Janet Whitehurst

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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **METSULFURON-METHYL**: 6(A)(2) Reproduction Study

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 4/22/97
Toxicology Branch II Section II,
Health Effects Division (7509C)

THRU: K. Clark Swentzel K. Clark Swentzel for TEP 5/8/97
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Yiannakis Ioannou, Ph.D. Y.M. Ioannou 5/15/97
Acting Chief, Toxicology Branch II/HED (7509C)

TO: Michael Metzger
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

Registrant:	DuPont Agricultural Products
Chemical:	Metsulfuron-methyl; Ally
Submission No.:	none
DP Barcode:	D232959
Caswell No.:	419H
CAS #:	74223-64-6
P.C.Code:	122010
MRID No.:	44163302
Action Requested:	Please review 6(A)(2) data.

Comment: The Registrant submitted a 2-generation reproduction study conducted by the Shriram Institute, Delhi, India. Metsulfuron methyl was administered orally. There were no individual data provided and, therefore, no DER was generated. A summary of the findings is provided below.

MRID 44163302 - Two Generation (4 Litters) Reproduction Study in Albino Rats. EXECUTIVE SUMMARY: In a 2-generation reproduction study [MRID 44163302], Ally technical (93% a.i.) was administered to 10 male Wistar rats/20 female Wistar rats/dose [via oral gavage apparently] at dose levels of 0, 20, 100, and 500 mg/kg/day during their respective spermatogenic and estrus cycles [P_1 ≈70 days for males and 14 days for females pre-mating] and dosing was continued

"till F_2 generation". F_{1b} generation [P_2] were dosed via the diet for 90 days premating, followed by two matings. All rats survived until study termination. There were no adverse effects on body weight or body-weight gain of the P_1 parental rats [premating; data for P_2 were not provided]. There were no apparent effects on organ weights or gross pathological findings, although the high-dose P_1 males displayed slightly lower testes weights [absolute 91%/relative 89% of control] and the high-dose P_2 females displayed lower liver and uterus weights compared to the controls. Microscopic findings [degenerative changes] were observed in both sexes at the mid- and high-dose levels [both P_2 and F_{2b} generations] in the liver and kidney, reduced spermatogenesis was observed in the mid- and high-dose P_2 males, and an unidentified lesion was listed in 2 of the 5 F_{2b} females at the high-dose level. The reproductive findings are listed in Tables 1 through 4, below. There was a dose-related decrease in the fertility index of the P_1 rats/second litter and the P_2 rats/both litters. The gestation index was not affected by treatment and with the exception of the last litter of the P_2 rats, which showed a slight decrease, the live birth index was comparable among the groups. There was a dose-related decrease in the viability index in the first generation [both litters] but not in the second generation. The lactation/weaning index was slightly decrease at the high-dose level compared to the controls in the first generation/first litter and in the second generation/second litter. With the exception of the first litter of the second generation [100% survival for all groups], litter survival was decreased compared to the control value at the high-dose level. There was a dose-related decrease in mean pup body weight in both litters of both generations. **The NOEL appears to be at the 20 mg/kg/day dose level, and the LOEL is 100 mg/kg/day, based on an apparent, slight decrease in the fertility index and the lactation index and decreased pup body weight.** This guideline [§83-4; OPPTS 870.3800] 2-generation reproduction study in rats is classified Unacceptable due to a lack individual animal data and to the numerous discrepancies observed in the study report. Additionally the lack of any effect on body weight/gain of the parental rats is not consistent with other studies on ALLY that have demonstrated decreased body weights at lower dose levels. In the 2-generation reproduction study [dated 1/21/85] submitted by the registrant [Accession # 073332], there were no adverse effects on reproductive performance observed at any dose level [5, 25, 500, 2500, and 5000 ppm (≈250 mg/kg/day)]. The maternal NOEL was 500 ppm and the LOEL was 5000 ppm, based on decreased body weight. The effects observed in the current study [degenerative changes in the liver and kidneys of both sexes at the mid- and high-dose levels in the P_2 and F_{2b} generations and reduced spermatogenesis in the mid- and high-dose P_2 males] for which the study was submitted under 6(a)(2) have not been reported previously for this active ingredient. TB II notes that in a supplementary 21-day dermal toxicity study in rabbits, a mild testicular degeneration was observed [125, 500, 2000 mg/kg/day]. Because of the deficiencies in the reporting of this study, no further action with respect to this 6(a)(2) is required at this time. Further action as appropriate should occur during the normal reregistration process of this active ingredient.

Table 1. Reproduction Data - P_1 Dams and Pups of F_{1a} Generation				
Parameter/Dose [mg/kg/day]	0	20	100	500
# of matings	20	20	20	20
# of pregnancies	20	20	20	20
fertility Index [%]	100	100	100	100
# litters born	20	20	20	20
gestation Index [%]	100	100	100	100
# pups born	168	167	162	162
# pups born alive	166	165	160	159
live birth index [%]	98.8	98.8	98.8	98.1
viability index [%]	91.5	90.9	89.4	83.0
# pups left to nurse	152	150	144	132
# pups weaned	128	117	120	98
lactation/weaning index [%]	84.2	78.0	83.3	74.2
litter survival %	95	90	85	80
mean pup body weight [g]				
day 0	5.68	5.57	5.42	5.2*
day 4	8.55	7.55	7.77	6.94**
day 14	16.3	15.40	13.92	12.6*
day 21	19.4	19.0	20.37	17.7

* $p<0.05$; ** $p<0.01$; data from Tables 1 of the report [unnumbered page 13] and Tables 8a-8d [unnumbered pages 20-23].

Table 2. Reproduction Data - P_1 Dams and Pups of F_{1b} Generation				
Parameter/Dose [mg/kg/day]	0	20	100	500
# of matings	20	20	20	20
# of pregnancies	19	18	17	15
fertility Index [%]	95	90	85	75
# litters born	19	18	17	15
gestation Index [%]	100	100	100	100
# pups born	152	144	142	140
# pups born alive	152	144	142	140
live birth index [%]	100	100	100	100
viability index [%]♦	97.4	91.7	90.1	87.1
# pups left to nurse	148	132	128	122
# pups weaned	135	119	112	107
lactation/weaning index [%]	91.2	90.2	87.5	87.7
litter survival %	100	88.8	100	80
mean pup body weight [g]				
day 0	5.81	5.76	5.20*	4.8*
day 4	9.14	8.54	8.54	8.21
day 14	19.20	18.90	17.57*	17.20
day 21	27.60	26.10	25.0*	24.70

* $p<0.05$; data from Table 2 of the report [unnumbered page 14] and Tables 9a-9d, unnumbered pages 24-27; ♦ calculated by reviewer [not provided in Table 2 [# pups left to nurse ÷ # pups born alive]

Table 3. Reproduction Data - P_2 Dams and Pups of F_{2a} Generation				
Parameter/Dose [mg/kg/day]	0	20	100	500
# of matings	20	20	20	20
# of pregnancies	19	18	17	16
fertility Index [%]	95	90	85	80
# litters born	19	18	17	16
gestation Index [%]	100	100	100	100
# pups born	157	153	152	150
# pups born alive	157	151	150	148
live birth index [%]	100	98.7	98.7	98.7
viability index [%]	96.8	97.35	96	95.9
# pups left to nurse	152	147	144	142
# pups weaned	135	130	126	123
lactation/weaning index [%]	88.8	88.4	87.5	86.6
litter survival %	100	100	100	100
mean pup body weight [g]				
day 0	5.8	5.7	5.5	5.08*
day 4	9.08	8.67	8.4	8.0
day 14	19.1	18.9	18.5	18.0
day 21	27.3	27.0	26.3	26.0

* $p<0.05$; data from Table 3 of the report [page 15] and Tables 10a-10d, unnumbered pages 28-31

Table 4. Reproduction Data - P_2 Dams and Pups of F_{2b} Generation				
Parameter/Dose [mg/kg/day]	0	20	100	500
# of matings	20	20	20	20
# of pregnancies	20	18	17	16
fertility Index [%]	100	90	85	80
# litters born	20	18	17	16
gestation Index [%]	100	100	100	100
# pups born	152	152	154	155
# pups born alive	152	150	151	148
live birth index [%]	100	98.7	98.05	95.48
viability index [%]	92.76	92.67	92.05	93.24
# pups left to nurse	141	139	139	138
# pups weaned	120	125	117	101
lactation/weaning index [%]	85.1	89.9	84.17	73.19
litter survival %	90	94	82.4	75
mean pup body weight [g]				
day 0	5.98	5.85	5.54	5.40
day 4	9.1	8.83	8.75	8.35**
day 14	19.21	18.47	18.32	18.07
day 21	26.80	26.75	26.50	23.58

** $p<0.01$; data from Table 4 of the report [unnumbered page 16] and Tables 11a-11d, unnumbered pages 32-35

Deficiencies: There were no individual data provided. There are numerous discrepancies in the data presented. For example, in Tables 2 and 5, unnumbered pages 14 and 17, the number of pregnant females and the number of litters born are listed as 16/20 for the high-dose F_{1b} generation, but the number should be 15/20, as noted in Table 9d, unnumbered page 27 of the report. Also in Table 9d, female # 12 is listed with 14 pups on day 0 and 17 on day 4; this should read 14 since the total number of pups for day 4 is listed as 122 and adding all of the pups for all of the dams using 17 gives 125. The headings for Tables 12b and 13b are inaccurate [data are for the relative organ weights, not the absolute organ weights]. In Table 1 [unnumbered page 13], there are several discrepancies: (1) the lactation/weaning index is listed as 84.1% for the low-dose group; this should read 78%; (2) the litter survival for the mid-dose group should read 85%, not 90%; (3) body weight of the low-dose pups for day 4 should read 7.55, not 8.15 [as listed in Table 8b of report]; (4) the mid-dose pup body weights for days 0, 4, 14, and 21 should read 5.42, 7.77, 13.92, and 20.37, not 5.2, 7.9, 14.4, and 19.0, respectively [as listed in Table 8c of the report. In Table 2 [unnumbered page 14], (1) the viability index is not listed; (2) the litter survival for the high-dose group should be 80%, not 81.2%; (3) Day 4 low-dose pup body weight should read 8.54, not 8.64; (4) high-dose pup body weight for day 14 should read 17.20, not 17.25. In Table 3 [unnumbered page 15], (1) minor decimal errors are noted; (2) high-dose pup mean body weight on day 0 should read 5.08, not 5.2; (3) day 14 high-dose mean pup body weight should read 17.19, not 18.0; (4) day 21 mid-dose mean pup body weight should read 26.3, not 26.5. In Table 4, unnumbered page 16, in addition to minor decimal errors, the lactation/weaning indices for all groups are incorrect. These should read 85.1%, 89.9%, 84.2%, and 73.2% instead of 78.95%, 83.33%, 77.48%, and 68.24% for the control, low-, mid-, and high-dose groups, respectively. TB II notes that each group in both generations and both litters had the same animal numbers for the dams [1-20]; i.e., no unique identification numbers were given to the animals. The age of the rats at study start, the sex ratio, and the number of implantation sites were not provided. Additionally, on the first page of the report, the study is identified as Toxicology Study Report, Project No. TOX/1 and in the right-hand top corner as "Annexure to Report No,: 163691 [Dt.: 25.02.95]. Table 11a [unnumbered page 32] is in a different font [or typed on a different typewriter or a fax], and the top of the page is the NO. 9426. None of the other pages is identified with a study number. In Table 17 [unnumbered page 45], the histopathological lesion is listed for the 2/5 high-dose F_{2b} females is not identified, nor is there any mention of it in the text of the report. The route of administration is stated to be oral on the title page; however, it is not clear how dosing occurred. On page 1, paragraph 2, it states that there was a 90-day feeding phase for F_b generation. In paragraph 3 on that page it states that three dosage levels were given by oral intubation. Page 4 lists the route as oral (gavage).