study [OCSPP 870.4200; OECD 451] in mice.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided. A Data Confidentiality statement was not located in the study report.