DATA EVALUATION RECORD

DICAMBA BAPMA SALT

STUDY TYPE: PRENATAL DEVELOPMENTAL TOXICITY STUDY – RAT
OCSPP 870.3700a [§83-3a]; OECD 414

MRID 49441802

Prepared for
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DATA EVALUATION RECORD

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

PC CODE: 100094 **DP BARCODE:** Not provided.

TEST MATERIAL (PURITY): Dicamba BAPMA salt [84.7% w/w Dicamba BAPMA; 69.5% w/w Dicamba (acid equivalent)].

SYNONYMS: None provided.

CITATION: Schneider, S., M. Becker, and B. van Ravenzwaay (2014) Dicamba BAPMA salt: Prenatal developmental toxicity study in Wistar rats, oral administration (gavage). BASF SE (Ludwigshafen, Germany). Laboratory study number 30R0519/13R078, June 26, 2014. MRID 49441802. Unpublished.

SPONSOR: BASF SE (Ludwigshafen, Germany).

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 49441802), Dicamba BAPMA salt [84.7% w/w Dicamba BAPMA; 69.5% w/w Dicamba (acid equivalent), batch# 1781-6] was administered to 25 female Wistar rats/dose in 1% aqueous carboxymethylcellulose suspension by oral gavage at dose levels of 0, 29, 86, or 288 mg/kg bw/day (corresponding to 20, 60, or 200 mg/kg bw/day Dicamba acid) on gestation days (GDs) 6 through 19, inclusive. Body weights and food consumption were monitored regularly until sacrifice on GD 20. Dams were necropsied, and gravid uterine weight, numbers of corpora lutea, and numbers and distribution of live and dead fetuses and early and late resorptions were recorded. Fetuses were sexed, weighed, and investigated for external findings; approximately one-half of the fetuses of each litter were examined for soft tissue findings and the remaining fetuses for skeletal findings (inclusive of cartilage). Individual placental weights also were recorded.

At 86 and 288 mg/kg bw/day, maternal toxicity was characterized by increased incidences of adverse clinical signs, including unsteady gait, convulsions, and ataxia (occurrences/affected animals at 86 mg/kg/day: 114/24, 3/2 and 4/2; at 288 mg/kg/day: 74/20, 187/25 and 63/20, respectively, out of 25 total animals for both groups). Observations in the mid-dose females began after dosing and persisted for a maximum of 3 hours, with the earliest observations recorded on GD 6 (unsteady gait) or GDs 12-13 (convulsions/ataxia), while those in the high-dose females began after dosing, persisted for a maximum of 4 hours, and were first noted on GDs 6-7. Also in the 288 mg/kg/day females, body weight gain and food consumption was significantly

reduced compared to controls during intervals at the beginning of treatment, and non-statistically significantly reduced for the overall treatment period as follows: body weight gain: -20% during GDs 6-13, -8% during GDs 6-19; food consumption: -8% during GDs 6-10, -7% during GDs 6-19. The corrected (for gravid uterine weight) body weight gain was significantly lower in the high dose group by 16%, indicating that the decreased weight gain was a maternal effect. No maternal toxicity was apparent at the low dose of 29 mg/kg/day. No treatment-related effects on maternal cesarean section parameters were noted at any dose level for this study.

The maternal LOAEL for Dicamba BAPMA salt in rats is 86 mg/kg bw/day (corresponding to 60 mg/kg bw/day Dicamba acid equivalent), based on adverse clinical signs of unsteady gait, ataxia, and convulsions. The maternal NOAEL is 29 mg/kg bw/day (corresponding to 20 mg/kg bw/day Dicamba acid equivalent).

No developmental toxicity was evident as a result of maternal treatment with up to 288 mg/kg/day of Dicamba BAPMA salt. Fetal weights, fetal sex ratios, post implantation loss and numbers of viable fetuses, implantation sites, resorptions, and corpora lutea in all dose groups were comparable to the control group. The infrequent occurrence and nature of fetal malformations observed in the study were not considered treatment-related, and visceral and skeletal variations were comparable to controls and/or did not exhibit a dose-response relationship.

The developmental LOAEL for Dicamba BAPMA salt in rats was not determined. The developmental NOAEL is greater than or equal to 288 mg/kg bw/day (200 mg/kg bw/day Dicamba acid equivalent).

The developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; OECD 414) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Dicamba BAPMA salt

Description:	White to yellowish solid
Batch #:	1781-6
Purity:	84.7% w/w Dicamba BAPMA; 69.5% w/w Dicamba (acid equivalent)
Compound stability:	Stability under storage conditions (room temperature, protected from humidity) was guaranteed by the sponsor. Expiry date: June 12, 2015.
CAS #:	Not provided
Structure:	Not provided

2. **Vehicle and/or positive control:** The vehicle was 1% carboxymethylcellulose (lot/batch #, purity not provided) in drinking water. No positive control was used.

3. Test animals:

Species:	Rats, females
Strain:	Wistar (Crl:WI[Han])
Age/weight at study initiation:	10-12 weeks old; 149.2-193.7 g
Source:	Charles River Laboratories, Research Models and Services (Germany GmbH)
Housing:	Individually in Makrolon type M III cages (floor area of ~800 cm^2) supplied by Becker & Co. (Castrop-Rauxel, Germany) with dust-free wooden bedding and wooden gnawing blocks for enrichment.
Diet:	Ground Kliba maintenance diet mouse/rat "GLP", meal (Provimi Kliba SA, Kaiseraugst, Switzerland), *ad libitum*
Water:	Tap water in water bottles, *ad libitum*
Environmental conditions:	**Temperature:** 20-24°C **Humidity:** 30-70% **Air changes:** 15/hr **Photoperiod:** 12 hrs dark/12 hrs light
Acclimation period:	Supplied on day 0 of gestation

B. PROCEDURES AND STUDY DESIGN

1. **In life dates:** Start: January 8, 2014; End: January 29, 2014.

2. **Mating:** Animals were paired by the breeder and supplied on gestation day (GD) 0, which was defined as the day vaginal plug/sperm were detected. No further details were provided.

3. **Animal assignment:** The study was carried out in two cohorts, which started the study on consecutive days. Upon arrival, each cohort of females was distributed randomly in each of the four test groups, as indicated in Table 1. Each cohort was evenly distributed among the dose groups.

TABLE 1. Animal assignment [a]				
Dose of Dicamba BAPMA salt (mg/kg bw/day)	0	29	86	288
Dose of Dicamba acid equivalent (mg/kg bw/day)	0	20	60	200
Number of Females	25	25	25	25

[a] Data obtained from page 23 of the study report (MRID 49441802).

4. **Dose selection rationale:** The dose levels were selected at the request of the sponsor, but no rationale was provided.

5. **Dosage preparation:** Test formulations were prepared at the beginning of the administration period and at appropriate intervals thereafter, taking into consideration the 7-day stability period. The vehicle (1% carboxymethylcellulose suspension in drinking water) was added to an appropriate amount of test substance in a calibrated beaker and vigorously mixed with a homogenizer. The preparations were stored in a refrigerator prior to use and kept homogeneous with a magnetic stirrer during administration. Samples from the first batch of formulations used in the study were analyzed for concentration (all dose levels) and homogeneity (low and high concentrations). The samples for the homogeneity analysis were taken from the top, middle, and bottom of each preparation while the magnetic stirrer was running. Prior to the start of the study, stability was analyzed for a prepared sample of 9.9 mg/100 mL over a 7 day period, with storage at room temperature.

   Results:

   Homogeneity analysis: The measured concentrations sub-samples from the top, middle, and bottom of the 0.29 and 2.88 g/100 mL formulations were within 4% (RSD: 1.9%) and 3% (RSD: 1.4%) of each other, respectively.

   Stability analysis: The initial analyzed concentration was 9.41 mg/ 100 mL and was 10.13 mg/ 100 mL (107.6% of initial concentration) after 7 days.

   Concentration analysis: The measured concentrations of the 0.29, 0.86 and 2.88 g/100 mL formulations were 0.292 g/100 mL (100.6% of target), 0.835 g/100 mL (97.1% of target), and 2.864 g/100 mL (99.4% of target), respectively. Analysis of the vehicle control was not conducted to confirm absence of test material.

   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. It should be noted that the stability analysis was conducted on a much lower concentration of the test substance in vehicle (9.9 mg/100 mL) compared to the actual test formulations (290 to 2880 mg/100 mL). However, the less concentrated samples should be less stable than the more concentrated samples and the approach utilized was conservative.

6. **Dosage administration:** All doses were administered once daily by oral gavage, on GDs 6 through 19 (inclusive), in a volume of 10 mL/kg body weight. Dosing was based on the most recent body weight determination.

C. OBSERVATIONS:

1. **Maternal observations and evaluations:** The animals were checked once or twice daily for mortality (twice daily on working days and once daily on weekends and holidays) and at least once daily for clinical signs. It was not specified whether the observations were conducted at the anticipated time of peak effect. Body weights were recorded on GDs 0, 1, 3, 6, 8, 10, 13, 15, 17, 19 and 20; food consumption was recorded for the corresponding intervals. Females were sacrificed on GD 20 under isoflurane anesthesia by decapitation, in randomized order, necropsied, and assessed for gross pathology. The uteri and the ovaries were removed and the following data were recorded: gravid uterine weight; corpora lutea count; number and distribution of implantation sites; live and dead fetuses; and early and late resorptions. Uteri were stained according to the Salewski method to confirm non-pregnant females and empty individual uterus horns in the case of single horn pregnancy. After weighing the uterus, all subsequent evaluations of the dams and the gestational parameters were conducted by technicians blind to treatment group.

2. **Fetal evaluations:** Fetal evaluations were conducted by technicians unaware of the treatment group. At necropsy, each fetus was weighed, sexed, and examined macroscopically (external tissues and all orifices). The viability of the fetuses and the condition of placentae, umbilical cords, fetal membranes, and fluids were examined, and placentae were weighed individually. The fetuses were sacrificed by a subcutaneous injection of pentobarbital, and approximately one half of the fetuses per litter were placed in Harrison's fluid for fixation; the other half were eviscerated, skinned and fixed in ethanol. The fetuses fixed in Harrison's fluid were examined for any visceral findings according to the method of Barrow and Taylor, and then discarded. The skeletons of the fetuses fixed in ethanol were stained according to a modification of the method described by Kimmel and Trammell, examined under a stereomicroscope, and then archived individually. Observations were classified as malformations or variations according to the following definitions: malformations are permanent structural changes that are likely to adversely affect survival or health; variations are changes that also occur in the fetuses of control animals and/or are unlikely to adversely affect survival or health (including delays in growth or morphogenesis that have otherwise followed a normal pattern of development). The term "unclassified observation" was used for those fetal findings which could not be classified as malformations or variations.

D. DATA ANALYSIS:

1. **Statistical analyses:** Dunnett's test (two-sided) was used to detect differences in all dose groups compared to the control group for the following parameters: food consumption (no analysis was performed for the "mean of means" values); body weight and body weight change; uterine weight; numbers of corpora lutea, implantations, resorptions, and live fetuses; pre- and post-implantation loss; and litter mean fetal body weight and placental weight. Fisher's Exact test (one-sided) was used to determine differences between each dose group and the control group for the following parameters: mortality; number pregnant at terminal sacrifice; and number of litters with fetal findings. The Wilcoxon test was used to compare each dose group with the control group to detect differences in the proportions of fetuses with malformations, variations, and/or unclassified findings in each litter.

2. **Indices:** The following indices were calculated:

$$\text{Conception rate (\%)} = \frac{\text{No. pregnant animals}}{\text{No. fertilized animals}} \times 100\%$$

$$\text{Pre-implantation loss (mean \%)} = \frac{\text{No. corpora lutea} - \text{No. implantation sites}}{\text{No. corpora lutea}} \times 100\%$$

$$\text{Post-implantation loss (mean \%)} = \frac{\text{No. implantation sites} - \text{No. live fetuses}}{\text{No. implantation sites}} \times 100\%$$

3. **Historical control data:** The provided historical control data included data from 21 studies (2 inhalation and 19 gavage administration) collected from March 2009 through August 2013 and included maternal body weights from 490-514 females, intrauterine parameters from 511-514 dams, and fetal malformation and variation observations from 5139 fetuses (511 litters). Data were provided in aggregate form: maternal data were presented as overall means and ranges; morphological findings were presented as total numbers of affected fetuses and litters with each finding, overall percentages of affected fetuses and litters with each finding, and the range of percentages across all of the studies.

II. RESULTS

A. MATERNAL TOXICITY:

1. **Mortality and clinical observations:** There were no unscheduled deaths. Treatment-related clinical signs are summarized in Table 2. In the high dose group, these included convulsions in all females and unsteady gait and/or ataxia (in 20 of 25 females) on one or more occasions during the treatment period (GD 6-19). These began after dosing and persisted for a maximum of 4 hours and were first noted on GDs 6-7. Observations in the mid-dose females included unsteady gait (24 of 25) on one or more occasions, as well as convulsions (2 of 25) and ataxia (2 of 25) on 1-2 occasions during the treatment period. These began after dosing and persisted for a maximum of 3 hours, with the earliest observations recorded on GD 6 (unsteady gait) or GDs 12-13 (convulsions/ataxia). No treatment-related clinical signs or behavioral observations were detected in any female in the low-dose group during the entire study period.

TABLE 2. Treatment-related clinical signs (Total occurrence/ # of animals) [a]

Observation	Dose in mg/kg bw/day (# of Dams)			
	0 (25)	29 (25)	86 (25)	288 (25)
Unsteady gait	0	0	114/24	74/20
Convulsion	0	0	3/2	187/25
Ataxia	0	0	4/2	63/20

[a] Data obtained from page 52 in the study report (MRID 49441802).

2. **Body weight:** Body weight and body weight gain data are summarized in Table 3. Mean absolute body weights of these females were comparable to the controls throughout the study period. Mean body weight gain for the high dose females during the treatment period (GD 6-19) and the overall study period (GD 0-20) was lower than controls by 8% and 5%,

respectively, but did not achieve statistical significance. This was largely due to significantly lower weight gain in this group during GDs 6-8 and GD 10-13, with an overall decrease of 20% during GDs 6-13 (27.7 g vs. 34.4 g in control vs. high-dose females). Body weight gain was essentially similar to controls during GDs 13-20 (64.9 g vs 64.1 g in control vs. high-dose females). The corrected body weight gain was significantly lower in the high dose group by 16%, suggesting that the difference in body weight gain was a maternal effect. Mean body weight, body weight gain, and corrected body weight gain of the low- and mid-dose rats were comparable to the controls throughout the study period.

TABLE 3. Mean (±SD) maternal body weight and body weight gain (g) [a]

Gestation day or interval	Dose in mg/kg bw/day (# of Dams)			
	0 (n=22)	29 (n=24)	86 (n=25)	288 (n=23)
Body weight				
GD 0	169.0±12.9	169.5±11.4	168.5±10.3	169.2±8.4
GD 6	199.2±14.9	200.6±15.6	199.5±11.5	199.6±11.5
GD 8	208.1±16.7	208.1±16.9	208.2±12.2	204.5±11.6
GD 10	217.0±16.9	217.1±18.1	218.0±12.7	214.2±12.7
GD 13	233.6±18.5	234.3±18.7	234.1±13.9	227.3±12.6
GD 15	243.9±18.5	244.7±19.7	245.1±14.4	238.9±13.9
GD 17	263.7±21.0	264.5±21.5	265.4±16.0	257.1±15.4
GD 20	298.5±27.4	298.9±25.3	301.5±19.1	291.4±19.3
Gravid uterine weight (g)	55.5±14.2	56.5±9.0	57.9±12.0	55.0±10.0
Body weight gain				
GDs 0-6	30.1±4.7	31.1±5.7	31.0±3.8	30.4±5.3
GDs 6-8	8.9±3.2	7.5±2.9	8.7±2.6	4.9±2.5** (-45) [b]
GDs 8-10	8.9±1.6	9.0±2.6	9.8±1.9	9.8±2.0 (+10)
GDs 10-13	16.6±3.3	17.2±2.3	16.1±2.6	13.1±2.7** (-21)
GDs 13-15	10.3±3.3	10.4±3.4	11.0±2.4	11.5±2.3 (+12)
GDs 15-17	19.8±4.1	19.8±2.9	20.4±3.4	18.2±2.9 (-8)
GDs 6-19	86.0±14.9	84.8±10.4	87.6±11.9	78.7±9.2 (-8)
GDs 0-20	129.4±18.6	129.4±16.9	133.1±14.8	122.3±14.4 (-5)
Corrected BW gain: GDs 6-20 [c]	43.8±6.5	41.8±8.2	44.1±7.2	36.9±6.1** (-16)

[a] Data obtained from pages 55-58 in the study report (MRID 49441802).
[b] Numbers in parentheses are percent change from control, calculated by the Reviewer.
[c] Body weight on GD 20 – uterine weight – body weight on GD 6
** Statistically different (p <0.01) from the control.

3. **Food consumption:** Food consumption data are summarized in Table 4. Mean food consumption of the females in the high dose group was significantly decreased by up to 8% at the beginning of the treatment period (GD 6-10), and non-statistically significantly decreased by 7% and 5% during the treatment period (GD 6-19) and entire study period (GD 0-20), respectively (statistical analysis was not performed for these overall periods). Mean food consumption of the low- and mid-dose dams was comparable to controls throughout the entire study.

TABLE 4. Mean (±SD) food consumption (g/animals/day) [a]

Gestation Day or Interval	Dose in mg/kg bw/day (# of Dams)			
	0 (22)	29 (24)	86 (25)	288 (23)
GDs 0-6 [c]	17.0±3.1	17.2±3.7	17.1±3.4	17.1±3.0
GDs 6-8	20.3±1.7	20.2±2.0	20.7±2.2	18.8±1.6* (-7)
GDs 8-10	21.0±1.8	21.3±2.1	20.9±1.7	19.4±2.6* (-8)
GDs 10-13	22.8±2.1	23.2±2.2	22.8±1.8	21.5±1.8 (-6)
GDs 15-17	24.4±2.7	24.6±2.2	25.3±2.2	22.9±2.2 (-6)
GDs 6-19 [c]	22.9±2.0	22.9±1.9	23.0±1.9	21.4±2.0 (-7)
GDs 0-20 [c]	21.2±3.6	21.3±3.6	21.3±3.7	20.2±3.0 (-5)

[a] Data obtained from pages 53-54 in the study report (MRID 49441802).
[b] Numbers in parentheses are percent change from control, calculated by the Reviewer.
[c] Reported as a mean of means and not subjected to statistical analysis.
* Statistically different (p <0.05) from the control.

4. **Gross pathology:** No treatment related macroscopic findings were noted. One spontaneous finding (dilated renal pelvis) was noted in a single female of the low-dose group and was not considered treatment-related.

5. **Cesarean section data:** As summarized in Table 5, there were no treatment related effects on cesarean section parameters, including the following: pregnancy rate, numbers of corpora lutea, implantation sites, litter size, fetal body weight, placental weight, sex ratio or pre- or post-implantation loss.

TABLE 5. Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	29	86	288
# Animals assigned (mated)	25	25	25	25
# Animals pregnant	22	24	25	23
Pregnancy rate (%)	88	96	100	92
# Non-pregnant	3	1	0	2
Maternal wastage	0	0	0	0
No. died	0	0	0	0
No. aborted	0	0	0	0
No. Premature delivery	0	0	0	0
Total No. corpora lutea **(Corpora lutea/dam)**	254 11.5±2.0	262 10.9±1.5	282 11.3±2.3	261 11.3±1.9
Total No. implantations **(Implantations/dam)**	233 10.6±2.5	255 10.6±1.5	274 11.0±2.3	244 10.6±1.9
Total No. litters	22	24	25	23
Total No. live fetuses **(Live fetuses/dam)**	218 9.9±2.6	236 9.8±1.5	260 10.4±2.3	232 10.1±1.8
Total No. dead fetuses **(Dead fetuses/dam)**	0 0	0 0	0 0	0 0
No. resorptions **Early** **Late**	15 15 0	19 19 0	14 13 1	12 11 1
Resorptions/dam **Early** **Late**	0.7±0.8 0.7±0.8 0±0	0.8±0.8 0.8±0.8 0±0	0.6±0.8 0.5±0.7 0±0.2	0.5±0.8 0.5±0.8 0±0.2
Litters with total resorptions	0	0	0	0
Mean fetal weight (g) **Males (g)** **Females (g)**	3.5±0.18 3.6±0.22 3.4±0.17	3.6±0.18 3.7±0.21 3.6±0.19	3.5±0.20 3.6±0.21 3.4±0.20	3.4±0.16 3.5±0.20 3.3±0.15
Sex ratio (% male)	48.2	47.5	47.7	46.6
Pre-implantation loss (mean %)	8.9±14.5	2.5±5.9	2.8±5.3	6.3±7.8
Post-implantation loss (mean %)	8.3±14.9	7.3±7.6	5.0±7.0	4.8±7.4

[a] Data obtained from pages 60-63 in the study report (MRID 49441802).

B. **DEVELOPMENTAL TOXICITY:** There were no effects on fetal development that were attributed to treatment. The number of fetuses (litters) evaluated was 218 (22), 236 (24), 260 (25), and 232 (23) in the control, 29, 86, and 288 mg/kg/day groups, respectively, with malformations found in 0 (0), 3 (3), 2 (2), and 0 (0) fetuses (litters) and variations found in 119 (22), 131 (24), 142 (25), and 121 (23) fetuses (litters) in the same respective groups. There was a slightly higher value for the total malformation rate of affected fetuses per litter in the 29 mg/kg/day group ($p<0.05$), but there was no dose-dependency and the value was within the range of historical controls; therefore it was not considered treatment-related and not adverse.

1. **External examination:** There were no treatment-related effects on fetal external morphology (malformations or variations). A single fetus in the mid-dose group had a malformed mandible, which was associated with a skeletal malformation (fused mandible).

2. **Visceral examination:** There were no treatment-related effects on fetal visceral morphology; selected non-treatment related findings are summarized in Table 6a. One fetus each in the

low- and mid-dose groups had soft tissue malformations; anophthalmia and situs inversus were noted in the respective fetuses. These incidences were comparable to historical control data and were not considered treatment-related. Soft tissue variations occurred in all groups, including the control group, and were neither significantly different from control nor dose-dependent; these included dilated renal pelvis and dilated ureter as well as single incidences of dilated cerebral ventricle and short innominate in the control group. Two unclassified observations (intestinal convolutions grown in between liver lobes, and discolored testis) were noted in one fetus each from the mid- and high-dose groups and were not considered biologically significant.

3. **Skeletal examination:** There were no treatment-related effects on fetal skeletal morphology; selected incidental findings are summarized in Table 6b. Skeletal malformations were detected in two fetuses from the low-dose group (i.e., cleft sternum, cervical hemivertebra, and misshapen cervical vertebra) and one fetus from the mid-dose group (i.e., fused mandible). Skeletal variations were noted in all groups, including the control group, with statistically significant increases in some variations (misshapen sacral vertebra or sternebrae, unchanged cartilage; 14th rib, cartilage present) detected only in the low-dose group. Variations were comparable to historical controls and/or not dose-dependent and therefore not attributed to treatment. Isolated unclassified cartilage findings occurred in all groups, including the control, and were related to the skull, vertebral column, sternum and ribs, but did not impact the respective bony structure or show any dose-dependency; the most common finding was bipartite processus xiphoideus, present in all litters.

TABLE 6a. Visceral examinations [a b]

Observations	Dose (mg/kg bw/day)			
	0	29	86	288
# Fetuses (litters) examined	102 (21)	112 (24)	120 (25)	109 (23)
Malformations				
Total # Fetuses (litters) affected	0	1 (1)	1 (1)	0
Situs inversus	0	0	1 (1)	0
Anophthalmia	0	1 (1)	0	0
Variations				
Total # Fetuses (litters) affected	4 (4)	7 (5)	3 (3)	2 (1)
Dilated renal pelvis	2 (2)	7 (5)	2 (2)	2 (1)
Dilated ureter	0	2 (2)	1 (1)	1 (1)

[a] Data obtained from pages 69-72 in the study report (MRID 49441802).

[b] Data given as number of fetuses (number of litters) with each finding.

TABLE 6b. Skeletal examinations [a b]

Observations	Dose (mg/kg bw/day)			
	0	29	86	288
# Fetuses (litters) examined	116 (22)	124 (24)	140 (25)	123 (23)
Malformations				
Total # Fetuses (litters) affected	0	2 (2)	1 (1)	0
Fused mandible	0	0	1 (1)	0
Cleft sternum	0	1 (1)	0	0
Cervical hemivertebra, misshapen cervical vertebra [c]	0	1 (1)	0	0
Variations				
Total # Fetuses (litters) affected	115 (22)	124 (24)	139 (25)	119 (23)
Misshapen sacral vertebra	2 (1)	11 (7)* [d]	4 (3)	2 (2)

TABLE 6b. Skeletal examinations [a] [b]

Observations	Dose (mg/kg bw/day)			
	0	29	86	288
Misshapen sternebrae, unchanged cartilage	45 (20)	68 (23) [d]	63 (24)	62 (22)
Supernumerary rib (14th), cartilage present	6 (4)	16 (11)* [d]	9 (6)	5 (4)
Supernumerary rib (14th), cartilage not present	59 (18)	73 (22)	71 (23)	63 (21)
Incomplete ossification:				
Basisphenoid	24 (11)	23 (13)	24 (13)	16 (12)
Parietal, unchanged cartilage	17 (10)	17 (12)	14 (8)	15 (8)
Interparietal, unchanged cartilage	36 (16)	37 (19)	39 (22)	35 (18)
Supraoccipital, unchanged cartilage	62 (21)	53 (23)	63 (23)	59 (20)
Sternebra, unchanged cartilage	105 (22)	107 (24)	128 (25)	107 (23)

[a] Data obtained from pages 73-87 in the study report (MRID 49441802).
[b] Data given as number of fetuses (number of litters) with each finding.
[c] Occurring in the same fetus
[d] Also significant when percent of affected fetuses/litter was analyzed.

III. DISCUSSION AND CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: Under the conditions of this prenatal developmental toxicity study, oral administration of Dicamba BAPMA salt to pregnant Wistar rats from GD 6-19 at doses of 86 and 288 mg/kg bw/day caused evidence of maternal toxicity, characterized by adverse clinical observations (convulsions, ataxia, unsteady gait). At 288 mg/kg bw/day, reduced food consumption and body weight gain also were noted. All females of the 288 mg/kg bw/day group exhibited convulsions after treatment during the treatment period (GD 6-19), and almost every female in this group showed unsteady gait and/or ataxia after treatment. At 86 mg/kg bw/day, unsteady gait was frequently observed in almost all females while convulsions and ataxia were less frequent, affecting only individual animals on single occasions. These effects are considered to be treatment-related. No toxicologically relevant effect was noted for the animals in the 29 mg/kg bw/day group.

No differences of toxicological relevance between the control and the treated groups up to 288 mg/kg bw/d were determined for any reproductive (e.g., conception rate, numbers of corpora lutea or implantations, and pre- and post-implantation loss) or fetal (e.g., weight, sex ratio, morphology) parameters.

In conclusion, the no observed adverse effect level (NOAEL) for maternal toxicity is 29 mg/kg bw/day Dicamba BAPMA salt, corresponding to a Dicamba acid dose of 20 mg/kg bw/day. There were no toxicologically relevant adverse fetal findings evident. Thus, the NOAEL for prenatal developmental toxicity is 288 mg/kg bw/day, corresponding to a Dicamba acid dose of 200 mg/kg bw/day.

B. REVIEWER COMMENTS:

1. **Maternal toxicity:** The Agency concurs that maternal toxicity was evident at the mid- and high-dose levels of 86 and 288 mg/kg/day, characterized by adverse clinical signs of unsteady gait, convulsions, and ataxia. Treatment-related reductions in body weight gain and food consumption in the 288 mg/kg/day females occurred during the treatment period, primarily due to significant reductions during the beginning of treatment, however not considered

adverse due to the lack of adverse effects on body weight. No treatment-related effects on maternal cesarean section parameters were noted at any of the dose levels in this study.

The maternal LOAEL for Dicamba BAPMA salt in rats is 86 mg/kg bw/day (corresponding to 60 mg/kg bw/day Dicamba acid equivalent), based on adverse clinical signs of unsteady gait, ataxia, and convulsions. The maternal NOAEL is 29 mg/kg bw/day (corresponding to 20 mg/kg bw/day Dicamba acid equivalent).

2. **Developmental toxicity:**

   a. **Deaths/resorptions:** There were no fetal deaths, and the numbers of resorptions were comparable among all groups.

   b. **Altered growth:** Fetal body weights were comparable across all groups, and there was no evidence of altered ossification rates.

   c. **Developmental variations:** There were no treatment-related effects on developmental variations.

   d. **Malformations:** There were no treatment-related effects on developmental malformations.

   The developmental LOAEL for Dicamba BAPMA salt in rats was not determined. The developmental NOAEL is greater than or equal to 288 mg/kg bw/day (200 mg/kg bw/day Dicamba acid equivalent).

The developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; OECD 414) in the rat.

C. **STUDY DEFICIENCIES:** It was not specified in the study report whether the daily (cage-side) observations were conducted at the peak period of anticipated effects after dosing (as specified under OCSPP 870.3700).