2-7-78

DATE: 2/7/78

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#470A

SUBJECT: EPA Reg. No. 359-684 and -685, Chipco 26019

[3-3,5-dichlorophenyl-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide]

FROM: R.B.Jaeger
TB

TO: Eugene Wilson
PM 21

Data submitted on EPA Reg. No. 359-685 (50% WP) are reviewed as follows:

1. "Acute Oral Toxicity in Rats", Food And Drug Research Labs., Inc., 8/26/76, Lab No. 5170, submitted by Rhodia, Inc., 1/13/78 (Acc#232709).

a. Protocol: Acute Oral LD50

Substance Tested: EPA Reg. No. 359-685, 50% WP (same a.i. as above)

Species: Wistar Rats

Sex and Age: M/F, young adult (wt 200-400 g and 150-240g, respectively)

Number of Animals: 5M/5F per each of 5 dosage groups (5, 7.5, 10, 20 and 25 g/kg); as a 50% solution.

Conduct of Test:

Dosage/Duration: Animals housed in wire mesh bottom cages with food and water available ad lib after dosage. Dosages administered by intragastric intubation. Animals weighed prior to dosing and at termination (14 days). Animals observed daily for 14 days.

NOTE: There were two AO LD50 studies following the exact same protocol and with same Lab. No. and date.

b. Results:

Mortality:

LD50 calculated to be: 12.5 ± 2.15 g/kg and
11.4 ± 1.8 g/kg

1 3/3

Deaths denoted by sex were not reported separately. The above LD50's are therefore, combined values for both M & F.

No necropsy report.

No slope reported.

Toxic symptoms were not reported.

c. Conclusions:

Study is considered SUPPLEMENTARY Data. Several omissions in the protocol, as noted above, need further clarification. Since this is a new product, TB needs to know the toxic symptoms, general behavior, and other meaningful observations (including wt. gain or loss) which supposedly were conducted but not reported. Further, LD50 values should be reported according to sex. Also, were necropsy evaluations conducted and if so, what tissues or organs were examined?

2. "Acute Dermal Toxicity Study in Rabbits", Fodd and Drug Research Labs., Inc., 8/30/76, Lab No 5170, submitted by Rhodia, Inc., 1/13/78 (Acc#232790).

a. Protocol: Acute Dermal LD50

Substance Tested: Same as 1. above

Species: Albino Rabbit

Sex and Age: Adult, sex not given

Number of Animals: 25 with 5 per dose (20, 200, 2000, 3000, 5000 mg/kg)

Conduct of Test:

Dosing/Duration: Details of protocol indeterminate as submitted.

b. Results:

LD50 > 5 g/kg

c. Conclusions:

Study is considered SUPPLEMENTARY Data because the protocol is inadequately described and results reported are insufficient, for

many of the same reasons as 1. above. When complete information above is submitted it will be reevaluated in light of such data to determine if the study can be upgraded. As is, the study does not support the registration. Further, what type of "albino rabbit" was used?

3. "Primary Skin Irritation Study with Rabbits", Food and Drug Research Labs. Inc., 8/16/76, Lab No 5170, submitted by Rhodia, Inc., 1/13/78 (Acc#232709).

a. Protocol: Primary Skin Irritation Study with Rabbits .

Substance Tested: Same as 1. above (it is not clear whether it was administered as a WP or as dry powder).

Species: Albino Rabbits

Sex and Age: Adult, sex not stated.

Number of Animals: 6

Conduct of Test:

Dosing/Duration: The back of each animal was shaved free of hair; an abraded and intact skin site on each animal. 0.5 g of test material was introduced under a 1 inch sq. patch of gauze; removed after 24 hrs and observed. Observations again at 72 hrs.

b. Results:

P.I. Index = 2.5/8.0 (moderately irritating)

Erythema and edema present in 6/6 throughout the study. There was no apparent differences between intact and abraded skin reactionx. Readings showed signs of increased irritation both for erythema (2/6) and edema (1/6).

c. Conclusions:

Study is considered CORE:Minimum Data

Some questions which need to be answered:

(1) was material administered as a WP (moistened) or "as received" (in powder form)?

(2) how was material removed --- washing, wiping, ?

(3) how was the skin abraded and how deep?

Toxicity Category III "CAUTION"

4. "Eye Irritation Test In Rabbits", Food and Drug Research Labs. Inc., 8/16/76, Lab No 5170, submitted by Rhodia, Inc., 1/13/78 (Acc#232709)

a. Protocol: Eye Irritation

Substance Tested: Same as 3. above

Species: Albino Rabbit (what strain, etc.?)

Sex and Age: Young adult, sex not stated

Number of Animals: 9

Conduct of Test:

Dosing/Duration: Test material at the level of 0.1 ml or 0.1 g was applied to the right eye of each animal. 6/9 rabbits received material and remained unwashed; while 3/9 received material and then washed 4 sec. after instillation. All eyes were observed and readings taken at 24, 48, 72 hrs and 7 days after instillation of test material.

b. Results:

Unwashed - no corneal involvement; mild iritis clear in 72 hrs; severe redness and discharge noted in 2/6 at 24 hrs, mild at 72 hrs. No irritation at 7 days.

Washed - no corneal involvement; no iritis; no discharge and mild redness of conjunctiva. Clear in 7 days.

c. Conclusions:

Study is considered CORE: Minimum Data.

Some questions which need to be answered:

(1) was the test material administered as a WP (moistened) or "as received" (dry powder)?

(2) how were eye reactions read - had-held lit lamp, etc.?

(3) was sodium fluorescein used to evaluate cornea reaction?

Toxicity Category III "CAUTION"

5. "Acute Inhalation Toxicity", Huntington Research Center, 3/19/77, RHP 74/77241, submitted by Rhodia, Inc., 1/13/78 (Acc#232709).

a, Protocol: Acute Inhalation LC50

Substance Tested: Same as in 1. above (formulated product - dust)

Species: Hysterectomy-derived, barrier sustained, SPF Albino Rats (Sprague-Dawley)

Sex and Age: M/F, age not stated

Number of Animals: 7M/7F per each of 3 dose levels

Conduct of Test:

Dosing/Duration: Animals caged in groups of 7 of same sex; free access to food (Spratt's Lab Diet) and water. A control group received only clean air (Gp 1); one treatment group was exposed to the dust generated from the packed bulk powder sample (Gp 2); the other treatment group was exposed to the fraction of the bulk sample that passed through a 53 um mesh sieve (Gp 3). Observed for 14 days post exposure. 2M/2F from each group were killed immediately following exposure to assess any primary irritant effects of the dust on the lungs and respiratory tract.

Description of Equipment: Dust was generated using a Wright Dust Generator. A scraper blade removes the powder from a pre-packed cannister. As the powder is scraped off, dry compressed air passes into the canister and disperses the powder into an exposure chamber at a rate of 20 l/min. Internal volume of chamber is 0.1 m^3 . Galvanized metal grills divide each chamber into 6 separate compartments, into which the animals are placed during

exposure. The dust dispersed evenly throughout each chamber and exited through a series of small holes around the base of each chamber, below animal level. Animals were exposed for 4 hrs (dust generated continuously). Particle size was sampled twice during the 4 hr exposure; concentration sampled each hr. (approx. 5-10 min) during the 4 hr period.

Observations: Rats observed "frequently" during exposures for appearance, behavior, mortality.

Necropsy: All animals had their lungs removed and weighed and macroscopically examined.

b. Results:

Mortality: None

Dust Concentration:

Gp 2 - 1.96 g/m^3 (1.96 mg/l)

Gp 3 - 1.57 g/m^3 (1.57 mg/l)

Particle Size:

Gp 2 - 71% less than 5.5 um

Gp 3 - 63% less than 5.5 um

Observations: Blinking, sneezing, licking inside mouth; difficulty in breathing. Appeared normal 2 hrs post-treatment and for the remaining 14 days of observation period. No change in body wt.

Necropsy:

No significant differences were noted or reported.

c. Conclusions:

Study is considered CORE:Minimum Data.

Problems noted are as follows:

(1) it would appear the group mean body wts. were biased towards

the treatment groups (i.e. Gp 2 animals weighed more than Gp 3 weighed more than Gp 1 - appears to depend on exposure concentration). Why? This makes it very difficult to compare body wt. changes and pathological changes, particularly since the treatment groups are either older or apparently healthier animals.

(2) insufficient examination of lung and associated tissues

(3) the dust concentration generated was not sufficiently great enough to place the material in Tox. Cat. III (i.e. 1.96 and 1.37 mg/l), which are less than the upper limit of 2 mg/l). However, based on the information provided, the fact that no mortality occurred, and the highest concentration of 1.96 mg/l make it possible to assign this material to Tox. Cat. III "CAUTION ".

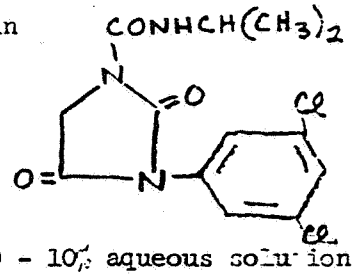
TB recommends against registration of EPA Reg. No 359-685 until the discrepancies noted above are answered satisfactorily.

The Toxicity Data submitted for EPA Reg. No. 359-684 are reviewed as follows:

6. "Acute Toxicity and Local Tolerance", Société des Usines Chimiques Rhône-Poulenc, 4/7/74, Exemplaire No 3, submitted by Rhodis, Inc. 1/13/78 (Acc#232701)

a. Protocols: Acute Oral, Acute Dermal, Eye and Skin Irritation

Substance Tested: Technical Isopropylcarbomoyl-1(dichloro-3,5 phenyl) -3 hydantoin



For AC LD50 - 10% aqueous solution of arabic gum

For AD LD50 - suspension in acetone-oil mixture

For Eye/Skin Irritation - technical grade as received

- Acute oral toxicity (mouse, rat and dog)

A - Protocol

The experimental protocol is described in the following table and paragraphs.

Animals					Oral administration		Observation period
Species	Strain	Weight	Number per dose: males	Number per dose: females	Doses (g/kg p.o.)	Unit volume (ml/kg)	Days
Mouse (C.O.B.S.) (x)	CD_1	19 to 22 g	5	5	10.0 6.7 4.5 3.0 2.0 1.3	50	15
Rats (C.O.B.S.) (x)	CD	220 to 290 g	10	10	2 (xx) 1	5	15
Dogs	Beagle or Common	7.5 à 10.7 kg	2	2	2 (xx) 1	7.5 5	15

(x) Caesarean Originated, Barrier Sustained (animals coming from Charles River France)

(xx) Maximal possible dose for the volume of administration chosen.

Wt. measured before treatment before treatment, at 5, 10, and 15 days after

Macroscopic exam (rat only) of trachea, lungs, G.I. Tract, liver, kidneys, spleen after 15 days (or at death)

b. Results:

Mouse - LD50 approx. 4 g/kg (M: 4.0, F: 4.4)

Symptoms: depression, dyspnea, emaciated

Rat - LD50 > 2g/kg

Symptoms: no significant differences (in wt gain or macrosppic exam)

Dog - LD50 > 2 g/kg , slight vomiting and anorexia

- Percutaneous acute toxicity (rat and rabbit)

A - Protocol

The experimental protocol is described in the following table and the paragraphs :

Animals					Percutaneous administration		Observation period
Species	Strain	Weight	Number per dose		Doses (xx) (g/kg p.c.)	Unit volume (ml/kg)	(Days)
			males	females			
Rats (C.O.B.S.) (x)	CD	180 to 220 g	10	10	2.5	5	15
Rabbits	New-Zealand White	2.3 to 3.1 kg	4	4	1.0	2	15

(x) Caesarean Originated, Barrier Sustained (animals from Charles River France).

(xx) Maximal possible dose for the chosen volume of administration.

Material applied as a suspension in a mixture of 2 parts acetone and 1 part peanut oil on the shaved skin area of the back. After application animals are placed in individual cages and occlusive dressing applied. After 24 hrs collars or occlusive dressing are removed and treated area carefully washed with warm soapy water, then dried.

Animals weighed before and 5, 10, and 15 days after treatment.

Macroscopic exam of trachea, lungs, G.I.tract, liver, kidneys, and spleen

b. Results:

Rat - LD50 > 2.5 g/kg

Symptoms: decreased wt gain in males; no mortality; no macroscopic findings

Rabbit - LD50, etc. not reported (assumed LD50 is > 1.0 g/kg)

- Eye Irritation

a. Protocol - Draize method, 6 New Zealand White Rabbits (weighing 3- 3;7 kg) received 100 mg of technical product applied in the conjunctival sac of one eye. Eyes evaluated at 1, 24, 48, 72, 84 hrs and 7 days after application.

b. Results:

No irritation noted.

- Skin Irritation

a. Protocol: Draize method, 6 N. Zealand White Rabbits (weighing 2.5 - 3 kg) received 0.5 g of technical product (applied as paste; water added) applied to shaved (intact & abraded) areas of the skin. Material maintained in contact for 24 hrs . Local reaction observed after 24 and 72 hrs.

b. Results:

No irritation noted

c. Conclusions:

Studies are considered CORE: Minimum Data

7. "Acute Oral Toxicity in Rats", Food and Drug Labs., Inc., 11/22/76, Lab. No. 5274, submitted by Rhodia, Inc. 1/13/78 (Acc#232701).

a. Protocol: Acute Oral LD50

Substance Tested: Technical grade material (same as 6. above) administered as 25% in corn oil

Species: Wistar Rat

Sex and Age: Young adult M/F

Number of Animals: 5M/5F per each of 5 dosage groups (1.25, 2.5, 5, 10, and 20 g/kg)

Conduct of Test: Same as 1, above

b. Results:

Mortality: LD50 3.7± 0.63 g/kg

same as 1. above

c. Conclusions:

Study is considered SUPPLEMENTARY Data. Same comments as study 1. above.

8. "Acute Dermal Toxicity Study inRabbits", Food and Drug Research Labs., Inc., 11/22/76, Lab No 5274, submitted by Rhodia, Inc., 1/13/78 (Acc#232701)

a. Protocol: Acute Dermal LD50

Substance Tested: same as 7. above (except administered as received)

Species: Albino Rabbit (?)

Sex and Age: Adult, sex not given

Number of Animals: 25 with 5 per dose (2, 5, 10 and 30 g/kg)

Conduct of Test: same as 2. above

b. Results:

LD50 > 30 g/kg

c. Conclusions:

Study is considered SUPPLEMENTARY Data for same reasons as study 2. above.

9. "Primary Skin Irritation Study in Rabbits", Food and Drug Research Labs., Inc., 11/22/76, Lab No 5274, submitted by Rhodia, Inc., 1/13/78 (Acc#232701)

a. Protocol: Primary Skin Irritation

Substance Tested: same as 8. above

Species: Albino Rabbit (?)

Sex and Age: Adult, sex not stated

Number of Animls: 6

Conduct of Test: same as study 3. above

b. Results:

No irritation noted

c. Conclsions:

Study is considered CORE:Minimum Data

Same questions as study 3. above.

10. "Eye Irritation Test In Rabbits", Food and Drug Research Labs., Inc., 11/22/76, Lab No 5274, submitted Rhodia, Inc., 1/13/78 (Acc#232791)

a. Protocol: Eye Irritation

Substance Tested: Same as 8. above

Species: Albino Rabbit (?)

Sex and Age: Young adult, sex not stated

Number of Animals: 9

Conduct of Test: same as 4. above

b. Results:

Unwashed - no corneal involvement or iritis; mild redness, chemosis and discharge at 72 hrs. No irritation at 7 days

Washed (4 sec) - no corneal opacity or iritis; no irritation noted

c. Conclusions:

Study is considered CORE:Minimum Data

Same questions as noted in study 4. above

11. "Acute Inhalation Toxicity", Huntington Research Center, 1/29/77, RHP 75/775, submitted by Rhodia, Inc. 1/13/78, (Acc#232701)

a. Protocol: Acute Inhalation LC50

Substance Tested: same as 8. above

Species: same as 5. above

Sex and Age: M/F, age not stated

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Number of Animals: 7M/7F per each of 3 dose levels

Concuct of Test: same as study 5. above

b. Results:

Mortality: NONE

Dust Concentration:

Group 2 0.65g/m^3 (0.65 mg/l)

Group 3 3.29g/m^3 (3.29 mg/l)

Particle Size:

Group 2 71% less than 5.5 um

Group 3 63% less than 5.5 um

Observations and Necropsy:

same as study 5. above

c. Conclusions:

Study is considered CORE:Minimum Data

Same questions as study 5. above

TB recommends against registration of EPA Reg. No. 359-684 until discrepancies noted above are answere satisfactorily.

Robert B. Jaeger, Physiologist
Toxicology Branch

2/14/78