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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700 [§83-3]; OECD 414.

PC CODE: 623001 **DP BARCODE:** D335563

TEST MATERIAL (PURITY): RPA 203328 (99% purity a.i.; Batch No. NMI874; white powder with small aggregates)

SYNONYMS: 2-methanesulphonyl-4-trifluoromethylbenzoic acid; metabolite of pyrasulfotole and isoxaflutole

CITATION: Repetto-Larsay, M. (1999) RPA 203328 Developmental Toxicology Study in the Rat by Gavage. Unpublished report by: Rhône-Poulenc Agro, Centre de Recherche, 355, rue Dostoïevski, BP 153, F-06903 Sophia Antipolis Cedex. Laboratory Report No. SA 98427, June 24, 1999. MRID 45655906.

SPONSOR: Aventis Crop Science (formally Rhône-Poulenc Ag Company), Research Triangle Park, NC 27709

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 45655906) RPA 203328 (99% purity a.i.; Batch No. NMI874) was administered to 25 Sprague-Dawley rats/dose by gavage at dose levels of 0, 75, 250, or 750 mg/kg bw/day from days 6 through 20 of gestation. Maternal body weight and food consumption were recorded for all females throughout the gestational period. Clinical observations were recorded daily. At sacrifice on gestation day 21, the gravid uterine weight was recorded and the dams evaluated for number of corpora lutea and number and status of implantations. Live fetuses were removed from the uteri, counted, weighed, sexed, and examined externally. Half of each litter was fixed in Bouin's fixative and dissected for internal examination. The remaining half was eviscerated, fixed in alcohol, and stained with alizarin red S for skeletal examination.

Maternal toxicity was evident in the study. An increased incidence of salivation was observed at 250 (6/25) and 750 mg/kg/day (18/25). This finding was associated with red nasal discharge shortly after treatment in 3 animals at 750 mg/kg. Both salivation and nasal discharge were resolved within approximately one hour after treatment. Piloerection was also observed around the time of treatment in 2/25 and 3/25 dams at 250 and 750 mg/kg/day, respectively. Piloerection

was associated with reduced motor activity in 1 animal at 750 mg/kg. No abnormal clinical signs were observed during the study period in the low dose (75 mg/kg/day) group. Corrected body weight change was significantly reduced by 31% and 37% in dams of the 250 and 750 mg/kg/day groups, respectively. These decreases were supported by significant decreases (>25%) in maternal body weight gain during treatment at the same doses. Administration of the test substance also significantly reduced food consumption during the treatment period in the same groups noted above. **The maternal LOAEL is 250 mg/kg bw/day, based on clinical signs (salivation and piloerection around the time of treatment), decreased body weight change, decreased corrected body weight change, and decreased food consumption. The maternal NOAEL is 75 mg/kg bw/day.**

External, internal, and skeletal examination of the fetuses did not reveal any findings which were treatment-related. **The developmental LOAEL was not observed. The developmental NOAEL is 750 mg/kg bw/day.**

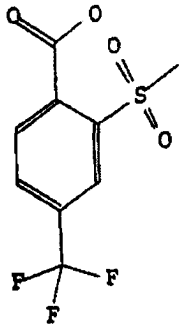
The developmental toxicity study in the rat is classified **acceptable (guideline)** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Statement of No Data Confidentiality Claims statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: RPA 203328

Description:	White powder with small aggregates
Lot/batch #:	NMI874
Purity:	99% a.i.
Compound stability:	Determined in study SA 98333
CAS #of TGAI:	142994-06-7
Structure:	

2. Vehicle and/or positive control: 0.5% Methylcellulose 400

3. Test animals:

Species:	Rat
Strain:	Sprague-Dawley Crl: CD (SD) BR
Age/weight at study initiation:	Age not reported; 237-306 g at mating
Source:	Charles River Laboratories, St Aubin les Elbeuf, France
Housing:	Animals were individually housed in suspended, stainless steel wire mesh cages.
Diet:	Certified Rodent pellet diet AO4C (Usine, d'Alimentation Rationnelle, Villermoisson-sur-Orge, France) was available *ad libitum*.
Water:	Water from the municipal supply was provided *ad libitum* with an automatic watering system. Filters servicing the watering system were changed regularly and sterilization of the system was periodically performed. Routine analysis of feed and water indicated that there was no contamination which could have been expected to have compromised the study.
Environmental conditions:	**Temperature:** 20-24°C **Humidity:** 40-70% **Air changes:** 10 /hr **Photoperiod:** 12 hrs dark/ 12 hrs light
Acclimation period:	14 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates: Start: October 20, 1998; End: November 12, 1999

2. Mating: Females were mated on a one-to-one basis with stock males of the same strain and same supplier. Each morning following pairing, rats showing spermatozoa in a vaginal smear or sperm plug *in situ* were considered pregnant. The day on which evidence of mating was found was designated as gestation day 0 (GD0).

3. **Animal assignment:** Animals were assigned to control and treated groups at the end of each week of mating using a body weight dependent procedure (no further details given). Animals were assigned to dose groups as indicated in Table 1.

TABLE 1: Animal Assignment				
Dose (mg/kg bw/day)	0	75	250	750
Number of Females	25	25	25	25

4. **Dose selection rationale:** The range of doses was selected in agreement with the sponsor representative and was based on the results obtained in a previous range finding study in the rat (SA 98333). In the range-finding study, doses were 0, 50, 100, 300, 600, and 1000 mg/kg. Maternal body weight and body weight gain were decreased at 1000 mg/kg/day compared to controls. In addition, corrected body weight changes were significantly decreased at 600 and 1000 mg/kg/day. In the present study, the high dose of 750 mg/kg/day was based on maternal toxicity at 1000 mg/kg/day in the range-finding study. Other doses were chosen to give a graded response.

5. **Dosage preparation and analysis:** Test material-vehicle mixture was prepared periodically by mixing appropriate amounts of test substance with 0.5% methylcellulose 400 with storage at 5°C (± 3°C) temperature. Homogeneity of the suspensions was checked during the first formulation for the lowest and highest concentrations. Stability of the test substance in suspension in the vehicle was determined in the range-finding study (SA 98333). All concentrations were checked for each new formulation.

Results:

Homogeneity analysis: Homogeneity was checked on the formulations at 7.5, 25, and 75 g/L. The sampling was done at three levels, the surface, middle, and bottom. All three samples measured 7.4 g/L for the 7.5 g/L sample (99% of nominal concentration). For the 25 g/L samples, the measurements were 25.7 g/L for surface, 26.0 for the middle, and 25.8 g/L at the bottom. These were 103, 104, and 103% of nominal concentration respectively. The measurements for the surface, middle, and bottom of the 75 g/L samples were 76.7 g/L (102% of nominal concentration), 77.1 g/L (103% of nominal concentration), and 77.6 g/L (103% of nominal concentration) respectively. The results were within the target range (90 to 110% of nominal concentration for concentration ranging from 5 to 250 g/L).

Stability analysis: The stability of preparations was checked in the range-finding study (SA 98333). Preparations were stored at 5°C ± 3°C with daily four-hour periods at ambient temperature (~20°C) under magnetic stirring to reproduce the conditions of utilization. Two samples from these preparations (1.0 and 100 g/L) were taken after 0, 7, 14, and 21 days. The measured concentration was 1.0 g/L at all time points (100% of nominal concentration) for the 1.0 g/L sample. The measured concentration for the 100 g/L sample was 105 g/L, (Day 0, 105% of nominal concentration), 102 g/L (Day 7, 102% of nominal concentration), 105 g/L (Day 14, 105% of nominal concentration), and 102 g/L (Day 21, 102% of nominal concentration). The results were within target ranges.

25°

Concentration analysis: Mean values obtained from the homogeneity checks were used as measured concentrations. The values ranged from 7.4-7.4 g/L for the 7.5 g/L sample, 24.3-25.83 g/L for the 25 g/L sample, and 72.8-77.13 g/L for the 75 g/L sample. The results were within the target range.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** All doses were administered once daily by gavage, on gestation days 6 through 20, in a volume of 10 mL/kg of body weight/day. Dosing was based on the body weight of the most recent body weight determination.

C. OBSERVATIONS:

1. **Maternal observations and evaluations:** The animals were checked for mortality or clinical signs daily. Body weight was recorded on gestation days 0, 3, 6, 8, 10, 12, 14, 16, 18, and 21 and food consumption was recorded during the periods GD 1-3, 3-6, 6-8, 8-10, 10-12, 12-14, 14-16, 16-18, and 18-21. Dams were sacrificed on day 21 of gestation. Examinations at sacrifice consisted of macroscopic examination of the visceral organs, weighing and examination of the reproductive tract including number of corpora lutea, implantation sites, resorption sites, live and dead fetuses, and the sex and weight of live fetuses.

2. **Fetal evaluations:** The fetuses were examined as follows. Half of each litter was immersed in Bouin's fluid for subsequent internal examination following free-hand sectioning. The remaining half was eviscerated and placed in absolute ethanol before staining. A modification of Staples and Schnell staining technique (alizarin red) was used and subsequent skeletal examination was performed. Structural deviations were defined as malformations, anomalies, or variations. Malformations were described as major abnormalities that are rare and/or probably lethal. Anomalies were described as minor differences from normal that are detected relatively frequently and not obviously detrimental. Variations were described as structural changes occurring frequently in the control population.

D. DATA ANALYSIS:

1. **Statistical analyses:** Statistical analyses were performed using SAS programs. Results of maternal body weight changes and corrected body weight change, food consumption, and mean litter weights were compared between the treated groups and the control group by use of Bartlett's test for homogeneity, analysis of variance (ANOVA) when Bartlett's test indicated homogeneous variances, and Dunnett's test if ANOVA was significant. When Bartlett's test indicated heterogeneous variances, the Kruskal-Wallis non parametric one-way ANOVA was performed, followed by the Mann-Whitney test when the Kruskal-Wallis test was significant. Data from non-pregnant, dead or killed "*in extremis*" animals were not included in group mean calculations of all maternal parameters.

   Litter data were analyzed statistically using the Kruskal-Wallis test, followed by the Mann-Whitney test when the Kruskal-Wallis test was significant.

The significance levels for each statistical comparison were 0.05 and 0.01.

2. **Indices:** The following indices were calculated from records of animals in the study:

Body weight (BW) change and food consumption (FC) for interval periods were calculated as follows:
BW (Day 6 to Day 8) = BW D8 - BW D6
FC (Day 6 to Day 8) = (FC D6 + FC D7)/2

Corrected body weight change (CBWC) was calculated as follows:
CBWC = (BW D21 - BW D0) - gravid uterine weight

Pre-implantation loss (%) = ((number of corpora lutea - number of implantations)/ number of corpora lutea) x 100

Post-implantation loss (%) = ((number of implantations - number of viable fetuses)/ number of implantations) x 100

Male sex ratio = number of male fetuses/total number of fetuses

Percentage of live fetuses = (number of live fetuses/ (number of live fetuses+ number of dead fetuses)) x 100

3. **Historical control data:** Historical control data were not provided to allow comparison with concurrent controls.

II. RESULTS:

A. MATERNAL TOXICITY:

1. **Mortality and clinical observations:** There was no treatment-related mortality in the study. At 250 and 750 mg/kg/day, 6 (24%) and 18 (72%) females respectively, had at least one occurrence of transient salivation during the entire treatment period. At 750 mg/kg/day, the salivation was associated with red nasal discharge a few minutes following administration in some animals. The observations disappeared approximately one hour after treatment. Piloerection was also observed on the day of treatment in 2/25 and 3/25 dams at 250 and 750 mg/kg bw/day, respectively. Piloerection was associated with reduced motor activity in 1 animal at 750 mg/kg.

2. **Body weight:** Body weight data are summarized in Table 2. Absolute maternal body weight during the pre-dosing period was similar among all the groups. Body weight parameters at 75 mg/kg/day were comparable to control body weight parameters. During GD10-14 and GD8-10 in the 250 and 750 mg/kg/day groups respectively, mean maternal body weight change was statistically significantly reduced (>25%) compared to control body weight during these same time periods. There was a trend of decreasing body weight due to decreased body weight gain and food consumption in the mid and high dose dams. From treatment day 14 until day 21, dams in the 250 and 750 mg/kg/day groups had a mean body weight that was consistently 5% and 7% respectively, less than control body weight. At 250 and 750 mg/kg/day, corrected body weight changes were statistically significantly reduced by 31% and 37% of control weight respectively, indicating maternal systemic toxicity.

TABLE 2 Mean (±SD) maternal body weight (g), body weight change (g), and food consumption (g/d) [a]				
Interval	Dose in mg/kg bw/day (# of Dams)			
	Control (24)	75 (25)	250 (25)	750 (25)
Pretreatment: Day 0	270.5 ± 14.66	270.1 ± 14.38	267.2 ± 13.85	266.6 ± 13.90
Pretreatment: Day 3	291.1 ± 14.79	291.0 ± 17.45	286.5 ± 13.88	287.0 ± 15.10
Treatment: Day 6	306.8 ± 16.43	305.7 ± 19.31	300.4 ± 14.21	301.0 ± 14.62
Treatment: Day 10	325.3 ± 17.78	321.5 ± 21.70	313.4 ± 16.81	309.2 ± 17.87
Treatment: Day 14	346.8 ± 20.91	342.0 ± 24.59	329.4 ± 18.86	325.2 ± 24.36
Treatment: Day 18	390.7 ± 24.88	385.1 ± 31.46	372.0 ± 19.28	367.3 ± 28.20
Posttreatment: Day 21	445.8 ± 30.28	439.9 ± 38.89	423.7 ± 23.95	415.7 ± 29.85
Weight Change: Days 0-3	20.6 ± 5.34	20.9 ± 6.71	19.4 ± 5.22	20.4 ± 5.92
Weight Change: Days 6-8	8.0 ± 4.34	5.7 ± 3.67	5.7 ± 4.28	4.6 ± 6.99
Weight Change: Days 8-10	10.4 ± 2.93	10.1 ± 4.54	7.3 ± 5.98	3.6 ± 9.63**
Weight Change: Days 10-14	21.5 ± 5.13	20.5 ± 5.83	16.0 ± 7.33**	16.0 ± 14.5
Weight Change: Days 14-18	43.9 ± 8.31	43.1 ± 10.24	42.6 ± 8.81	42.1 ± 8.15
Weight Change: Days 18-21	55.1 ± 9.18	54.8 ± 12.26	51.7 ± 12.12	48.4 ± 9.44
Corrected Body Weight Change	68.2 ± 17.02	63.9 ± 19.47	46.8 ± 18.66**	43.1 ± 18.44**
Food Consumption: Days 1-3	27.7 ± 3.18	27.0 ± 3.09	26.8 ± 2.45	26.9 ± 2.60
Food Consumption: Days 6-8	29.5 ± 4.11	28.3 ± 4.20	27.6 ± 3.12	25.9 ± 3.52**
Food Consumption: Days 8-10	29.5 ± 3.40	29.0 ± 4.46	26.4 ± 3.40**	24.7 ± 4.98**
Food Consumption: Days 16-18	29.4 ± 3.61	28.4 ± 3.98	26.3 ± 4.48*	26.2 ± 3.96*
Food Consumption: Days 18-21	28.9 ± 4.05	28.1 ± 4.20	25.2 ± 2.75*	25.4 ± 3.43*

[a] Data obtained from pages 33-40 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

3. **Food consumption:** Food consumption data are summarized in Table 2. Food consumption at 75 mg/kg/day was comparable to control food consumption. Mean food consumption during GD8-21 was significantly reduced at 250 mg/kg/day and during the entire treatment period at 750 mg/kg/day.

4. **Gross pathology:** There were no treatment-related observations at necropsy.

5. **Cesarean section data:** Data are summarized in Table 3. Twenty-four of the twenty-five females mated in the control group were pregnant. All females in the other study groups were pregnant. Group means and litter average for corpora lutea, implantation losses, and sex ratio were comparable in all experimental groups. There were no dead fetuses. Litter means of fetal body weight per sex and with sex combined were comparable between all study groups.

TABLE 3 Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	75	250	750
No. Animals assigned (mated)	25	25	25	25
No. Animals pregnant	24	25	25	25
Pregnancy rate (%)	96	100	100	100
No. Nonpregnant	1	0	0	0
Maternal wastage				
No. died	0	0	0	0
No. Died pregnant	0	0	0	0
No. Died nonpregnant	0	0	0	0
No. Aborted	0	0	0	0
No. Premature delivery	0	0	0	0
Total No. corpora lutea Corpora lutea/Dam	431 18.0 ± 3.57	432 17.3 ± 2.57	445 17.8 ± 2.40	417 16.7 ± 1.25
Total No. implantations Implantations/Dam	398 15.9 ± 2.19	381 15.2 ± 3.31	409 16.4 ± 1.19	396 15.8 ± 1.25
Total No. litters	24	25	25	25
Total No. live fetuses Live fetuses/Dam	354 14.8 ± 2.35	368 14.7 ± 3.32	391 15.6 ± 1.38	377 15.1 ± 1.44
Total No. dead fetuses Dead fetuses/Dam	0 0.0 ± 0.00	0 0.0 ± 0.00	0 0.0 ± 0.00	0 0.0 ± 0.00
Total No. resorptions	28	13	18	19
Early	26	13	15	17
Late	2	0	3	2
Resorptions/Dam				
Early	1.1 ± 1.41	0.5 ± 0.71	0.6 ± 0.71	0.7 ± 0.56
Late	0.1 ± 0.28	0.0 ± 0.00	0.1 ± 0.33	0.1 ± 0.28
Litters with total resorptions	0	0	0	0
Mean fetal weight (g)	5.39 ± 0.350	5.34 ± 0.232	5.26 ± 0.261	5.27 ± 0.302
Males	5.53 ± 0.339	5.52 ± 0.275	5.40 ± 0.296	5.39 ± 0.318
Females	5.26 ± 0.364	5.21 ± 0.221	5.11 ± 0.238	5.13 ± 0.309
Sex ratio (% male)	0.49 ± 0.147	0.46 ± 0.154	0.52 ± 0.133	0.52 ± 0.135
Preimplantation loss (%)	8.9 ± 17.06	11.1 ±18.07	7.0 ± 9.79	4.9 ± 4.90
Postimplantation loss (%)	7.1 ± 9.40	3.4 ± 4.62	4.4 ± 5.31	4.9 ± 3.43

[a] Data obtained from pages 42-45, 67-70 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

B. DEVELOPMENTAL TOXICITY:

In the control, 75, 250, and 750 mg/kg/day groups, the number of fetuses (litters) examined externally were 354 (24), 368 (25), 391 (25), and 377 (25), respectively; the number examined internally were 173 (24), 179 (25), 189 (25), and 183 (25), respectively; and the number examined for skeletal malformations were 181 (24), 189 (25), 202 (25), and 193 (25), respectively.

1. **External examination:** There were eight fetuses with body weight less than 4.0 g; two in control, one at 75 mg/kg/day, two at 250 mg/kg/day, and three at 750 mg/kg/day. One fetus at 75 mg/kg/day had agnathia and two fetuses at 250 mg/kg/day had anasarca (Table 4a). No effects related to treatment were noted.

2. **Visceral examination:** No treatment-related findings were noted in any group upon internal examination of the fetuses. Malformations, anomalies, and variations, including dilated renal pelvis, dilated ureter, and convoluted ureter, were common findings in fetuses from treated and control groups, were observed with a comparable incidence in all study groups and were not considered treatment-related (Table 4b).

3. **Skeletal examination:** An increased incidence of unossified 7th cervical centrum was observed sporadically without dose response in treated groups. Variations in vertebrae, sternebrae, and ribs were noted in all groups with no dose response relationship (Table 4c). There was an increase in the incidences of short 13th ribs, but the incidence was low, not statistically significant (Fisher's exact test used), and lacked dose-response. No treatment-related effects were observed.

TABLE 4a. External examinations [a]

Observations	Dose (mg/kg bw/day)			
	0	75	250	750
No. Fetuses(litters) examined	354 (24)	368 (25)	391 (25)	377 (25)
No. Fetuses(litters) affected	2 (2)	2 (2)	4 (3)	3 (3)
Body weight < 4.0 g	2 (2)[b]	1 (1)	2 (2)	3 (3)
Agnathia	0 (0)	1 (1)	0 (0)	0 (0)
Anasarca	0 (0)	0 (0)	2 (1)	0 (0)

[a] Data obtained from page 47 in the study report.
[b] Fetal (litter) incidence

TABLE 4b. Visceral examinations [a]

Observations	Dose (mg/kg bw/day)			
	0	75	250	750
No. Fetuses(litters) examined	173 (24)	179 (25)	189 (25)	183 (25)
No. Fetuses(litters) affected	60 (19)	58 (19)	63 (18)	73 (16)
Dilated renal pelvis	14 (9)[b]	17 (8)	17 (9)	23 (12)
Dilated ureter	46 (19)	41 (19)	46 (18)	50 (16)

[a] Data obtained from page 48 in the study report.
[b] Fetal (litter) incidence

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TABLE 4c. Skeletal examinations [a]				
Observations [b]	Dose (mg/kg bw/day)			
	0	75	250	750
No. Fetuses(litters) examined	181 (24)	189 (25)	202 (25)	193 (25)
No. Fetuses (litters) with sternebrae variations	32 (17) [c]	31 (17)	36 (20)	40 (22)
No. Fetuses (litters) with vertebrae variations	11 (8)	8 (6)	11 (10)	12 (11)

[a] Data obtained from pages 50-51 in the study report.

[b] Some observations may be grouped together.

[c] Fetal (litter) incidence

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

The study author concluded that administration of RPA 203328 by gavage to pregnant Sprague-Dawley rats from gestation days 6-20 resulted in signs of maternal toxicity at 250 and 750 mg/kg/day including decreased body weight change, decreased corrected body weight change, and decreased food consumption during the treatment period. None of the litter parameters recorded during cesarean section was affected by treatment. External, internal, and skeletal examination of the fetuses did not reveal any treatment-related findings. The maternal NOEL was 75 mg/kg/day and the developmental NOEL was 750 mg/kg/day.

B. REVIEWER COMMENTS:

1. **Maternal toxicity:** Maternal toxicity was evident in the study. Clinical signs of toxicity were observed in dams around the time of treatment at ≥250 mg/kg/day. Body weight changes and corrected body weight changes were significantly reduced in dams of the 250 and 750 mg/kg/day groups (mid and high-dose). Administration of the test substance significantly reduced food consumption during the treatment period in the same groups noted above. It is likely that test article administration led to decreased food consumption which resulted in decreased weight gain and decreased absolute body weight. The significantly reduced corrected body weight change supports maternal toxicity in the mid and high dose groups since no treatment-related effects were observed on fetal body weight.

   The maternal LOAEL in Sprague-Dawley is 250 mg/kg bw/day, based on clinical signs (salivation and piloerection around the time of treatment), decreased body weight change, decreased corrected body weight change, and decreased food consumption. The maternal NOAEL is 75 mg/kg bw/day.

2. **Developmental toxicity:**

   a. **Deaths/resorptions:** Maternal treatment with test article did not result in an increase in fetal or embryo death.

b. **Altered growth:** No adverse effects of maternal treatment were observed on fetal body weight or ossification rate.

c. **Developmental variations:** The number of litters containing fetuses with developmental variations was not increased as a result of maternal treatment.

d. **Malformations:** No treatment related external, visceral, or skeletal malformations were observed in fetuses from dams treated with RPA 203328.

The developmental LOAEL was not observed. The developmental NOAEL is 750 mg/kg bw/day.

C. STUDY DEFICIENCIES:

A minor deficiency is that the age of the mated females was not listed in the study report and differences in absolute body weight were not analyzed statistically.

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