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

004036

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dicamba Registration Standard.

TO: Bill Burnam
Branch Chief, Tox

WJB 8-8-83

William M. Butler 7/7/83

Attached please find the DERs for the available toxicology studies on dicamba as well as the one-liners, summary of the data gaps and tolerance reassessment.

Stephanie P. April

Stephanie P. April, Ph.D.

BEST AVAILABLE COPY

1 of 73

Acute Studies

A. Type: Primary Eye Irritation in albino rabbits

Citation: Wazeter, F.X., Goldenthal, E.T., Dean, W.P. Unpublished Study

Accesion No.: Not available

MRID: 00025371

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: IRDC

Study No.: 163-323

Date: January 24, 1975

Material Tested:

Banvel, 4 lb/gal. dimethylamine salt in water was received on November 29, 1974 as a brown liquid. No lot number was given.

Material and Methods:

Four male and 4 female New Zealand White rabbits weighing 2801-3969 grams were divided into 2 groups and tested with 0.1 ml of the test material instilled into the conjunctival sac of one eye. Eyes of five animals were washed at 5 minutes while 3 were unwashed for 24 hours. Observations lasted for 21 days.

Results and Conclusion:

The product induced corrosive of the conjuntival tissues and corneal injury which was reversible in 72 hours. The severity of the irritation was not indicated.

Tox. Cat. I

Classification: Core Minimum

B. Type: Primary Skin Irritation in Albino Rabbits

Citation: Wazeter, F.X.; Goldenthal, E.T.; Dean, W.P.: Unpublished Study.

Accession No.: Not available

MRID No.: 00025371

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: IRDC

Study No.: 163-25

Date: January 24, 1975

Material Tested:

Banvel, 4 lb/gal. dimethylamine salt in water was received on November 29, 1974 as a brown liquid. No lot number was given.

Material & Method:

Three male and 3 female rabbits weighing from 2640 to 3612 gms. were treated in 3 abraded and 3 intact clipped areas with 0.5 mls of the test material for 4 hours, protected with gauze after treatment, and observed for 72 hours.

Results:

PIS = 0.2

Slight erythema and edema were observed up to 72 hours.

Tox. Category III.

Core Classification: Core Minimum.

C. Study Type: Acute Dermal Toxicity in Albino Rabbits

Citation: Wazeter, F.X., Goldenthal, E.T., Dean, W.P. Unpublished Study.

Accession No.: Not available

MRID: 00025371

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: IRDC

Study No.: 163-323

Date: January 24, 1975

Material Tested:

Banvel, 4 lb/gal dimethylamine salt in water was received on November 29, 1974 as a brown liquid. No lot number was given.

Material and Methods:

Two male and 2 female rabbits weighing 2732 to 3000 gms were dosed on abraded (half of the animals) and intact (other half) areas of the skin with 2000 mg/kg of the material for 24 hours and observed for 14 days.

Results:

LD_{50} >2000 mg/kg

Toxicity Category: IV.

Core Classification: Supplementary, insufficient details were given. Inadequate number of animals were used.

D. Type: Primary Dermal

Citation:

Dean, W.F.; Jessup, D.C.; Thompson, G.; et al. (1978). Unpublished study.

Accession No.

MRID No.: 00028235

Sponsor: Velsicol Chemical Corp.

Contract Laboratory: IRDC

Date: October 4, 1978

Material Tested: Banvel D (Tech), the DMA salt of dicamba, 86.8% pure, lot #52625110 as beige chips received as Analytical Reference Standard on June 12 and July 3, 1978.

Protocol: Three male and 3 female rabbits from HARE Rabbits for Research, Hewitt, New Jersey, weighing from 2327 to 3430 gm. were individually housed with temperature and humidity control and given food (Purina Rabbit Chow) and water ad libitum.

The back of each rabbit was shaved so that each had 2 intact and 2 abraded sites (just enough to penetrate stratum corneum).

The Banvel D in physiological saline was applied to each site on the rabbit back and kept under gauze and wrapped in Saran wrap which was taped on. The results were read at 24 hours, 72 hours and at 7 and 14 days.

Results

The scoring of skin reaction was according to the "Skin Reaction Code, Principles and Procedures for Evaluating the Toxicity of Household Substances," NAS, 1977, p. 122.

The following table presents the individual rabbit scores. The computed primary irritation score is 1.2 and based upon the scoring technique it is slightly irritating and not a primary irritant.

Number of Rabbits Exhibiting Signs with Scoring "Value"/Number Dosed

Observations	Value	Intact Skin				Abraded Skin			
		Hours		Days		Hours		Days	
		24	72	7	14	24	72	7	14
Erythema, Eschar Formation	0		4/12	9/12	12/12	2/12	6/12	9/12	12/12
	1	12/12	8/12	3/12		10/12	6/12	3/12	
	2								
	3								
	4								
Edema Formation	0								
	1	4/12	10/12	12/12	12/12	5/12	10/12	11/12	12/12
	2	8/12	2/12			7/12	2/12	1/12	
	3								
	4								

Conclusion

The data obtained indicate that the test material is not to be considered a primary skin irritant.

Classification: Core minimum.

004036

E. Study Type: Acute Inhalation Toxicity in the Albino Rat

Citation: Wazeter, F.X., Goldenthal, E.T., Dean, W.P. Unpublished Study.
Accession No.: Not available

MRID: 00025371

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: IRDC

Study No.: 163-323

Date: January 24, 1975

Material Tested:

Banvel, 4 lb/gal dimethylamine salt in water was received on November 29, 1974 as a brown liquid. No lot number was given.

Material and Methods:

Five males and 5 females weight 206-232 gms were exposed for 4 hours in a 59.1 liter in a glass chamber to a mist of the material at a nominal concentration of 200 mg/l of Banvel 4 lb/gal DMA and observed for 14 days.

Results and conclusion:

LC_{50} >200 mg/l. Signs of toxicity: Lethargy, eye fluids discharge, erythema. There were no deaths.

Tox. Category: IV.

Core Classification: Supplementary, no actual exposure concentrations were given.

004036

F. Study Type: Acute Inhalation LC_{50} Rat

Citation: Wazeter, F.X., Goldenthal, E.I., Dean, W.P.; et al, 1976: Unpublished Study.

Accession No.: Not Available

MRID No.: 00028234

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: International Research and Development Corp.

Study No.: 163-191

Date: January 16, 1973

Material Tested:

Analytical Reference Standard Banvel D

Tech - 89.3% Lot A115-97-7 as a pale brown powder received November 20, 1972.

Material and Methods:

This study was performed in accordance with the regulations under the Federal Hazardous Substance Act. Ten male and 10 female rats weighing from 219 to 247 g were exposed for 4 hours, in a sealed 59.1 liter glass chamber, "to a dynamic atmosphere containing the dust of the test material". Animals were observed for signs of toxicity or unusual behavior. Animals were sacrificed after 14 days, and all which died were necropsied. The nominal concentration was 200 mg/l.

Results and Conclusion

Mortality:. one rat at 30 minutes another at one hour. Signs of Toxicity: erratic respiration, dyspnea prostration salivation, lacrimation, nasal discharge, ataxia. Such signs of toxicity were observed for up to the 9th day.

The material was observed to adhere to the body surface. Thus the results of the test for inhalation toxicity can not be fairly evaluated due to the introduction of dermal absorption. However, considering the large concentration in the atmosphere of the chamber, we can conclude that the product is not toxic by the inhalation route.

Tox. Category IV. LC_{50} >200 mg/l.

Classification - Supplementary, no actual exposure concentration given.

G. Study Type: Primary Eye Irritation

Citation: Dean, W.D.,: Unpublished results.

Accession No.: Not available

MRID No.: 00025368

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: IRDC

Study No.: 163-387

Date: March 5, 1976

Material Tested:

Dimethylamine salt of dicamba as Banvel 4 lbs/gal at pH 8.3. No date of receipt or lot number was given.

Procedure:

Six rabbits were treated with 0.1 ml of the test material in the eye and observed at the 24, 48, 72 hours and the seventh day. All rabbit eyes were unwashed.

Results and Conclusion

Severe eye damage as irreversible pannus was observed. Banvel is a severe eye irritant.

Category: I

Classification: Core minimum.

H. Study Type: Eye Irritation in Rabbits

Citation: Wazeter, F.X.; Goldenthal, E.T.; Dean, W.P.: Unpublished Study.

Accession No.: Not available

MRID No.: 00028222

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: IRDC

Study No.: IRDC 163-279

Date: 1974

Material Tested:

Ground pelleted/tableted dicamba acid was not further described.

Procedure:

Four males and 4 females albino rabbits were tested with 0.1 ml of the material instilled in the conjunctival sac of the eye. Five rabbit eyes were washed; after 5 minutes the other 3 were unwashed. Observations lasted till the 21 day post application.

Results and Conclusion

Corneal opacity that lasted for longer than 72 hours was observed but reversed by 7 days. Dicamba is a severe eye irritant. Dicamba acid was a severe eye irritant in this study.

Toxicity Category I.

Classification: Core Minimum.

I. Study Type: Eye Irritation in Rabbits

Citation: Dean, W.P.; unpublished data.

Accession No.: Not available

MRID No.: 00025366

Sponsor: Velsicol

Laboratory: IRDC

Project No.: IRDC 163-386

Date: March 5, 1976

Material Tested:

Banvel D, the dimethylamine salt in water at, 4 lb/gal pH 6.45 no other information was given.

Procedure:

Six rabbits were treated with 0.1 ml of the test material in the eye and observed at the 24, 48, 72 hours and the seventh day.

Results:

Although the product at a pH of 6.45 did not induce "pannus", the results indicate severe irritation such as corneal ulceration and conjunctival blanching and hemorrhage redness, chemosis, that lasted through the 7 day post treatment observation.

Conclusion:

Based upon the results obtained Banvel D would be considered an eye irritant.

Tox. Cat. I.

Classification: Core Minimum.

004036

J. Study Type: Primary Eye Irritation in Rabbits

Citation: Bier, C.B., Goyeche, L.: Unpublished study.

Accession No.: Not given

MRID No.: 00065846

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: Bio-Research Lab., Canada

Project No.: 12662

Date: July 16, 1980

Material Tested:

Banvel 4S, dicamba acid in water as a liquid pH, 7.45 from Velsicol was used. No other information was given.

Material and Methods:

Nine male New Zealand White rabbits, 2.0 to 3.5 kg, aged 10-13 weeks were individually housed at 22° x ± 2°C, 40-60% relative humidity, 12 hrs. light/12 hrs. dark and acclimated for 2 weeks with food and water ad libitum. The animals were randomly placed into two groups by use of a pseudo-random number generator as Group I, 3 washed and Group II, 6 unwashed eyes. One tenth ml of test material was applied to each animal once. The eyes of Group I animals were washed with water 20-30 seconds after the one minute application of the test material. The animals were observed at 24, 48, 72 and 96 hours and at 7, 10, and 13 days post-dosing. The tested eye of each animal was scored against their own control eye and scored according to the method of Draize.

Results:

Twenty four hours post dosing in the washed group resulted in mild to moderate (10 to 34) ocular irritation and moderate irritation (34-54) was found for the non-irrigated group. Both groups had mild to moderate erythema of palpebral conjunctivae with moderate periorbital discharge. A mild opalescence over the entire corneal surface persisted for 4 days. All animals in the irrigated group were normal by 7 days. The non-irrigated group effects persisted for 4 days in 4 animals but lasted 13 days for 2 animals.

Conclusions:

Banvel 4S was a mild to moderate ocular irritant in male rabbits. The severity of the ocular effect was decreased by washing.

Class: III washed/II unwashed

Classification: Core Minimum.

Reproduction

Study Type: Three Generation Reproduction Study in Rats.

Accession Number: Not available.

MRID Number: 00028249.

Sponsor: Velsicol Chemical Corp., 341 East Ohio Street, Chicago, IL.

Contracting Laboratory: University of Cincinnati, Dept. of Environmental Health, Cincinnati, OH, S. Witherup, K. L. Stemmer, and M. Roell.

Date: January 3, 1966

Test Material: The test article, Technical Banvel D, was received from the Velsicol Chemical Corporation at an unspecified date. The test article had a sample number of C-64184 and was described as light tan solid with a faint phenolic odor. An infrared analysis of the test article indicated a purity of 87.2%. No stability or storage information was reported.

Protocol:

Test System: The Charles River CD strain of albino rat was employed as the test system. Male and female rats were received from Charles River Breeding Laboratories at 21 ± 2 days of age. The animals were randomly assigned to one of six groups, each containing 20 females and 10 males. Subsequent generations were obtained from the F_{1b} and F_{2b} litters. Animals were housed four females or five males to a cage in a room maintained at 76 ± 2° F.

At approximately 100 days of age the F_0 animals were bred to produce the F_{1a} litters. One male and two females were placed together until pregnancy was ascertained by an increase in the body weight of the female rat. Pregnant females were individually housed in a cage with nesting material and observed daily. Mating continued for a maximum of four weeks at which time a male failing to impregnate either of the females was removed and replaced by a proven male.

The F_{1a} pups were examined shortly after birth for external appearance and sex, and the weights of the male pups as a group and the female pups as a group were obtained. After seven days of lactation, the F_{1a} pups were sacrificed and their viscera examined for gross abnormalities.

The F_0 females were allowed to rest for one week after the sacrifice of the F_{1a} litters and then remated to produce the F_{1b} generation in the manner described to produce the F_{1a} litters. The F_{1b} pups were allowed to nurse for 21 days, at which time they were grouped according to sex and weighed as a group. Each group of F_{1b} pups was reduced to 20 females and 10 males after weaning and maintained on the diets of their parents until approximately 90 days of age.

The selected animals of the F_{1b} litters (identified as the F_1 generation) were allowed to produce the F_{2a} and F_{2b} litters in a manner identical to that of the F_0 generation. The F_{2a} and F_{2b} pups were handled in a manner similar to that of the F_{1a} and F_{1b} litters, respectively.

This procedure was repeated with animals from the F_{2b} litters (now the F_2 generation) to produce the F_{3a} and F_{3b} litters with the exception that only 10 females and 5 males were remated to yield the F_{3b} litters. The F_{3b} pups were sacrificed at 21 days of age and their viscera examined for gross abnormalities. Tissues from the F_{3b} animals were examined microscopically for pathologic changes.

Test Article Administration: The test article was administered ad libitum via the feed beginning three weeks prior to the first mating of the F_0 generation and continuing until the sacrifice of the F_{2b}/F_{3b} generations. Prior to initial administration of the test article rats from the six groups received Purina Laboratory Chow. Approximate quantities of Banvel D were dissolved in an ethanol vehicle and mixed with Purina Laboratory Chow to yield the required dose levels of 50, 125, 250, and 500 ppm. The remaining two groups received identical vehicle control diets containing ethanol and Purina Laboratory Chow. The diet was prepared fresh weekly and offered to the animals for seven days at which time it was replaced with fresh diet.

Parameters to be examined:

1. Observations--The mated animals were observed daily for obviously pregnant females. Pups were examined for external anomalies at birth and at days 7 and 21 of lactation.

2. Pup Body Weight--The pups were weighed by sex at birth and at days 7 and 21 of lactation.

3. Reproduction Indices--The following indices were calculated:

$$\text{Fertility Index}^{a} = \frac{\text{Number of Pregnancies}}{\text{Number of Matings}} \times 100$$

$$\text{Gestation Index}^{a} = \frac{\text{Number of Litters with Live Pups}}{\text{Number of Pregnancies}} \times 100$$

$$\text{Viability Index}^{b} = \frac{\text{Number of Pups Alive at 7 days}}{\text{Number of Pups Born}} \times 100$$

$$\text{Lactation Index}^{c} = \frac{\text{Number of Pups Weaned}}{\text{Number Alive at 7 Days}} \times 100$$

4. The viscera of each pup of the "a" litters was grossly examined at sacrifice after day 7 of lactation. Sections of the visceral organs not listed of the F_{3b} pups were also examined histopathologically but no data was presented.

Statistics: No statistical analysis was performed.

Results

Clinical Observations

No compound-related clinical signs were observed during the course of this study. Six deaths occurred during the study that appeared to be related to pneumonia or the process of giving birth. The deaths involved two females fed Banvel D at 50 ppm, two females receiving the vehicle control diet, and two males from unspecified treatment groups. No abnormalities in external appearance were noted among the pups at the specified observation intervals (birth and days 7 and 21 of lactation).

---

[a] For all matings
[b] For all litters.
[c] For "b" litters only.

Pup Body Weights

The authors stated that the average body weights of the males and female pups at birth, day 7, and day 21 of lactation were similar between the six groups (two control and four dosed). The pup body weight data were not presented.

Reproduction Indices

The fertility indices at each generation were similar between the six groups of the study. This index was also similar between subsequent generations within each group. The fertility indices ranged from 77.5% to 97.5%, which was within the range expected for Sprague-Dawley rats.

The gestation indices at each generation were also similar between the six groups and between the subsequent generations within each group. The gestation indices ranged from 92.1% to 100.0%, a range not uncommon with Sprague-Dawley rats.

The viability indices, calculated for birth to day 7 of lactation, were similar between the six groups and between subsequent generations within each group. The day 7 of lactation viability indices ranged from 86.1% to 98.0%.

The lactation indices, which reflected the survival of the pups from days 7 to 21 of lactation, were similar between the six study groups and between subsequent generations within each group. The lactation indices ranged from 94.3% to 99.5%. These data indicated that a NOEL and LEL for an effect on reproduction as measured by the indices of this study were NOEL = 500 ppm, LEL greater than 500 ppm, the highest dose level tested.

Necropsy of Pups

No visceral abnormalities were detected among the pups which were examined grossly. A histopathological examination of the tissues from the F_{3b} pups revealed no abnormalities. The LEL for pathological change in the offspring of treated dams appeared to be greater than 500 ppm, the highest dose level tested in the study.

Discussion

This study, conducted in 1966, deviated from currently accepted protocols for three-generation studies at several points; none of these points seriously limited the study. The deviations were: exposure to the test material for the F_0 generation animals was for three weeks prior to mating (10-12 weeks of exposure are currently used); the animals were group housed during the nonmating periods; the animals were not observed or weighed during the nonmating periods;

females that did not become pregnant during the first mating were mated for the second litters; the method of selection of the animals to be parents for the subsequent generations was not made explicit; the viability of the pups was assessed from birth to lactation day 7 (current practice is from birth to day 4). In addition, the reproduction data were presented for each group but not for individual litters and were not analyzed statistically. This latter point did not adversely affect this review because the reported indices of reproduction never differed more than 5-10 percent from each other and showed no dose-related changes. Review of the study, however, was limited by the failure to report some of the data that was collected; observations on parental animals during the mating and on pups during lactation, pup body weight data, the number of viable and stillborn pups by sex at birth, and the results of the pathologic examinations were not presented.

Conclusion:

No evidence of toxicity was observed among the rats from any of the generations utilized on study. Pup body weights at birth, day 7, and day 21 of lactation were not adversely affected by the test article during any of the three generations. No test article-related effects ere evident for any of the reproduction indices examined during the course of the study. No grossly evident external anomali[illegible] or visceral lesions were evident among the pups examined m[illegible]oscopically. A histopathological examination of tissues from the F_{3b} pups produced no evidence of microscopic pathological changes. The findings of this study indicated that a NOEL 500 ppm was greater than 500 ppm of Banvel D (the highest dose tested) for adverse effects on the reproduction of the test animals and the general and external appearance and body weight of their offspring which was not reported through three generations.

Classification: Core Minimum.

Teratology

I. Study Type: Pilot Teratology Study in Rabbits.

Accession Number: 232102

MRID Number: 00025373.

Sponsor: Velsicol Chemical Corp., 341 East Ohio Street, Chicago, IL.

Contracting Laboratory: International Research and Development Corp.

Testing Facility: International Research and Development Corp. E.I. Goldenthal, D.C. Jessup, D.E. Rodwell.

Project No.: 163-436.

Date of Submission: September 13, 1977.

Reviewed by: Larry Anderson, 1/10/78.

A. Procedure.

1. Seventy one sexually mature female rabbits (New Zealand), 3-4 Kg, were mated twice, 1 hour apart, with different male rabbits of the same strain. Immediately after the second mating, each female received Gonamone, a chorionic gonadotropin (25 International Units), intravenously to stimulate ovulation. The day of copulation was considered day 0 of gestation.

2. After mating, rabbits were divided into 6 groups of 10 each which received 0.5, 1.0, 3.0, 10.0 or 20.0 mg/kg/day of Dicamba Technical in 0.5% Methocel or 1 ml/kg/day of 0.5% Methocel (controls) by gavage. Administrations were from day 6 through day 18 of gestation.

   Maternal observations of mortalities, toxic signs, and body weight changes were continued throughout 29 gestation days. Cesarean sections were done on all females sacrificed on day 29 of gestation. Cesarean section observations included numbers of viable and non-viable fetuses, early and late resorptions, total implantations, and corpora lutea. Fetal external development was evaluated.

B. Results

1. Maternal observations.

a. Mortalities: One given 10 mg/kg and one given 20 mg/kg.
b. Toxic Signs: Decreased activity in rabbits given 20 mg/k
c. Body Weight Changes: Weight gain reductions unrelated to dose level except for weight los exhibited by the 20 mg/kg group. Nongravid females were excluded from calculations of mean weights.

2. Cesarean Section Observations.

a. Non-gravid females/group: Control, 4; 0.5 mg/kg, 2; 1 mg/kg, 0; 3 mg/kg, 0; 10 mg/kg. 1; 20 mg/kg, 1.
b. Fetotoxicity: Number of resorptions (early and late) was increased and #live normal young/# implantations was decreased in 10 mg/kg and 20 mg/kg groups in a dose-related fashion. One fetal mortality was found in the 20 mg/kg group.
c. Fetal External Development: Left carpal flexure in fetus in the 0.5 mg/kg group; bilateral carpal flexure in 1 fetus in the 1.0 mg/kg group.

3. Discussion

The dosage level 20 mg/kg/day induced remarkable maternal and fetal toxic signs; however, the suggestion proposed by the registrant that the 10 mg/kg/day dosage level will permit delivery of live fetuses for teratological examination with reduction in maternal weight gain is acceptable. Abnormally high fetotoxicity evident in the 1.0 mg/kg group should be noted in regard to the observation that no maternal toxicity was apparent at this dose level; therefore the teratogenic and fetotoxic NOEL is 0.5 mg/kg/day. Velsicol has requested dietary samples for analysis of Dicamba, EPN, leptophos and TOCP and, if animals become morbid, histopathological examination of sciatic nerves, spinal cord, and brain.

Weight decreases in both males and females given 1000 ppm were found.

Classification: Supplementary, data on skeletal and soft tissues not given, too few animals used.

II. Study Type: Teratology Study in Rabbits.

Accession Number: Not available.

MRID Number: 00028236.

Sponsor: Velsicol Chemical Corporation, 341 East Ohio Street, Chicago, IL.

Contracting Laboratory: International Research and Development Corporation.

Responsible Professionals: E.I. Goldenthal, D.C. Jessup, D.E. Rodwell.

Testing Facility: International Research and Development Corporation.

Project No.: Study Number 163-436.

Date: October 4, 1978.

Procedure:

Five groups of female rabbits (31 to 35 per group) were dosed with 0.5% methyl cellulose at 1 ml/kg/day containing doses of 0, 1.0, 3.0, or 10.0 mg/kg/day of Banvel-technical. A positive control group was treated with 3 mg/kg/day of 6- aminonicotinamide on day 9 of gestation only. Banvel was administered on days 6 through 18 of gestation. Because of an insufficient number of pregnancies in the initial phases of the experiment, additional rabbits were added to each group at a later starting time.

Results:

1. Twenty one rabbits died as a result of a pulmonary involvement (apparently not compound related). The rabbits receiving the highest dose level had a slightly lower net weight gain. Maternal observations appearancy behavior, mortality and body way and no treatment related effects were found.

2. There were no statistically significant differences in the mean number of implantations, corpora lutea, and live fetuses. There appeared to be a dose dependent increase in males per females ratio (.91, 1.06, 1.16 and 1.39); however, at the highest dose some litters had more females than males and the difference was considered incidental.

3. There were slightly reduced fetal body weights and increased post implantation loss in the 10.0 mg/kg/day group.

4. Banvel treated rabbits did not give pups that were malformed in either soft tissue, skeletal appearance or external appearance to a greater extent than control treated rabbits. As expected, 6-amimonicotinamide treated dams produced pups with malformations. (Table 1)

Conclusion: Banvel was not found to be teratogenic in this study. There may be a fetotoxic effect at 10 mg/kg. Thus, the NOEL is 3.0 mg/kg/day for maternal toxicity.

Classification: Core minimum.

TABLE 2. Summary of the Incidence of Malformations and of Developmental and Genetic Variations.

	Control	6-Aminonicotinamide (mg/kg/day) 3.0	1.0	3.0	10.0
No. of litters examined:	20	20	21	21	21
Total no. of fetuses examined externally:	152[a]	115	153	147	153
Total no. of fetuses examined skeletally:	152[a]	115	153	147	153
Total no. of fetuses examined for soft tissue:	152[a]	115	153	147	153
	No. of Fetuses (No. of Litters)				
Malformations Observed:					
Scoliosis and/or fused ribs:	1(1)	76(16)	1(1)		1(1)
Carpal and/or tarsal flexure:	1(1)	13(5)	1(1)		
Skeletal limb anomalies:		1(1)		1(1)	
Cleft palate and/or cleft lip:		10(3)			
External hydrocephaly:					2(1)
Eye anomalies:		90(18)			1(1)
Other skull anomalies:		17(5)			
Caudel vertebrae anomalies:	3(2)	56(16)		2(2)	1(1)
Spina bifida:	1(1)	6(3)			
Fused sternabrae:	1(1)	2(1)	1(1)	2(2)	1(1)
Focal enlargement ribs T_7 T_8 & T_9[b]:				1(1)	
Forked rib:	2(2)				
Acrania with multiple anomalies:				1(1)	
Heart anomalies:	1(1)	16(11)	1(1)		2(2)
Diaphragmatic hernia:		17(6)			
Midline closure defect:		3(2)			
Kidney and/or ureter anomalies and/or bladder:	1(1)	13(6)			
Alimontary canal anomalies:		8(2)			
Total Malformations:	9(6)	98(18)**	4(4)	6(6)	6(6)

Variations - Developmental and Genetic Observed:

28 presacral vertebrae[c]:		1(1)		1(1)	
27 presacral vertebrae[c]:	46(17)	9(3)	22(10)	45(13)	49(16)
13 full pair of ribs[d]:	50(16)	6(3)	14(10)	37(12)	38(15)
13th unilateral full rib[d]:	17(11)	1(1)	17(10)	17(15)	19(10)
13th rudimentary rib(s)[d]:	23(14)	7(5)	26(14)	26(12)	23(14)
Sternabrae #5 and/or #6 unossified:	26(12)	37(9)	19(9)	25(9)	20(10)
Misaligned sternabrae:		9(5)	1(1)		2(1)
Accessory bone:		17(7)			
Reduced ossification of skull:	1(1)	9(6)			3(2)
Bent hyoid arch:	2(2)	1(1)	1(1)	3(2)	
Pubis unossified:					1(1)
Caudal vertebrae variations:		25(12)			
Major vessel variations:	45(17)	51(18)	33(14)	33(16)	31(15)
Gallbladder variations:		64(16)	1(1)		
Small stomach:		2(1)		1(1)	

163-436 [a]Includes one nonviable fetus.
[b]Dam 27209 had 5 normal fetuses and one malformed fetus. Fetus #6 had acrania, omphalocela, bilateral carpal and tarsal flexures, scoliosis, and the first digit on the right forelimb was absent. Also the following variations were observed - a bent hyoid arch, small stomach, sternebra #5 was unossified, and the left carotid was fused with the inominate.
[c]Not in these categories if a presacral vertebrae anomaly is present.
[d]Not in these categories if rib anomaly is present.
**Significantly different from Control group, $p<0.01$.

III. Study Type. Teratology Study in Rats - Pilot.

Accession Number: 070439.

MRID Number: 00084023.

Sponsor: Velsicol Chemical Corp., 341 East Ohio Street, Chicago, IL.

Contacting Laboratory: ToxiGenics, Inc., 1800 East Pershing Road, Decatur, IL.

Testing Facility: ToxiGenics, Inc.
S.H. Smith, C.M. Salamon, J.G. Page.

Project No.: 450-0459.

Date: May 20, 1981.

Reviewed by: S. P. April

Protocol: August 2, 1982.

Sixty-two young sexually mature virgin female Charles River CD Albino rats were mated with 15 male Charles River CD rats. Females identified as pregnant were randomly assigned five to each of 6 groups receiving 0, 50, 150, 350, 600 and 750 mg/kg dicamba. The technical dicamba was administered by gavage as a corn oil-Dicamba solution as was the vehicle in a dose of 10 ml/kg daily from day 6 through 19 of gestation to the individually housed rats. The test animals received ad libitum food (Purina Rodent Chow #5002) and water. The animals were observed twice daily for signs of toxicity, and weighed on day 0, 6 and 20 (sacrifice). At the time of sacrifice the uteri were excised, weighed and examined for determination of the number of implantation sites, resorption sites and fetuses.

Results

Dams in the 600 and 750 mg/kg groups had maternal toxicity, behavioral reactions and grossly apparent stomach lesions. Three of five dams at 750 mg/kg succumbed on day 7 as did one out of four of the 600 mg/kg group. Consistant antemortem observations in these groups revealed ataxia, stiffening of the body when held, urine soaked perigenital fur and salivation. Although there was no statistical difference from control, these groups had a comparative decrease in day 20 gestation weights, calculated net weight changes and estimated fetal body weight; however no increase in fetal resorption was found. Gross pathological maternal examination revealed

depression and/or discolorations in the stomach of some of the animals.

The mid-dose 350 mg/kg animals were not different from controls in maternal body weights, reproductive effects or average estimated fetal body weight; however, the mean gravid uterine weight was somewhat less than controls and similar behavioral reactions to those seen at the higher doses also occurred. No adverse changes were seen in the 50 and 150 mg/kg groups.

Conclusion:

The maternal toxicity NOEL for this study was 350 mg/kg.

Results:

There were no significant differences in body weights, food consumption, and antemortem observations throughout study in 0, 64 and 160 mg/kg dicamba test groups. In the 400 mg/kg test group the body weights at day 20 gestation were reduced, food consumption was lowered and the antemortem observations included ataxia, stiffening of the body when held, decreased motor activity as well as 3/20 deaths before the second dose.

There was no significant intergroup difference in the numbers of implantation sites, resorption sites and fetuses.

There was no differences between test and control groups in fetal development that are related to maternal exposure to Technical Dicamba. Two grossly malformed fetuses were found, one in the control group and one at 160 mg/kg dicamba. No external malformations, intergroup differences in body weight or differences in skeletal and visceral development were found.

Conclusion:

Technical Dicamba was not found to be teratogenic in this study at dose levels of up to 400 mg/kg (HDT). The NOEL for maternal Tox. is 160 mg/kg and the NOEL for Fetox. is 400 mg/kg.

Classification: Core minimum as a pilot study.

IV. Study Type: Teratology Study in Albino Rats.

Accession Number: 070439 S?

MRID Number: 00084024.

Sponsor: Velsicol Chemical Corp., 341 East Ohio Street, Chicago, IL.

Contracting Laboratory: ToxiGenics, Inc., 1800 East Pershing Road, Decatur, IL.

Testing Facility: ToxiGenics, Inc., Sandra H. Smith, Clare M. Julamon, J.G. Page, Ph.D.

Project No.: 450-0460.

Date: August 24, 1981.

Protocol:

Male Charles River CD albino rats were mated with young, sexually mature, virgin female rats of the same strain. Those females that were identified as pregnant were randomly assigned, 25 per group, to 0, 64, 160 and 400 mg/kg dicamba treatment groups. Dicamba in corn oil was given daily from day 6 through day 19 of gestation by gavage. The rats were individually housed and received water and Purina Rodent Chow #5002 ad libitum. The animals were observed at least twice daily for mortality, morbidity and overt signs of toxicity. Food consumption (daily) and maternal weight (at gestation days 0, 6 and 20) changes were monitored throughout the course of the experiment. The animals were all necropsied on day 20 or at time of death. They were checked for external developmental anomalies. Viable fetuses had total weights recorded as per sex/litter. They were fixed for internal histopathological examination. At necropsy the uteri were excised and examined to determine the number of implantation sites, resorption sites and fetuses.

Test Substance: The test article was technical dicamba. Its date of receipt and source were not specified in the final report although the protocol for the study indicated that the sponsor was the source of the test article. The test article, which had a lot number of 52625110, was described as a light tan crystalline powder, was assigned the ToxiGenics Test Article Code Number 3/81-202 and was stored at ambient temperatures. A stability study conducted as part of the pilot study found technical dicamba to be stable for a minimum of 7 days when stored in corn oil and refrigerated for 23 hours per day.

Results

No compound-related signs were noted among the females administered technical dicamba at 64 or 160 mg/kg. Occasional observations of crusty noses, red vaginal discharge, crusty eyes, crusty muzzles, alopecia, and wheezing were made among of animals of these groups and the vehicle control with comparable frequency. Indications of nervous system toxicity were evident in approximately 40 percent of the animals treated with 400 mg/kg of technical dicamba and included ataxia, stiffening of the body when held, salivation, decreased motor activity, and urine soaked or yellow fur. Several high dose animals also exhibited increased respiration, decreased respiration, reddish-brown stained fur, and moist rales. Crusty noses, crusty muzzles, and wheezing were also observed at a higher incidence among the high-dose animals than among the other three test groups.

No deaths occurred in the vehicle control, 64 or 160 mg/kg dose groups. Three of the 20 gravid females in the 400 mg/kg dose group were found dead during the study. These animals exhibited signs of toxicity prior to death and all were dead by day 8 of gestation, indicating that the deaths were compound-related.

Females in the 400 mg/kg test group consumed significantly less food ($p<0.05$) than the vehicle control animals on 10 of the 14 days of exposure to the test article and significantly less food than the females in the 64 or 160 mg/kg groups on 9 and 6 of the 14 exposure days, respectively. No other significant differences were observed.

No significant differences between the treatment groups in maternal body weights occurred at day 0 or day 6 of gestation. The day 20 of gestation body weights for the 400 mg/kg group were significantly less ($p<0.05$) than the body weights for the vehicle control and 160 mg/kg group; however, at p 0.01, body weights of the high-dose group were lower than those of the 160 mg/kg dose level only. The net body weight change (day 0 to day 20) for the high dose females was

significantly less ($p<0.01$) than the net body weight change for the vehicle control and low dose animals.

A statistical comparison between the treatment groups of the number of implantation sites, early resorption sites, late resorption sites, viable fetuses, and dead fetuses produced no significant differences according to the report. The percentage of implantation sites yielding resorption sites, dead fetuses, or viable fetuses, respectively were similar in the four treatment groups. These data are presented in Tables 1 and 2, respectively.

Table 1. Mean Numbers of Implantation and Resorption Sites, Viable and Dead Fetuses[a]

Test Group	Implantation Sites	Resorption Sites		Viable Fetuses	Dead Fetuses
		Early	Late		
Control	14.2 ± 1.81	0.9 ± 1.22	0.0	13.3 ± 2.40	0.0
64 mg/kg	12.3 ± 3.37	0.3 ± 0.64	0.0 ± 0.20	11.9 ± 3.40	0.0
160 mg/kg	14.3 ± 2.42	0.7 ± 0.65	0.0 ± 0.21	13.6 ± 2.46	0.0
400 mg/kg	13.1 ± 4.16	1.2 ± 3.33	0.1 ± 0.33	11.8 ± 3.56	0.0

[a]Mean of numbers per litter ± S.D.

Table 2. Mean Percentages Of Implantation Sites Resulting in Resorption Sites, Dead and Viable Fetuses[a]

Group	Percent of Implantations Sites Resulting In:		
	Resorption Sites	Dead Fetuses	Viable Fetuses
Control	6.4 ± 9.70	0.0	93.6 ± 9.70
64 mg/kg	3.0 ± 5.21	0.0	97.0 ± 5.21
160 mg/kg	5.3 ± 5.36	0.0	94.7 ± 5.36
400 mg/kg	8.7 ± 7.65	0.0	91.3 ± 7.65

[a]Mean of percent per litter ± S.D.

No treatment-related differences were observed when male fetal body weight, female fetal body weight, or the percentage of males and females per treatment group were statistically compared. Similarly, a statistical comparison of gravid uterine weight produced no significant differences between the treatment groups.

No compound-related effects on external fetal development were detected. One vehicle control fetus was undersized and exhibited gross external abnormalities consisting of anuria, exencephaly, cleft lip, cleft palate, clubbed limbs, and possible anopthalmia. One fetus from the 160 mg/kg dose level was anurous with a shortened body. The low incidence of these findings indicated they were of a spontaneous nature. No external fetal abnormalities were observed in the low and high dose groups. Examination of the fetal skeletons found high incidences of incompletely ossified frontal, parital, interparietal, occipital, hyoid, and sternebrae bones; non-ossified sternebrae and hyoid bones; and assymetrical sternebrae ossification in all groups, including control. These findings are not uncommon among Sprague-Dawley rat fetuses. In addition, misshapen interparietal, occipital, and parietal bones were observed, but only in the technical dicamba-exposed fetuses. These malformations occurred at low incidence rates, were not statistically significant, and showed no dose-related response (Table 3). However, the occurrence of any abnormality

Table 3. Incidence of Selected Malformations in Fetal Skeletal Development

Finding	Incidence (percent)			
	Control	64 mg/kg	160 mg/kg	400 mg/kg
Misshapen interparietal	0	3(1.5)	2(0.9)	0
Misshapen occipital	0	4(2.0)	1(0.5)	1(0.7)
Misshapen parietal(s)	0	3(1.5)	2(0.9)	1(0.7)

in a teratology study that affects one area of the body and does not occur among the controls suggests at least the possibility of a compound-induced effect on organogenesis. Thus, these findings suggested that dicamba exerted an effect on fetal skeletal development. The number of corpora lutea were not determined.

No indication of a test article-induced effect on fetal visceral development was detected. The visceral evaluations showed low incidences of hydronephrosis, and large or small atria. These observations occurred among all the test groups

and are not uncommon among this strain of rat. Two vehicle control fetuses from the same litter were observed to have visceral abnormalities. Cleft palate, exencephaly, diaphragmatic hernia, liver and stomach anterior to the diaphragm, microphthalmia, malformed retinas, fused hydronephratic kidneys, the uterus continuing anterior to the kidneys, and absent ovaries were found in the vehicle control fetus with external abnormalities. The other vehicle control fetus had slight hydrocephaly. One fetus from the 160 mg/kg dose level was found to have kidneys misplaced posteriorly, hydronephrosis, and uterus continuing anterior to the kidneys with malformed ovaries. This fetus had also been observed to have external abnormalities.

No grossly apparent lesions were observed among any of the females succumbing during the study nor among the females sacrified at day 20 of gestation.

Conclusion

The NOEL for maternal toxicity was 160 mg/kg and the LEL was 400 mg/kg. External and visceral evaluations of the fetuses produced no evidence of compound-induced abnormalities. The skeletal evaluation of the fetuses yielded a low incidence of malformations consisting of misshapen parietal, occipital, and interparietal bones that occurred only among the fetuses exposed to technical dicamba. Although the occurrence of these malformations was not statistically significant and did not appear to be dose-related, their occurrence only among the treated groups and the specificity of the action is suggestive of a teratogenic potential for technical dicamba that requires clarification. These data therefore, suggested that a NOEL for a teratogenic skeletal response was less than 64 mg/kg and the LEL may have been as low as 64 mg/kg.

Classification: Core Minimum.

CHRONIC

I. Study Type: Two-year Chronic Oral Toxicity in Rats.

Accession Number: Not available.

MRID Number: 00028260, 00028248 (duplicates)

Sponsor: Velsicol Chemical Corporation, Chicago, Illinois.

Contracting Laboratory: University of Cincinnati, Department of Environmental Health, Kettering Laboratory.
R. K. Davis, W. P. Jolley, and K. C. Stemmer

Date: February 23, 1962

Protocol

Test Article

Identification:. Dicamba (2-methoxy-3,6-dichlorobenzoic acid).

Sample Identification and Purity: No lot number was given. The test material contained 90% active ingredient, 2-methoxy-3,5-dichlorobenzoic acid.
Control Vehicle/Solvent Used: Alphacel (a non-nutritive cellulose flour).

Concentration: 5, 50, 100, 250, and 500 ppm in the ed.

Route of Administration: Orally via the diet.

Materials and Methods

Species/Strain: Sprague-Dawley Rats.

Number and Sex: 224/sex.

Age/Weight at Initiation: The animals were approximately 13 weeks old at the initiation of the study. Initial body weights were not given.

Supplier: Not given.
Housing: The animals were group housed 4 to a cage.

Feed: Ad libitum.
Water: Ad libitum.

Environmental Conditions: The rats were kept in an air-conditioned room with the temperature maintained at 77° F.

Procedure: The animals were separated at random into seven groups as described in Table 1.

Table 1. Experimental Design Summary

Dose Group (ppm in Diet)	Initial Number Of Anmals in Group		No. of Animals for Interim Sacrifice		No. of Animals for Terminal Studies		Histo-pathology
	Male	Female	Male	Female	Male	Female	
0 ppm	32	32	0	0	32	32	complete
0 ppm	32	32	12	12	20	20	complete
5 ppm	32	32	12	12	20	20	complete
50 ppm	32	32	12	12	20	20	complete
100 ppm	32	32	12	12	20	20	complete
250 ppm	32	32	12	12	20	20	complete
500 ppm	32	32	12	12	20	20	complete

Observations:

Event	When Performed
Signs of illness and mortality	regularly
Individual body weights	semi-monthly
Group food consumption	weekly
Hematologic examinations	3-month intervals

Parameters measured included hematocrit, hemoglobin, total and differential leukocyte counts. Analyses were performed on five male and five female rats per group at each time point except hematologic analyses were recorded at 24 months.

Reproduction

After 3 months of feeding, two male and four female rats from the high dose group (500 ppm) were mated. Two male and four female control rats were also mated at the same time. In addition, two males and four females from the 500 ppm dose group were mated with an identical number of control rats.

Interim sacrifices at 6, 9, 12, 15, 18, and 21 months

Two male and two female animals from each group were to be sacrificed at each of the indicated time points.

Terminal sacrifice 24 months

Organ weights 24 months

Organ weights of brain, heart, liver, lungs, spleen, kidneys, gonads, adrenals, and thyroid were recorded.

Histopathology Interim and final sacrifices and animals that died during the study.

Tissues from all rats except those exhibiting advanced post mortem changes were prepared for microscopic examination. The following tissues were examined: brain, heart, lungs, liver, spleen, kidneys, pituitary, thyroid, parathyroid, adrenal, gonads, stomach, and small and large intestine.

Results

1. Clinical Observations

No data were presented for observations of general behavior and appearance. Although information in the test protocol indicated that two animals/group were sacrificed at 3-month intervals beginning at 6 months, mortality data indicated two animals/group were sacrificed at 6-month intervals except for one control group which had no interim sacrifices. Mortality was significantly higher among male animals than female animals. However, there were no dose-related effects attributable to the test compound in either sex. Based on these findings, there was no mortality at 500 ppm.

2. Body Weights

No initial individual body weights were presented for this study. The only available information concerning body weights were average weight gain data for one and two years and final body weights. Although there did not appear to be any dose-related effect on weight gain, statistical significance could not be calculated since the average data were presented with no standard deviation. Therefore, a NOEL could not be determined for body weights.

No individual food consumption data were available for this study. Average food consumption data at one year and

two years were presented by groups with no standard deviation or statistical analysis. Consequently a NOEL could not be determined for food consumption.

3. Hematology

Hematologic data consisting of hemoglobin, hematocrit, total and differential leukocyte counts were reported for 5 animals/group/sex prior to initiation of the study and at 3, 6, 9, 12, 15, 18, 21, and 24 months. No statistical analysis of the data was provided.

No statistically significant differences or dose- or time-related effects were seen for leukocyte counts for either sex. The hematocrit was not statistically significant different or dose- or time-related were found for the male animals. For females at 12 months, the hematocrit was significantly depressed for the high dose group when compared to the control (p=0.02). However, this result did not appear at other doses. Observed for hematocrit at 12 months. In addition, no time related effect was observed for females for hematocrit and the value observed for high dose females at 12 months was within the normal range for hematocrit for the rat according to the report.

Hemoglobin was significantly depressed for high dose males at 12 months when compared to controls (p=0.05). However, there was no apparent dose-related effect found for hemoglobin for males at 12 months and no time-related effects were seen for hemoglobin for male animals. In addition, the depressed value for hemoglobin for high dose males was within the normal range of hemoglobin for the rat (12-17.5 gm/100 ml) according to the report. Therefore, this result did not appear to be biologically significant.

A decrease in hemoglobin values was also observed for high dose (500 ppm) females when compared to controls at 12 months (p=0.02). However, no apparent dose-related effect was found for hemoglobin for females at 12 months. In addition, decreased hemoglobin level was still within the normal range of hemoglobin for the rat according to the report. Therefore, this result did not appear to be biologically significant.

Although several statistically significant differences were observed with respect to hematologic parameters, there were no dose- or time-related effects found for any of the parameters which were statistically analyzed. Therefore the NOEL for hematology was 500 ppm for both sexes.

4. Reproduction

Rats were mated twice using the technique described in the Experimental Methods Section. When control female rats and females receiving 500 ppm Dicamba were mated with control males, there was no difference in the number of successful matings (5/8). Mating of 500 ppm males with control females resulted in four out of eight successful matings. When dosed males were mated with dosed females there were only two out of eight successful matings. Statements in the final report that irregularities in reproduction were related to endocrine tumors were not substantiated by the histopathologic findings reported. None of the animals mated had an endocrine-related tumor. However, the final report stated that three of five control rats and five of six dosed animals showing reproductive irregularities had endocrine tumors of some type. Although there is an apparent effect of Dicamba on reproduction capability in this study, a more complete reproduction study is needed to assess the effects of Dicamba on reproduction in the rat. Other reproductive data (i.e., average number of pups/litter, average weight of pups, sex ratio, etc.) could not be confirmed as the data presented was a summation of control versus experimental female data irrespective of the test status of the male.

5. Organ Weights

Individual relative organ weights were present for all final sacrifice animals. In order to evaluate the data, the reviewer calculated means and standard deviations (see Table 5). Statistical significance was determined by comparing the control and high dose values using the t-test. No statistically significant differences or dose-related effects were noted for organ weights. Therefore, the NOEL for organ weights was 500 ppm for both sexes.

6. Histopathology

The protocol and the final report indicated that the following tissues were examined microscopically: brain, heart, lung, liver, kidney, spleen, gastrointestinal tract, thyroid, adrenals, pituitary, parathyroid, and gonads. However, individual histopathologic data were only reported for heart, lung, liver, and kidney. A column was also presented for other tissues which occasionally contained abnormal findings for tissues other than the four for which data were reported.

Incidences of abnormal histopathologic findings for the heart for males was elevated in the 5, 50, 100, and 500 ppm dose groups when compared to controls. Findings included

myocarditis, fibrosis, thrombosis, and pancarditis. However, there was no apparent dose-related effect for abnormal histopathologic findings for the heart in males. In females, abnormal heart findings were increased in the 5, 50, 100, 250, and 500 ppm dose groups compared to the control group. The cardiac abnormalities found in the female rats appear to be dose related. These abnormal findings included endocarditis, fibrosis, myocarditis, atherosclerosis, and abdominal thrombosis.

For the lung in males, there was an increased incidence of abnormal findings in the 5, 50, and 500 ppm dose groups compared to the control. However, there was no dose-related effect seen for the lung in males. Findings included pneumonia, pneumonitis, bronchiectasis, emphysema, chronic pulmonary congestion, edema, metaplasia, papillomatous epithelial hyperplasia, lymphoid hyperplasia, hyperemia. For females the incidence of abnormal lung findings was elevated at 5, 250, and 500 ppm when compared to control. The elevations of abnormal findings among the test groups did not appear to be dose related.

Findings reported included pneumonia, pneumonitis, bronchiectasis, emphysema, epithelial metaplasia, edema, and chronic congestion.

Increased abnormal findings occurred at 50, 100, and 500 ppm compared to the male rat liver) control. There was no apparent dose-related effect. Findings reported included degeneration, cirrhosis, necrosis, chronic congestion, and abscesses. In females, increased in abnormalities occurred in the 50, 250, and 500 ppm dose groups compared to the control groups; however, there was no dose-response relationship evident. Findings reported included degeneration, chronic congestion, diffuse necrosis, chronic peritonitis, and leukemia.

Increased incidences of abnormal findings in the male kidneys occurred on the 5, 50, 100, and 500 ppm dose groups compared to controls. These increases did not appear to be dose-related. Findings reported included nephritis, abscesses, hemorrhagie infarction; and embryonal carcinoma. Increased incidences of abnormal histologic findings in the females occurred in the 5, 50, 100, and 250 ppm dose groups when compared to the control group. However, the increases were not dose related. The findings reported included nephritis, diffuse necrosis, and tubular degeneration.

Incidences of neoplastic lesions were also reported for male and female groups combined. The group results are reported in Table 2. The individual neoplasms were not reported. There was a greater incidence of malignant neoplasms in the 5, 250, and 500 ppm dose groups compared to the control group; however, this effect did not appear to be dose-related.

There were increase numbers of benigh neoplasms in the 250 ppm group compared to the control. However, the effect did not appear to be dose-related. When the incidence of total neoplasms were considered, a somewhat increased incidence was seen in the 5 ppm and 500 ppm dose groups when compared to the control. No dose-related effect was apparent for total neoplasms.

Table 2

Number of neoplasms/total number of animals observed

Concentration in the Diet	Incidence of Tumors Malignant	Benign	Total Neoplasms (Malignant and Benign)
0	1/56	11/56	12/56
0	2/62	9/62	11/62
5	6/59	10/59	16/59
50	2/55	11/55	13/55
100	0/54	12/54	12/54
250	3/56	17/56	20/56
500	3/56	10/56	13/56

High mortality was reported among all test animals, including control. The mortality was higher among male animals the female animals.

Table 2A	% Mortality of 18 months						
Dose	0 ppm	0 ppm	5 ppm	50 ppm	100 ppm	250 ppm	500 ppm
Male	40.6	38.5	34.6	34.5	38.5	34.6	38.5
Female	9.4	20.1	23.0	7.7	27.0	35.0	19.0

No individual or group abnormalities were presented precluding the ability to determine whether or not this study was compromised by a nontreatment related health effect. No gross pathology data were presented. No individual initial body weight data or individual food consumption data were presented. Although brain, heart, lungs, liver, spleen, kidneys, pituitary, thyroid, parathyroid, adrenal, gonads, stomach, and small intestines were to be examined as required by the protocol and indicated as examined by the final report, histopathologic findings were reported only for heart, lungs, liver, and kidneys. A complete histopathologic evaluation should have been conducted instead of the limited histopathology

reported. Although the protocol indicated that interim sacrifices (2 rats/sex group) were to be conducted at 3-month intervals starting at 6 months, mortality data in the final report indicated that interim sacrifices were conducted at 6-month intervals starting at 6 months in all groups except one control group in which no interim sacrifices took place. The reproduction study included in this report was quite deficient. A more complete study, including two generations, with at least three dose groups, necropsy of offspring, more animals per test group, etc., is needed before the effects of Dicamba on reproduction can be adequately assessed.

No observations for clinical signs of toxicity or pharmacological effects were presented. No blood chemistry or urinalysis data were presented. Erythrocyte count for hematology should have been reported. Mean values and statistical analysis were not provided for hematology.

No animal identification procedure was given although individual numbers were assigned. No date of receipt of animals or date of initiation or termination of the study was presented.

Conclusions

No data were present for observations of general behavior and appearance. Mortality data were presented which indicated there were no dose-related effects on mortality. A NOEL for the study cannot be calculated since insufficient data was presented.

Classification: Supplementary, for the following reasons:

1. No observations for toxicity and pharmacologic effects were presented.
2. No blood chemistry.
3. No urinalysis.
4. No individual abnormalities.
5. No gross pathology.
6. Only scant histopathology.

II. Study Type: Two-Year Chronic Oral Toxicity in Dogs

Accession Number: Not available.

MRID Number: 00028260/00028248/00050492.

Contracting Laboratory: University of Cincinnati, Department of Environmental Health, Kettering Laboratory. R. K. Davis, W. P. Jolley, K. L. Stemmer.

Date: February 23, 1962.

Protocol:

Material Tested: Dicamba (2 methoxy-3,6-dichlorobenzoic acid) 90% pure dissolved in corn oil (control diet 1% corn oil) was administered orally in the diet feed at 5.25 and 50 ppm. Approximately seven month old pure bred beagle dogs (Cornell University), 3/sex/group housed individually at 74°F were given food for one-half hour per day and water ad libitum.

Procedure:

The animals were randomized into four groups containing 3 males and 3 females as described in the experimental design summary below.

Dose Group (ppm in diet)	Initial No. of Animals in Group		No. of Animals for 12 months Interim Sacrifice		No. of Animals for Terminal Sacrifice		Histo-pathology
	M	F	M	F	M	F	
Control	3	3	1	0	2	3	All
5	3	3	1	0	2	3	All
25	3	3	1	0	2	3	All
50	3	3	1	0	2	3	All

Observations performed according to the schedule:

Event	When Performed
1. Signs of illness	Daily
2. Body weights	Weekly
3. Food consumption	Weekly
4. Hematology studies[a]	3 month intervals
5. Urinalysis[b]	6 month intervals
6. Interim sacrifice[c]	12 months

Event	When Performed
7. Terminal sacrifice[d]	24 months
8. Organ weights[e]	24 months
9. Gross pathology[f]	12 and 24 months
10. Histopathology[g]	12 and 24 months

[a] Parameters studied included hemoglobin, hematocrit, and total and differential leukocytes.

[b] Urinalysis included volume, specific gravity, pH, albumin, ketone, sugar, occult blood, and bilirubin.

[c] Performed on 1 male dog from each group, method not specified.

[d] Performed on all surviving dogs at 24 months.

[e] Organ weights for brain, heart, lung, liver, gonads, kidneys, and spleen were reported for individual animals at final sacrifice.

[f] No gross abnormalities were reported for any of the dogs in the study; however, there were no data presented for evaluation.

[g] Histopathologic examinations were performed on only the heart, lung, liver, and kidney.

Results

There were no individual observations, gross toxicological or pharmacotoxic effects presented and no mortality data. All the animals appeared to survive to interim and terminal sacrifice.

Body Weight and Food Consumption:

Except for final individual body weights all other data were presented as group means graphically. There appears to be a dose related decrease in male body weights. The percent body weight gain was depressed at 25 and 50 ppm compared to the controls in the males and at 50 ppm in the females. Since the initial body weights of treated males were less than females and more than those of the controls these observations could be in error due to differences in the timing of the maturation phase. The NOEL was 5 ppm and LEL 25 ppm for the males while the females had a NOEL of 25 ppm and LEL of 50 ppm.

The food consumption was presented graphically as group mean data with no statistical analysis.

Hematology

Hematologic data consisting of hemoglobin, hematocrit, total and differential leukocyte counts were reported for all animals prior to initiation of the study and 3, 6, 9, 12, 15, 18, 21, and 24 months. One male dog from each group was sacrificed at 12 months; therefore hematological data for male animals at 15, 18, 21, and 24 months were present for only 2 animals/group. Mean group values were presented graphically in the final report. Individual hemotologic data were also present in the final report; however, there did not appear to be any statistically significant difference for hematocrit or leucocyte count at any of the time points. The hemoglobin values although depressed at 6 months in the male were still within normal range limits. There did not appear to be a statistically significant difference for the female hemoglobin. The hematology NOEL for both males and females appears to be 50 ppm (HDT).

Clinical Chemistry

There were no data presented.

Urinalysis:

Urinalysis data consisted of pH, specific gravity, occult blood, sugar, ketone, albumin, and volume for all animals at 6, 12, 18, and 24 months. Individual data were presented in the final report, no mean values or statistical analysis was provided.

No significant differences or dose- or time-related effects were seen for urine volumes or pH for either sex. For males, no significant differences or dose-related effects were seen for specific gravity. For females the specific gravity for the high dose group was apparently greatly different than the control value. In addition, the low dose group also showed significant elevation above the control value. However the effect did not appear to be dose-related since the mid-dose level was not significantly elevated compared to the control. In addition, there was no indication of a timerelated effect. Based on these findings the NOEL for urinalysis was 50 ppm (HDT).

Organ Weights

Organ weight data were reported for all terminal sacrifice animals. The weights of brain, heart, lung, liver, gonads, kidneys, and spleen were reported for individual animals. No mean organ weights or statistical analysis were present in the final report.

No apparent significant differences or dose-related effects were noted for either male or female animals with respect to absolute organ weights. Based on these findings, the NOEL for organ weights is 50 ppm (HDT).

Gross Necropsy Observations

Although the final report indicated that the gross post-mortem examination performed indicated normal viscera, there were no data available for evaluation. Therefore a NOEL for gross pathology could not be determined.

Histopathology Evaluation

A table was presented in the final report indicating histopathologic findings for heart, lung, liver, kidneys, and other tissues for interim and final sacrifice animals. Normal findings were reported for all heart, liver, and kidney tissues examined. The only abnormal finding reported for lung was pneumonia. Focal pneumonia was reported for the following male final sacrifice animals: 1 of 2 control animals, 1 of 2 animals in the 5 ppm dose group, and 1 of 2 animals in the 25 ppm dose group. Abnormal lung findings for the female animals included slight bronchopneumonia for 1 of 3 animals in the 5 ppm group and focal pneumonia for 1 of 3 animals in the 25 ppm dose group. No dose-related effect was seen among the abnormal findings reported. Based on these findings, the NOEL for histopathology is 50 ppm (HDT).

Discussion:

The number of animals per group, three, was small. The histopathology was only on 4 tissues whereas all tissues of all interim and final sacrifice animals should have been presented as well as gross pathological observations. The frequency of diet preparation, the test compound stability and homogeneity of the feed were not discussed.

The randomization of test group animals and animal identification method was not indicated. There was no stated animal sacrifice method.

This study did not detail observations, mortality, date of animal receipt or study initiation. There was no statistical analysis or mean values for hematology, urinalysis or organ weights. The adrenal weight should have been given.

No biochemistry data or erythrocyte count was given.

Conclusion

A 24-month feeding study was conducted to evaluate the toxicity of Dicamba (2-methoxy-3,6-dichlorobenzoic acid) when administered orally, via the diet, to purebred Beagle dogs. Four test groups, 3 dogs/sex group received 0, 5, 25, or 50 ppm Dicamba in the diet. The control group received corn oil (solvent) at the same level (1%) as the experimental groups. Interim sacrifice of 1 male dog/group occurred at 12 months. Parameters monitored during the in-life phase of the study included signs of illness, body weights, food consumption, hematology and urinalysis. Gross necropsy, organ weights, and histopathologic evaluations were conducted at 12 months (1 male dog/group) and at 24 months.

No data were present for observations, toxicologic signs, pharmacotoxic effects, or mortality. From the data reported, all animals appeared to survive to interim and final sacrifices.

Although complete statistical analysis of the body weight data was not possible due to a lack of individual initial body weights, there was an apparent dose-related decrease observed for body weight gain for males. Body weight gain was depressed at 25 and 50 ppm compared to controls. For females the percent body weight gain was depressed at 50 ppm compared to controls. Based on these findings, the NOEL was 5 ppm for body weight for males (LEL 25 ppm). For females the NOEL was 25 ppm and the LEL was 50 ppm for body weight.

Classification: Supplementary

Individual data was not presented. There were no observations or pharmacologic effects presented. There was no gross pathology and incomplete histopathology presented. There was no clinical chemistry.

Acute Oral

I. Citation: Wazeter, F.X.; Buller, R.H.; Geil, R.G., 1966, Unpublished.

Accession No: Not available

MRID No: 0078444

Sponsor: Velsicol

Contracting Lab: IRDC, Mattawan, Mich.

Project No: IRDC 163-007

Date: June 8, 1966

Material Tested: Banvel D, acid form was received May 11, 1966 and was 99.7% pure for Lot No. RS-M36:81062

Materials and Methods:

Male Spartan Sprague Dawley rats, 127-148 grams, were housed 5 per cage in air conditioned environment of unspecified temperatures with food and water ad libitum until 14 hours prior to oral administration.

Each group of 5 received dosage levels of 1470, 1780, 2150, 3160, 3830 or 4640 mg/kg. Observations for pharmacodynamic and/or toxic signs were made at 0-60 minutes, 60-150 minutes, 150-3000 minutes, 24 hours and daily for 14 days. The dead were necropsied.

Results:

Observations: Within 60 minutes of compound administration the following signs were seen: partial eye closure, bradycardia, bradypnea, diarrhea, peripheral vasodilation, hypoactivity, spasticity, ataxia, sedation, inhibited placing, pinna, corneal reflexes, and death. In the higher doses, depression, sedation and hypoactivity persisted in surviving rats for 4 or 5 days. Those rats that recovered were normal by 14 days. These signs were dose related in degree, incidence and duration according to the report but were not individually presented for verification.

Deaths appear to be dose and time related.

Dose (mg/kg)	No of Deaths	Time
1470	1	2 hrs.
2150	1	2 hrs.
3160	3	24 hrs.
3830	3	24 hrs.
4640	5	24 hrs.

Necropsy:

The necropsy results were not presented in the report which stated that the only effect that was dose related was pulmonary congestion.

Conclusion:

The LD_{50} and confidence limits for Banvel D was 2740 (2010-3740) mg/kg. Category III.

Classification: Core minimum

II. Citation: Wazeter, F.X.; Buller, R.H.; Geil, R.G., 1966, Unpublished data.

Study Type: Acute oral in the mouse

Accession No.: 114913

MRID No.: 00078443

Sponsor: Velsicol

Contracting Lab: IRDC, Mattawan, Michigan

Project No.: IRDC 163-006

Date: April 30, 1966

Material Tested: Banvel D, the acid form was received as a fine white powder on April 4, 1966. Lot number not given.

Material and Methods:

The test material suspended in corn oil (Mazola) was given orally by intubation to nonfasted male albino CF-1 mice, 18-22 grams at various dosage levels in randomly selected groups of 10 animals. The treated animals were observed continuously for four hours postdosing and once a day for 14 days.

Necropsies were performed on all treated mice.

Administration volumes were constant at 20 ml/kg body weight for dosages of 681, 1000, 1470, 2150, 3160 and 4640 mg/kg.

Results:

Within 5 minutes of dosing hypoactivity, flaccidity, sedation, ataxia and negative placing reflex were observed at all dosage levels. Bradypnea, dyspnea, decrease pinna and corneal reflexes, prostration, cyanosis, and death followed. The intensity of these signs were dose related but not inidividually presented. Surviving animals began to recover after 3 hours except that sedation persisted to the following day.

Dose	Deaths
680, 1000, 1470	0
2150	1 at 7 days
3160	3 at 24 hours; 1 at 9 days
4640	3 at 24 hours

Necropsy:

One of the deaths at 4640 mg/kg had slight pulmonary congestion. No lesions were found in the other two deaths. Three mice dead in 24 hours at 3160 mg/kg had pulmonary edema which was also seen in the 2150 mg/kg mouse (dead in 7 days). No gross lesions were found in any of the sacrificed mice at 14 days.

Conclusion:

The acute oral toxicity in male albino mice for Banvel D is 4640 mg/kg.

Category: III.

Classification: Core minimum

III. Study Type: Acute Oral Toxicity in Albino Rats.

Citation: Wazeter, F.X., Goldenthal, E.T., Dean, W.P. Unpublished Study.

Accession No.: Not available

MRID: 00025371

Sponsor: Velsicol Chem. Corp., Chicago

Laboratory: IRDC

Study No.: 163-323

Date: January 24, 1975

Material Tested:

Banvel, 4 lb/gal dimethylamine salt in water was received on November 29, 1974 as a brown liquid. No lot number was given.

Material and Methods:

25 male and 25 female rats weighing from 200-248 gms were dosed with the material five/sex/dose, as a suspension in corn oil, orally at dose levels of 1281, 2034, 3229, 5126 and 8137 mg/kg and observed up to the 14th day.

Results and Conclusion:

LD_{50} male = 2155 (1293-3109) mg/kg

Female = 3083 (2301-4130) mg/kg

Combined = 2629 (mg/kg

Signs of Toxicity: Not stated.

Body weight: Appeared normal

There were no individual mortality data

Tox. Category: III

Classification: Core Minimum

Subchronic Inhalation

Citation: Ulrich, C.E.; Rop, D.A.; Geil, R.G. et al., unpublished study

Study Type: Subchronic Inhalation Study in Rats.

Accession Number: Not available

MRID Number: 00032247

Sponsor: Velsicol Chemical Corporation, Chicago, Illinois

Contracting Laboratory: International Research and Development Corp., Mattawan, Mi.

Project No.: IRDC No. 163-619

Date: August 13, 1979

Protocol:

Material tested: Dicamba (Banvel 4S) as a clear amber liquid which is composed of the acid in water of unspecified purity was received in three 5 gallon containers on April 2, 1978. This material was tested in an inhalation experiment at nominal concentrations of 0.202 mg/liter, 2.01 mg/liter and 20 mg/liter.

Material and Methods:

Exposure Chamber: Exposures were conducted in a one cubic meter, cubical stainless steel and glass chamber with a pyramidal top and bottom. A rotary centrifugal air pump located at the exhaust side of the chamber was used to maintain a constant airflow.

Aerosol Generation: Aerosols of Banvel 4S were generated by metering the liquid with a Harvard Syringe Pump for the 0.202 mg/l aerosol and with a Dual Syringe Precision Pump for the 2.01 mg/l and 20.0 mg/l aerosols, into a positive pressure atomizer near the chamber air inlet at the top of the exposure chambers. An air pressure of 10 psig with an airflow rate of 8 l/min was applied to the atomizer. The rate of dispersion of the test product into the chamber was not given. Rats were exposed for 6 hours/day, 5 days/week for a total of 10 exposures in two weeks. The total airflow rate through the chamber was not reported.

Monitoring of Chamber Concentration: The report indicated that nominal concentration of the compound in the chamber

atmosphere was calculated from the ratio of the rate of test material dispersed/time (mg/min) to the total chamber airflow rate (l/min); however, the values for these two parameters were not available in the report.

Particle Size Distribution Analysis: The particle size distribution of the Banvel 4S aerosol was determined using an Andersan 8 stage cascade impactor. The chamber atmosphere was drawn through the sampler at a rate of 28.3 l/min. The weight of the aerosol particles impacted was determined gravimetrically and the weight-percent of each size category was calculated. The cumulative weight-percent of partcles smaller than a certain indicated diameter was plotted on logarithmic-probability graph paper. The equivalent aerodynamic mass median diameter was determined graphically. One sample was taken each day from each exposure chamber during the 10 days of exposure.

CD-1 rats, 20/sex approximately 6-8 weeks of age (males 201-227 g; females 208-229 g) from Charles River Breeding Laboratories, Portage, Michigan, were housed in wire mesh cages for an acclimatization period of 8 days with food and water ad libitum at controlled but unspecified temperature and humidity.

Animals were randomized using the IRDC computer radomization program into 4 groups of 5 rats each as described in the Summary of Experimental Design (Table 1).

Table 1. Summary of Experimental Design

Nominal Concentration (mg/l)	Initial No. of Animals		No. of Animals for Terminal Laboratory Studies		Histopathology
	Male	Female	Male	Female	
Control	5	5	5	5	Complete
0.202	5	5	5	5	Partial
2.01	5	5	5	5	Partial
20.0	5	5	5	5	Complete

Observations:

The following observations were made at the specified times:

	Event	When Performed
1.	Pharmacotoxic signs	Twice daily, before and after exposure
2.	Individual body weights	Twice weekly during the two weeks of exposure
3.	Hematology tests[a]	Terminal sacrifice
4.	Biochemical tests[b]	Terminal sacrifice
5.	Urinalysis[c]	Terminal sacrifice
6.	Terminal sacrifice[d]	Two weeks
7.	Gross necropsy examination[e]	Termination
8.	Organ weights[f]	Termination
9.	Histopathology[g]	Termination

---

[a]Parameters measured included hemoglobin, hematocrit, erythrocyte count, total and differential leukocyte count, and bone marrow smear.

[b]Parmeters measured included alkaline phosphatase, blood urea nitrogen, serum glutamic pyruvic transaminase and fasting blood glucose.

[c]Parameters measured included volume, appearance, specific gravity, pH, glucose, acetone, protein, bilirubin, and occult blood.

[d]Performed on all surviving rats at two weeks by carbon dioxide asphyxiation.

[e]Performed examination for gross abnormalities of organs and tissues on all terminal sacrifice animals as well as all animals that died during the study.

[f]Weights were recorded for terminal sacrifice animals for the following tissues: adrenals, brain, testes/ovaries, kidneys, liver, pituitary, spleen, and thyroid.

gTissues from rats in the control and 20.0 mg/l exposure level groups were embedded in paraffin, sectioned, and stained with hematoxylin and eosin and examined microscopically. Animals from terminal sacrifice as well as those animals dying during the study. Tissues were prepared and examined by IRDC. Tissues examined for the control and 20.0 mg/l exposure level groups were:

adrenals	mammary gland	urinary bladder
aorta	nasal turbinate	uterus
bone	pancreas	trachea
brain	pituitary	
esophagus	peripheral nerve	
gonad	skeletal muscle	
heart	spinal cord	
intestine (colon, duodenum, ileum, jejunum)	salivary gland	
	skin	
	spleen	
kidneys	stomach	
liver	thymus	
lung	thyroid	
mesenteric lymph nodes		

The following tissues were examined from the 0.2 and 2.0 mg/l exposure level groups:

brain	lung	skin	stomach
kidney	nasal turbinate	spleen	trachea
liver	mammary gland		

Statistics:

All statistical analyses compared the treatment groups with the control group. Body weights, hematology, biochemistry, absolute and relative organ weights were compared by analysis of variance (one-way classification), Barlett's test for homogeneity of variances and the appropriate t-test (for equal or unequal variances) using Dunnett's multiple comparison tables to determine significance of differences.

Results:

Chamber concentrations:

Animals were exposed to aerosols of test material which had average nominal concentrations of 0.202, 2.01, and 20.0 mg/l. However, these nominal concentrations could not be verified due to the lack of data on the quantity of test material injected into the chamber and on the total chamber air flow rate. Actual concentrations in the breathing zones

BEST AVAILABLE COPY

of the animals were not reported. The average aerodynamic mass median diameter of the delivered test material was 4.25 um with a geometric standard deviation of 2.07 um which indicated that 92-95% of the particles were less than 10 um in diameter. No analytical determinations of test material in the exposure chamber were made.

Clinical Observations and Mortality:

No data were present for observations of ocular and nasal irritation, dyspnea, and other pharmacotoxic signs. However, the final report indicated that at the high concentration, "the rats exhibited reddish ocular discharge, eye squint, dyspnea, and general physical weakness." In addition, the final report indicated that "the fur of the rats exposed to this concentration was heavily coated with the dried compound after each exposure." At the intermediate concentration rats exhibited a "dried reddish discharge around the nares." No adverse effects were noted at the low concentration.

No deaths were reported for the control, low, and intermediate concentrations. Table 2 summarizes the mortality data. Exposure to the high concentration (20.0 mg/l) resulted in 80% mortality in both sexes. The NOEL for mortality was 2.01 mg/l for both sexes. The LEL was 20.0 mg/l for both sexes.

Table 2. Mortality Data

Group/Sex	Deaths Recorded During Days 1-5	Deaths Recorded During Days 6-10	% Survival at 10 days	Deaths Recorded During Days 11-14	% Survival at 14 Days
Control M	0	0	100	0	100
0.202 mg/l M	0	0	100	0	100
2.01 mg/l M	0	0	100	0	100
20.0 mg/l M	0	4	30	0	20
Control F	0	0	100	0	100
0.202 mg/l F	0	0	100	0	100
2.01 mg/l F	0	0	100	0	100
20.0 mg/l F	1	2	40	1	20

Body Weights and Food Consumption:

Individual and group mean body weights were present for all animals for days 1, 2, 5, 9, 12, 14, and 15. Male and female rats in the low and intermediate dose groups had body weight gain comparable to the controls. The high concentration (20.0 mg/l) group had statistically significant depressed

body weights at day 5 compared to controls for both sexes. By day 9, four of five male rats and three of five female rats had died in the high dose group and the remaining rats showed a slight increase in body weight during the rest of the study period. Based on these findings, the NOEL for body weights was 2.01 mg/l for both sexes. The LEL was 20.0 mg/l for both sexes.

There was no food consumption data present for this study. Therefore, a NOEL could not be determined for this parameter.

Hematology:

Hematology data consisting of erythrocyte count, hemoglobin, hematocrit, total and differential leukocyte counts were reported for all terminal sacrifice animals. Group mean data for selected hematologic parameters for each sex and statistical analysis of this data were present in the final report. No statistically significant differences were seen for erythrocyte count, hemogloglobin, hematocrit, or leukocytes for males. For females, erythrocyte count was significantly decreased ($p = 0.05$) at the intermediate concentration level (2.0 mg/l) compared to controls. Hemoglobin was also significantly depressed at the intermediate concentration level compared to controls ($p = 0.05$). Both decreases were compound-related with decreases also noted at 0.2 mg/l. Data from the 20.0 mg/l groups of both sexes were not included in the statistical analysis since only one animal survived in each of these groups. No statistically significant differences for males were noted for either hematocrit or total leukocyte count. Based on these findings and since the 20.0 mg/l group was not included in the statistical analysis, the NOEL for hematology for males was 2.0 mg/l. For females the NOEL for hematology was 0.2 mg/l (LEL 2.0 mg/l).

Biochemistry:

Biochemistry data consisting of glucose, BUN, alkaline phosphatase and SGPT were reported for all terminal sacrifice animals. Group mean data for each sex and statistical analysis of this data were present in the final report. For males, glucose was significantly depressed at 0.2 mg/l and 2.0 mg/l compared to control and the effect was compound-related. No other statistically significant differences were noted for males. For females, glucose was significantly depressed at 2.0 mg/l and the effect appears to be compound-related. No other significant differences were noted for females. Based on these findings, the NOEL for Biochemistry was less than 0.2 mg/l for males (LEL 0.2 mg/l) and the NOEL for females was 0.2 mg/l (LEL 2.0 mg/l).

Urinalysis:

Urinalysis data consisting of volume, color and appearance, pH, specific gravity, glucose, acetone, protein, bilirubin, and occult blood were present for all terminal sacrifice animals. Group mean data and statistical analysis of the data were present in the final report.

No statistically significant differences were noted for females. However, the 20 mg/l group was not included in the statistical analysis since only one animal in this group survived. For males, pH was significantly decreased at 2.0 mg/l compared to controls and the effect appeared to be compound-related since a decrease (although not significant) was also noted at 0.2 mg/l. Based on these findings the NOEL for females was 2.0 mg/l. For males the NOEL was 0.2 mg/l (LEL 2.0 mg/l).

Organ Weights:

Organ weight data for adrenals, brain, ovaries/testes, kidneys, liver, pituitary, spleen, and thyroid were present for all terminal sacrifice animals. Mean group absolute (actual) and relative (% of body weight) organ weight data and statistical analysis of these data were present in the final report. Absolute and relative organ weights for both males and females showed some incidences of statistically significant differences when compared to controls.

Organ	Exposure Level (mg/l)	Sex	Weight	Change	p
Kidney	2.0	F	relative	increase	0.05
Liver	2.0	M	relative	increase	0.05
Pituitary	0.2	F	absolute	decrease	0.05
Thyroid	0.2	F	absolute/ relative	decrease	0.01/0.01
Thyroid	2.0	F	absolute/ relative	decrease	0.01/0.05

Of these significant differences the increase in the mean relative kidney weight of the 2.0 mg/l females and the increase of the mean relative liver weight of the 2.0 mg/l males are the primary findings with possible biological significance. Both effects appear to be compound related.

Based on the statistical significance of kidney and liver effects at the intermediate exposure level, the NOEL for organ weights was 0.2 mg/l (LEL 2.0 mg/l) for both sexes.

Gross Necropsy Examinations:

All animals were examined for gross pathological findings. External findings consisting primarily of yellow crystalline material on hair and blood around nose/eyes was increased at the high exposure level compared to the control. Lymph node findings consisting of red lymph nodes were increased at the low and intermediate exposure levels compared to controls for males and increased at intermediate exposure levels compared to the control group for females. Stomach findings of primarily brown red and/or hemorrhagic foci were increased at the high exposure level compared to control for males and at the intermediate and high exposure levels for females. Liver findings consisting primarily of yellow foci and dark red/brown coloration were increased at the high exposure level compared to controls for males and females. No obvious exposure-related effect was seen for males or females.

Histopathology Evaluation:

Complete histopathology was performed on all control and 20.0 mg/l animals. A partial list of tissues was examined for the 0.2 and 2.0 mg/l groups. The histopathology was prepared by IRDC and evaluated by Dr. R.G. Geil, consulting pathologist.

The number of lesions in the lung for males was increased at low, intermediate, and high exposure levels compared to controls. In females the number of lesions in the lung was increased only at the high exposure level (20.0 mg/l). Lung findings reported included parenchymal hemorrhage, interstitial inflammatory cell infiltrate, capillary/vascular congestion, microgranuloma, perivascular inflammatory cell accumulation, alveoli macrophages, and edema.

In the lungs, capillary/vascular congestion was significantly increased at 20.0 mg/l compared to controls for both male and females. Edema was increased at 0.2, 2.0, and 20.0 mg/l for males and at 2.0 and 20.0 mg/l for females compared to controls. This effect appeared to be treatment related.

In males, the number of lesions in the stomach were increased at the low, intermediate, and high exposure levels compared to controls. For females, the number of lesions in the stomach were increased at the intermediate and high doses compared to controls.

In the liver, the incidence of hepatocellular necrosis was increased at 20.0 mg/l in males and at 2.0 and 20.0 mg/l in females compared to controls. In the spleen the incidence of focal necrosis was increased at 20.0 mg/l for both sexes

compared to controls. This effect was probably compound related since the finding was not present in either of the control groups.

Based on the treatment-related effect of edema in lungs, the NOEL for histopathology for males was less than 0.2 mg/l (LEL 0.2 mg/l) and the NOEL for females was 0.2 mg/l (LEL 2.0 mg/l).

Discussion:

A two-week subchronic inhalation study was conducted to evaluate the toxicity of an aerosol atmosphere of Dicamba (Banvel 4S) in CD-1 rats. Four test groups, 10 rats/sex group, were exposed to a nominal concentration of 0, 0.202, 2.01, and 20.0 mg/liter of Banvel 4S for 6 hours/day, 5 days/week for a total of 10 exposures in two weeks. Airflow rate through the exposure chamber was not reported. Aerosol particle size distribution analyses were performed daily and the results indicate that 92-95% of the particles had a diameter less than 11uM. Parameters monitored during the in-life phase of the study included observations of pharmacotoxic signs and body weights. Food consumption data were not recorded. Hematology, biochemistry, urinalysis, organ weights, gross and microscopic pathologic examinations were performed at the end of the study.

Although the nominal concentrations of test material in the atmosphere of the test chamber were specified in the report and the airflow through the atomizer was given (9 l/min), the nominal concentration values cannot be verified. This is due to the absence of data in the report on the rate of test material dispersion into the chamber and on the total chamber airflow rate. This is basic information to the determination of the nominal concentrations.

Analysis of the chamber respirable atmosphere should have been performed as stated in the Guidelines.

No data were present for observation of pharmacotoxic signs; however, the final report indicated pharmacotoxic signs occurred at 2.0 mg/liter and 20.0 mg/liter. No adverse reactions were noted at 0.20 mg/liter.

No deaths were reported for the control, low, and intermediate concentrations. Exposure to the high concentration 20.0 mg/l resulted in 80% mortality in both sexes (LEL 2.0 mg/l).

Male and female rats in the low and intermediate dose groups had body weight gain comparable to the controls. At the high concentration (20.0 mg/l) there was significant depression of body weights at day 5 for both sexes. Based on these findings, the NOEL for body weights was 2.0 mg/l and the LEL was 20.0 mg/l for both sexes.

With respect to hematology, erythrocyte count was significantly depressed at 2.0 mg/l for females. Hemoglobin was also significantly depressed at 2.0 mg/l for females. Both decreases were compound-related with decreases also reported at 0.20 mg/l which were not significantly different from control values. No statistically significant changes were observed for males for any of the hematological parameters tested. Data from the 20.0 mg/l group of both sexes were not included in the statistical analysis since only one animal survived in each group. Based on these findings, the NOEL for hematology for males was 2.0 mg/l. For females, the NOEL for hematology was 0.2 mg/l (LEL 2.0 mg/l).

With respect to biochemistry, glucose levels for males were significantly depressed at 0.2 mg/l and 2.0 mg/l compared to control. For females glucose was significantly depressed at 2.0 mg/l and the effect was compound-related. Therefore, the NOEL for females was 2.0 mg/l and the NOEL for males was 0.2 mg/l (LEL 2.0 mg/l).

For urinalysis, no statistically significant differences were noted between control and dosed females. However, data from the female 20 mg/l group were not included in the statistical analyses since only one animal survived in this group. In males, the pH was significantly decreased at 2.0 mg/l compared to controls and the effect was compound-related. Therefore, the NOEL for females was 2.0 mg/l and the NOEL for males was 0.2 mg/l (LEL 2.0 mg/l).

For organ weights, a significant increase in the mean relative (% of body weight) kidney weight at 2.0 mg/l for females and a significant increase in the mean relative liver weight for males at 2.0 mg/l were both compound-related effects. Based on these findings, the NOEL for organ weights was 0.2 mg/l (LEL 2.0 mg/l) for both sexes.

With respect to gross pathology, no exposure-related effect was seen for males or females. Therefore, the NOEL for gross pathology was 20.0 mg/l for both sexes.

For histopathology in the lungs, edema was increased at 0.2, 2.0, and 20.0 mg/l for males and at 2.0 and 20.0 mg/l for females compared to controls. The effect appeared to be treatment-related. Based on these findings, the NOEL for

histopathology for males was less than 0.2 mg/l (LEL 0.2 mg/l) and the NOEL for females was 0.2 mg/l (LEL 2.0 mg/l).

Conclusion:

The NOELs and LELs for the biological parameters measured based on the stated nominal concentrations (calculations unverifiable) were as follows:

Parameter	Individual Data Present	NOEL (mg/l) M	NOEL (mg/l) F	LEL (mg/l) M	LEL (mg/l) F
Observations	no	--	--	--	--
Mortality	yes	2.0	2.0	20.0	20.0
Body Weights	yes	2.0	2.0	20.0	20.0
Food Consumption	no	--	--	--	--
Hematology	yes	2.0	2.0	--[a]	2.0
Biochemistry	yes	<0.2	0.2	0.2	2.0
Urinalysis	yes	0.2	0.2	2.0	--[a]
Organ Weights	yes	0.2	2.0	2.0	2.0
Gross Pathology	yes	20.0	20.0	--	--
Histopathology	yes	<0.2	0.2	0.2	2.0

[a]Data from the 20 mg/l group of both sexes were not included in the statistical analysis since only one animal survived in each group. Therefore, an LEL could not be set for this parameter.

The systemic NOEL for subchronic inhalation was <0.2 mg/l for this study.

Classification: Supplementary

This study did not report actual exposure concentrations, air flow rates and animal observations. This study was conducted with a two week exposure rather than the recommended 90 days.

Metabolism:

I. Citation: R. Tye and Engle, T., J. Agr. Food Chem., 15, 837-840 and Cleveland et al.

Study Type: Distribution and Excretion in Rats.

Accession Number: 070030

MRID Nos.: 00028261, 0028257 (duplicates), 00023107, 00087668

Sponsor: Velsicol Chemical Corporation

Contracting Lab: Department of Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio Kettering Laboratory

Date: 1967

Material Tested: Technical Dicamba, labeled with C^{14} in the carboxyl position, 98% pure.

Protocol:

Groups of 4 males and 8 females per dose of Charles River CD rats (6 months) received a single oral dose (0.1 or 0.93 gm/kg) in peanut oil by esophageal intubation. The rats were sacrificed at intervals ranging from one hour to 72 hours after dosing. Tissues, urine and blood were retained for subsequent analysis.

One male and one female Charles River CD rat, 7 months old, received a single injection subcutaneously of C^{14} labeled dicamba. The rats were sacrificed at 72 hours. Urine and feces were retained for analysis.

Groups of 5 male and 5 female rats per dose housed in individual metabolic cages were fed C^{14} labeled dicamba at 10, 100, 1000, 10000 and 20000 ppm for 24 days. Rats were sacrificed at 1, 3, 6, 13 and 24 days. Tissues and excreta were retained for analysis.

Results:

Excretion of intact dicamba and the glucuronide of dicamba was nearly 100% when administration was by dermal application or subcutaneous injection. Dietary ingestion resulted in 96% urinary excretion in 48 hours and 4% via the feces. Fairly equal tissue distribution occurred initially but tissue levels did not persist beyond a few hours indicating no bioaccumulation.

Discussion:

The radioactive counting for tissue samples was corrected for quenching and internal standards were used. This study was apparently performed adequately.

Conclusion:

When administered orally to rats, ^{14}C-dicamba is rapidly absorbed and excreted. Over 95% is excreted in the urine and the compound is not metabolized or appreciably accumulated by the tissues. A fraction of the Dicamba in the urine (ca. 13%) is conjugated as the glucuronide.

Classification: Core Minimum

II. Citation: Whitacre, P.M., Diaz, L.I., Shnur, P. (1976) Metabolism of ^{14}C-Dicamba. Report No. 180068; submitted by Velsicol Chemical Corp., Chicago, IL; CDC225558A.

Study Type: Pharmacokinetics.

Accession Number: 070030

MRID Number: 00025363

Sponsor: Velsicol Chemical Corporation

Project No.: 480068

Date of Submission: August 31, 1976

Material Tested: C^{14}-Dicamba (specific activity 11.37 mCi/mM)

Method: Two female Holtzman rats, each weighing 176 g housed in individual metabolism cages after a single oral dose of dicamba. Urine and feces were analyzed.

Results: 88% of the unchanged dicamba was excreted in the urine in 96 hours. 2-3% was eliminated in the feces. The tissues and CO_2 were not analyzed.

Classification: Supplementary, inadequate number of animals and failure to account for the metabolic fate of total administered dicamba adequately.

Subchronic 21 Day Dermal in Rabbits

1. Technical Banvel, IRDC #163-620, Accession No. 070030, October 30, 1979.

Material Tested:

Technical Banvel 4S Liquid

Material and Methods:

Sixteen male and female New Zealand White rabbits, 1.8 to 2.5 kg, were housed individually at constant temperature, humidity and light with doof and water ad libitum for two weeks prior to initiation of the study. During this incubation period Triple Sulpha (0.11% to 0.02%) was administered in drinking water as a disease prevention measure.

The animals were divided into treatment groups using a computer-generated random number table.

Dose Banvel Mg/Kg/Day	Vol. Ml/Kg	No. Rabbits M	No. Rabbits F
0	2.1 (0.9% NaCl	4	4
100	0.08	4	4
500	0.42	4	4
2500	2.10	4	4

The test material was applied with a syringe and spread evenly with a glass rod over the clipped dorsal area of the body for 6 hours per day, 5 days per week for three weeks. At the 6 hour exposure time each day, the excess material was removed and the dermal irritation scored.

Blood samples prior to testing and at 3 weeks were used for hematology and blood chemistry. Urinalysis was also done.

Results:

Eight animals died on test including two controls, 2 at 500 mg/kg/day and 4 at 2500 mg/kg/day. Some of the antemortem observations of the control and 500 mg/kg/day included distended abdomen, anorexia, diarrhea, hypoactivity, and cyanosis. The treated animals that died on test at 500 and 2500 mg/kg/day were observed to have nasal discharge, ataxia, dehydration and loss of righting reflex.

Dermal irritation was observed in all treated groups from very slight erythema and edema at 100 mg/kg/day to moderate edema and erythema at 2500 mg/kg/day.

Only the 2500 mg/kg/day females had a statistically significant difference in mean body weight loss from the controls. This group also was the only group where there was a decrease in hemoglobin concentration and a total blood protein decrease.

There were no other hematology, blood chemistry or urinalysis effects in this study.

Conclusion:

No compound related changes were seen in general behavior and appearance, biochemical studies and urinalysis.

Classification: Core Minimum

2. Technical Banvel, IRDC, #163-618, Accession No. 070030, August 22, 1979.

Material Tested:

Technical reference standard Banvel 86.8%, Lot 52625110.

Material and Methods:

Refer to previous study described above. The protocol is exactly the same for this study as IRDC #163-620.

Results:

Seven rabbits from control and test groups died or were sacrificed *in extremis* during the study although these events were not considered compound related.

There were no Banvel related changes in general behavior, appearance, body weight, or in blood and urine analysis. At the low dose (100 mg/kg/day), erythema was slight in intact and slight to moderate in abraded animals in weeks 2 and 3. There was also slight edema, atonia, desquamation, coriaceousness and fissuring.

At 500 mg/kg/day, the erythema in the 2nd week was moderate, subsiding to slight to very slight. The edema and other effects were slight to moderate in the intact and moderate in the abraded.

At 2500 mg/kg/day, the erythema was moderate to severe while the other skin effects were slight to moderate.

There were no compound related gross pathology lesions in the test animals. The histopathological examination revealed only skin lesions. There were no significant organ weight changes.

Conclusions:

Dermal application of Banvel results only in skin toxicity.

Classification: Core Minimum

D. Subchronic Oral Toxicity

Technical Banvel (Dicamba), IRDC, #163-671, Accession No. 070030, November 11, 1980. 13-week Oral Toxicity in Rats.

Material Tested:

Technical Banvel 86.82%, Beige Chips, Lot No. 52625110.

Material and Methods:

This study follows a 4-week pilot study in rats using dietary dosage levels of 5000, 7500, 10000, 12500 and 15000 ppm in 5 males and 5 females at each level. Based on the results of this study, a 13-Week Dietary Toxicity Study in rats was done on 20 male and 20 female rats at each of the following dosages: 1000, 5000 and 10000 ppm and 0 ppm.

The rats used were Charles River CD (111-164g) which were preconditioned at controlled temperature, humidity and light in individual cages and maintained with ad libitum water and Ralston Purina Rodent Chow #5002.

The animals were observed twice daily for appearance, behavior, mortality, body weight and food consumption. Clinical tests, including hematology, biochemistry and urinalysis, were performed.

At termination of the study pathological examination consisted of gross pathology, organ weights and histopathology.

Results:

In the range finding study, there was impaired mobility in the hind extremities in one animal at 12,500 ppm and in 7 rats at 15000 ppm. The body weight gains and food consumptions were slightly reduced at 12,500 ppm and moderately reduced at 12,500 and 15,000 ppm when compared with control rats. There was no mortality.

In the 13-week feeding study there was no compound related changes in general behavior and appearance. Three female rats died on study (one control, one mid-dose and one high-dose). There was a slight decrease in comparative body weight gains and food consumption at 10000 ppm versus controls. There were no gross lesions or organ weight variations in the treated groups. There was an absence or reduction of cytoplasmic vacuolation of hepatocytes indicating reduced ciycogen storage in the high-dose grops. NOEL = 5000 ppm (systemic).

Classification: Core Minimum

E. Chronic Study, rats

Technical Banvel, [BT #8580-10130, 24-month chronic oral toxicity study in Charles River CD-1 rats, May 16, 1980, and March 30, 1981. Accession No. 070030.

This study is an unvalidated IBT study which cannot be utilized at this time.

Discussion

The reviewer reviewed studies where either the technical acid in water or the technical dimethylamine (DMA) salt in water were tested. In water the DMA salt hydrolyzes to the acid and therefore these are considered to be toxicologically equivalent.

Risk Assessment

Risk Assessment need not be completed for dicamba since positive pivotal studies have not been demonstrated.

IBT Discussion

There is a mouse oncogenicity study which was mentioned in the previous data review section that has not yet been validated.

Tolerance Reassessment

Tolerances have previously been established for dicamba using a two year dog NOEL of 50 ppm with a 100-fold safety factor and the ADI was 0.0125 mg/kg/day. This study (2-year dog) was rereviewed and found to be supplemental. In 1982 the Agency reviewed a 90 day rat study which was found to be "core minimum" and recommends that all the tolerances be reevaluated on this basis. The print out is attached.

As mentioned above the previous data considered in setting the ADI was a 1962 two year feeding study in dogs which has now been core classified as "supplementary data." A 90 day subchronic study core classified as core minimum in rats has, therefore, now been substituted, as the basis for calculating the ADI. The rat subchronic study with a systemic NOEL of 500 ppm and 2000 fold safety factor yields an PADI of 0.0125 mg/kg/day and MPI of 0.7500 mg/day. Toxicology Branch approved tolerances result in 37.55% of the existing % ADI being occupied and a TMRC of 0.2816 mg/day (1.5 kg.). which were the same values as calculated for the supplementary 2 year feeding study in dogs.

004036

DCR-10740:StephenyAprilWorkOnly:8/1/83:TOX-31A and 31B :efs
REVISED-8/4/83:DCR-32952:TOX-31-A= p.1-54 & 31-B= p.55-77:efs

TABLE A
GENERIC DATA REQUIREMENTS FOR CHEMICAL X

Data Requirement	Composition[1/]	Use Patterns[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA Section 3(c)(2)(B)?[3/]
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Oral LD_{50} - Rat	TGAI		Yes		No
81-2 - Dermal LD_{50}	TGAI		No		Yes
81-3 - Inhalation LC_{50} - Rat	TGAI		No		Yes
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI		N/A		No
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding - Rodent, Non-rodent	TGAI		Yes/No		No/Yes
82-2 - 21-Day Dermal	TGAI		Yes		No
82-3 - 90-Day Dermal	TGAI		No		Yes
82-4 - 90-Day Inhalation - Rat	TGAI		No		Yes
82-5 - 90-Day Neurotoxicity - Hen/Mammal	TGAI		N/A		No

1/ Composition: TGAI = Technical grade of the active ingredient.
2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B=Terrestrial, Non-Food; C= Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.
3/ Data must be submitted no later than _____.

004036
71
ED_005172C_00001736-00071

004036

TABLE A
GENERIC DATA REQUIREMENTS FOR CHEMICAL X

72

Data Requirement	Composition[1/]	Use Patterns[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA Section 3(c)(2)(B)?[3/]
§158.135 Toxicology (continued)					
CHRONIC TESTING:					
83-1 - Chronic Toxicity - 2 species: Rodent and Non-rodent	TGAI		No		Yes
83-2 - Oncogenicity Study - 2 species: Rat and Mouise preferred	TGAI		No		Yes
83-3 - Teratogenicity - 2 species	TGAI		Yes		No
83-4 - Reproduction, 2-gneeration	TGAI		Yes		No
MUTAGENICITY TESTING:					
84-2 - Gene Mutation	TGAI		No		Yes
84-2 - Chromosomal Aberration	TGAI		No		Yes
84-2 - Other Mechanisms of mutagenicity	TGAI		No		Yes

1/ Composition: TGAI = Technical grade of the active ingredient.
2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.
3/ Data must be submitted no later than _____.

TABLE A
GENERIC DATA REQUIREMENTS FOR CHEMICAL X

Data Requirement	Composition[1/]	Use Patterns[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA Section 3(c)(2)(B)?[3/]
§158.135 Toxicology (continued)					
SPECIAL TESTING:					
85-1 - General Metabolism	PAI or PAIRA		Yes		No
85-2 - Domestic Animal Safety	Choice		-		No

1/ Composition: TGAI = Technical grade of the active ingredient.
2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.
3/ Data must be submitted no later than _____.

END